

Letter to Editor

Volumetric expansion of ocular defect with progressive conformers: An objective assessment

Surgeries such as enucleation, evisceration, and exenteration have devastating consequences for the patient.^[1] The loss of an eye whether by surgery or trauma often results in scar tissue leading to contraction. Postenucleation socket syndrome (PESS) is a common late complication of enucleation therapy.^[2] It is also known as anophthalmic socket syndrome and encompasses several anomalies such as ptosis, superior sulcus deformity, enophthalmos, and ectropion.^[3] PESS is associated with severe contracture leading to poor prosthesis esthetics and difficulty in insertion.

Placement of a conformer to fit the contours of the cavity has been advocated to prevent contraction of the socket.^[4] Conformers can be either stock or custom fabricated. Progressive expansion therapy involves the fitting of plastic stents or silicone expanders over time to develop the contracted ocular socket for optimal prosthetic results.^[5,6] Surgical correction with graft placement can be tried once the socket has been expanded to improve esthetics.^[7]

Use of progressive expansion therapy with custom conformers to increase socket size has been documented in literature. However, volumetric expansion of socket after using conformers has not been quantified.^[8] This article aims to quantify this expansion.

A young patient with a history of retinoblastoma treated by enucleation followed by chemotherapy and external

beam radiotherapy (EBRT) presented with PESS of the right eye. After thorough evaluation and interdisciplinary consultation, it was planned to manage the severe contraction by progressive expansion therapy followed by reconstructive socket surgery. The treatment plan was explained and informed consent obtained from the parents of the 9 years old. The following technique was followed:

1. Make an impression of the anophthalmic socket in irreversible hydrocolloid (Ophthalmicmoldite; Milton Roy Co., Sarasota, FL) and pour a two-piece split cast mold from the same [Figures 1 and 2]
2. Fabricate wax pattern on the mold and try in the patient's ocular defect
3. Finalize the pattern and invest
4. Fabricate custom ocular conformer in clear polymethyl methacrylate (PMMA) resin (Trevalon; Dentsply Pvt. Ltd.) after dewaxing [Figure 3]
5. Prepare a closed cylinder from a 5/10 ml syringe by blocking its nozzle
6. Fill the syringe with few ml of water and calculate conformer volume by noting the increase in this volume when placing the conformer in the syringe
7. This is considered as the baseline ocular defect/conformer volume
8. Instruct the patient to wear the conformer continuously for 3 weeks
9. Prepare the sequentially larger custom conformer



Figure 1: Right ocular defect with postenucleation socket syndrome



Figure 2: Two-piece mold obtained from the impression of the defect



Figure 3: Custom ocular conformer

followings steps 1–4. Measure ocular defect/conformer volume as outlined in step 6 and note the increase in volume

10. Repeat procedure at the third visit after another 3 weeks.

Following this, a comparative evaluation of volume expansion with sequentially larger sizes of conformers was done which showed an increase from a baseline of 2.0 to 2.4 ml and further to 2.6 ml [Figure 4] volume increase of approximately 30%.

At the end of progressive expansion therapy, the patient was prepared to undergo surgery.

Progressive expansion therapy has been documented to be an important part of the management of severely contracted orbital socket. Recently, self-inflating polymer expanders have been introduced. These lens-shaped expanders are implanted in the orbital tissue where they absorb lacrimal fluid from the mucosal socket or tissue fluid and swell.^[9] However, it is difficult to customize them and control the amount of expansion.^[9]

The method described in this article used is a simple yet accurate and validates expansion achieved by conformer therapy. Objective measurement of expansion offers several advantages such as better visualization of progress and further treatment planning like the size of orbital implant to be used or amount of graft required. Thus, the importance of measuring orbital expansion cannot be underplayed. However, this report is of a stand-alone case, and there may be more advanced instruments available to quantify the expansion. The authors intend to present a thought-provoking idea for further research into the same.

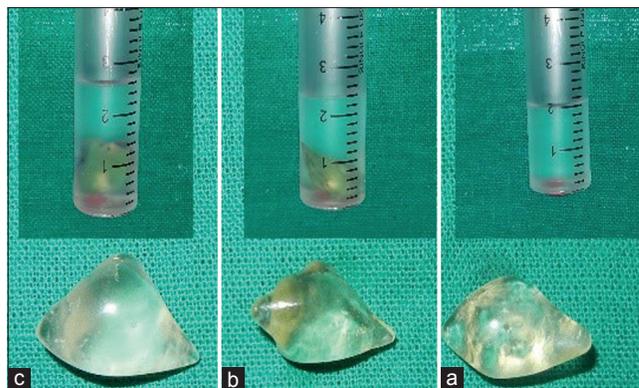


Figure 4: Progressively larger conformers. (a) Baseline conformer (b and c) progressively larger sizes of conformer, respectively. Note the increase in volume objectively measured wherein (c) > (b) > (a)

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Guide flange Prosthesis for management of hemimandibulectomy

ABSTRACT

Guide flange is given to patients who have undergone surgical hemi/segmental/subtotal mandibulectomy due to various reasons (leading cause being squamous cell carcinoma), with resultant mandibular deviation. If procedures such as secondary osseous grafting are planned, the clinician has to wait for healing of the graft, lesion, or radiotherapeutic effects to abate. Only after the healing of the graft, a definitive prosthesis can be planned. During this time lag, prosthesis must be given to the patient to correct mandibular deviation on account of unilateral muscle pull. Furthermore, in certain cases, a definitive prosthesis has to be put on hold due to failure of bone grafting or when the patient is not willing for a second surgery. This report describes the fabrication of such a mandibular guide flange prosthesis.

Keywords: Guiding flange, mandibulectomy, squamous cell carcinoma

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most commonly occurring cancers of the oral cavity and is the 12th most commonly occurring cancer in the world.^[1] It ranks among the top three most common malignant lesions in India.^[2] OSCC occurs most commonly on the lateral margins of the tongue and floor of the mouth, with the risk of invasion of the tumor to the mandible. This necessitates its resection in conjunction with large portions of the tongue, floor of the mouth, and regional lymphatics. Hence, management poses a difficult challenge for the surgeon, radiation oncologist, and prosthodontist to both control the primary disease and rehabilitate following treatment. Loss of mandibular continuity may result in severe impairments of mastication, speech and swallowing, deviation of the mandible toward the affected side during functional movements, rotation of the occlusal plane inferiorly, drooling of saliva, and severe cosmetic disfigurement.^[3]

Immediate mandibular reconstruction is desirable and aims to restore facial symmetry, arch alignment, and stable occlusion.^[4,5] Various alternative treatment modalities available are conventional guide flange prosthesis (GFP)

prostheses, surgical reconstructive procedures followed by cast partial dentures or use of osseointegrated implant retained fixed, and removable prostheses to reestablish the patients' oral functions and quality of life. These are often the options when the surgeon wants to rule out recurrence of lesion and hence opts out of primary reconstruction. GFP is often designed for the patient who is able to achieve a guided appropriate mediolateral position of the mandible but is unable to repeat this position voluntarily and consistently for adequate mastication.^[6] It accounts for the deviation in occlusion because of unilateral muscle pull, resection of condyle, and fibrosis of surgical site, till a more definitive treatment plan can be instituted. This

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case report describes GFP management of a patient who had undergone a hemimandibulectomy (from the left condyle to midline region) and a failed attempt at free fibula grafting.

CASE REPORT

A 42-year-old male was referred to the department of prosthodontics for prosthetic rehabilitation following a hemimandibulectomy (Cantor and Curtis Class III) and attempted but failed reconstruction with free vascular fibula graft 4 months back. History revealed that the patient had a tobacco chewing habit for 20 years and was diagnosed with squamous cell carcinoma of the left mandible 6 months back. Extraoral examination revealed diffuse swelling of the left side of the face, extending from the corner of the mouth to the superior border of neck superoinferiorly and from mandibular midline to left ear anteroposteriorly [Figure 1]. Intraoral examination revealed missing teeth in relation to #24–27, 31–37, and 41 [Figure 2]. It also revealed thick,

freely movable soft tissues with scar formation, loss of alveolar ridge, and obliteration of buccal and lingual sulci in the left half of mandibular region intraorally (mesial to right lateral incisor) [Figure 3]. Deviation of mandible was observed to the left side (about 16 mm from the midline on 30 mm of mouth opening) due to effect of normal right mandibular muscle action in the absence of contralateral left muscles. Frontal plane rotation was noted as the patient tried to close his mouth to maximum intercuspation. The patient was not able to achieve an appropriate mediolateral position of the mandible with the scissor bite being 1 mm after guided closure. Furthermore, the patient was unable to repeat this position himself for mastication. A postsurgical panoramic radiograph revealed missing left ramus, including coronoid process and body of the mandible up to the midline [Figure 4].

A stock tray and a sectional stock edentulous tray were used to record impressions of the maxillary and mandibular arch, respectively, with irreversible hydrocolloid (2002, Dentsply). The impressions were poured with Type III gypsum material (Kalstone; Kalabhai Karson) and casts were retrieved. A 19-gauge round, stainless steel orthodontic wire was manipulated [Figures 5 and 6] on the tooth-bearing segment of the remaining mandible to fabricate a framework for the GFP. Furthermore, C clasps were fabricated on both



Figure 1: Pretreatment view



Figure 2: Maxillary arch



Figure 3: Mandibular arch



Figure 4: Orthopantomogram



Figure 5: Framework of guide flange



Figure 6: Framework (occlusal view)

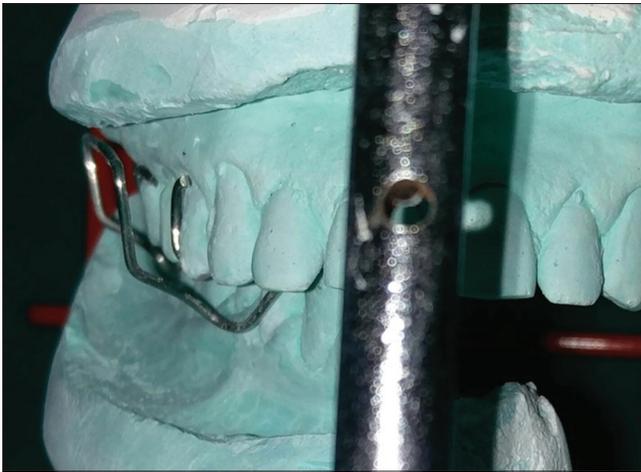


Figure 7: Framework (in occlusion)

first premolars and molars on the maxillary cast [Figure 7]. On the mandibular cast, the vestibular (buccal and lingual) flanges, occlusal surface to compensate for the scissor bite, and the mandibular guide-flange to the level 3 mm over the free gingival margin of the opposing maxillary teeth were waxed-up (Modeling wax; Deepti Dental Products) around the wire substructure with keeping a maxillary cast in occlusion. On the maxillary cast, a single thickness modeling wax was adapted covering the entire hard palate. Subsequently, both were acrylized into the clear heat-polymerized acrylic resin (DPI Heat cure clear; Dental Products of India) [Figure 8]. The GFP and maxillary plate were finished and polished.

The inclination of the guide-flange was adjusted by selectively trimming the surfaces of the GFP contacting the occlusal surface of maxillary teeth or adding autopolymerizing clear acrylic resin intraorally (DPI Cold cure clear; Dental Products of India, Mumbai, India) [Figures 9 and 10]. Thus, smooth gliding flange surface was developed intraorally to guide the mandible to occlusion. Care was taken to preserve the



Figure 8: Guide flange (postacrylization)

buccal-surface indentations of the opposing maxillary teeth in guiding the mandible to a final definite closing point during mastication. The flange height was adjusted from opening position to maximum intercuspation in a smooth unhindered path. The prosthesis was delivered and postinsertion instructions were given. The patient was followed up at the regular interval of 3 months for the next 1 year. The patient could use the prosthesis without much difficulty and could speak and masticate successfully.

DISCUSSION

Carcinoma affects a vast majority of individuals. Around 300,000 patients are annually estimated to have oral cancer worldwide.^[7] India has the ignominy of world's highest occurrence (nearly 20%) of oral cancers, with an estimated 1% of the population having oral premalignant lesions.^[8] Depending on the location and extent of the tumor in the mandible, various surgical treatment modalities such as marginal, segmental, hemi, subtotal, or total mandibulectomy can be performed.^[9] Deviation of remaining mandibular segment(s) occurs toward the defect when there is loss of mandibular continuity without reconstruction. A vertical acrylic projection from the buccal



Figure 9: Guide flange (intraorally)

aspect of mandibular teeth on the nonresected side extends to contact the buccal surfaces of maxillary teeth on the same side. This helps to maintain the mandible in approximately its proper mediolateral position. This mostly allows for vertical strokes but limited lateral movement. Intermaxillary fixation was used in the past to reduce the deviation associated with resection of the mandible but is currently not in favor. This was done using arch bars and elastics for 5–7 weeks postsurgically. It is feasible only in patients with resections confined to the mandible and with little associated soft-tissue loss. Scar contracture is, therefore, minimal and since ample soft tissue is available for closure, mandibular deviation is actually secondary to muscle imbalance and compromised proprioception. Using intermaxillary fixation in these patients maintains the proprioceptive sense of occlusion and enables most patients to readily assume appropriate intercuspal positions following removal of fixation. However, it is not feasible or appropriate if the patient required composite resection with a classical radical neck dissection and/or radiation therapy, if the oral wound was closed primarily, mandibular deviation is worsened, and the resulting scar contracture is more profound and unyielding. In such patients, scar contracture and tight wound closure contribute more to deviation than do muscle imbalance and/or loss of the proprioceptive sense of occlusion.^[10]

When surgical removal of segment of mandible is planned, ideally, it should be planned for immediate reconstruction. This helps the patient in maintenance of function. Despite advancements in procedures for reconstructive surgery and prosthodontic reconstruction and rehabilitation, more than 50% of reconstructed head-and-neck cancer patients still report impaired masticatory function.^[4,5] Advances in reconstructive surgery and procedures involving dental implants have allowed the patients to have hopes for marked improvement in the quality of life.



Figure 10: Guide flange (in function)

The disadvantage of dental implants is increase in treatment, time firstly due to tissue healing required post surgery and grafting, and secondly time taken for osseointegration of the implants.^[11] In this time lag, a mandibular guide flange can be given to the patient, as it will help the patient to guide the residual mandible into its normal position which will improve masticatory efficiency.

In this case, the patient was a middle-aged male who had already undergone a reconstruction, but the free fibula bone graft procedure failed and the patient did not want to undergo another surgical procedure. Furthermore, his maxillary teeth were absent on the side of mandibulectomy. The main aim of the treatment in this case was to guide the remaining mandible into normal position to allow the patient to carry out basic activity of mastication of food, and to some degree, compensate for the facial appearance due to the excessive deviation of remaining mandible. Furthermore, attempts were made to prevent tipping of maxillary teeth due to constant force of the mandibular guide flange on the teeth by giving the patient a maxillary stabilization plate. To enhance the esthetics to some degree, the prosthesis can be fabricated in clear acrylic and the wire components can be shifted as posterior as permissible. The prosthesis though should include as many teeth as possible and the flange should have sufficient extension to allow it to be stable and retentive, and at the same time, distribute stresses on an area as large as practically possible.

The GFP is commonly used on an interim basis as a training prosthesis until such a time when a permanent prosthesis is designed and fabricated. If the patient happens to successfully repeat the mediolateral position, the prosthesis can be discontinued. However, in certain cases, the patients may continue to wear the GFP for an indefinite amount of time due to various reasons such as financial constraints, time constraints, and guarded prognosis of the planned definitive treatment.

CONCLUSION

A GFP is given as an interim prosthesis in the aftermath of a mandibulectomy or postsurgical reconstruction of the defect to allow the patient to carry out his/her routine functions like mastication and to maintain esthetics to some extent by preventing the deviation of the jaw to the affected side. In certain cases, the patient may be forced to use the prosthesis for an indefinite amount of time due to reasons such as poor prognosis postbone grafting and financial constraints of the patient which precludes the expensive treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Tuberculosis of Foot Mimicking Mycetoma

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Abstract

Skin tuberculosis (TB) is a relatively uncommon form of extrapulmonary TB. Even in the countries with high pulmonary TB loads, cutaneous TB (CTB) cases are rarely reported. Here, we report a case of 35-year-old male who presented with diffuse swelling and multiple discharging sinuses over the right foot for 7 years nonresponding to any kind of treatment which was confused with mycetoma but the etiology came out to be tubercular on further workup leading to the diagnosis of CTB. This case highlights the importance of suspecting CTB particularly in a geographical area where TB in every form is very much predominant.

Keywords: Foot, mycetoma, sinus, skin tuberculosis

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of death worldwide. TB is one of the most common, rampant infectious diseases in underdeveloped countries, and the number of cases in industrialized countries has increased in recent years. The incidence of extra-pulmonary TB (EPTB) is also increasing but due to high pulmonary TB load, this area is not gaining focus of the practitioners. Moreover, it is highly confused with leprosy or mycetoma if it involves the peripheries. In this part of the world (India), where both these entities are common cutaneous TB (CTB) is commonly misdiagnosed as mycetoma or leprosy. CTB occurs when there is an invasion of skin, a natural barrier by *Mycobacterium tuberculosis* (MTB). The causative agent of skin TB is an acid-fast *Bacillus* (AFB). MTB, *Mycobacterium bovis* and under certain conditions the *Bacillus Calmette-Guerin* (BCG), an attenuated strain of *M. bovis* cause skin TB.

CASE REPORT

A 35 years nondiabetic nonhypertensive male, a farmer by occupation presented to our outpatient department with a complaint of swelling over the dorsum of the right foot since 7 years [Figures 1 and 2]. It was not tender and was associated with off and on fever since 1 year and loss of weight since 6 months. Loss of appetite was also present. Gradually, the swelling became hard and progressed with the formation of

multiple discharging sinuses over the course of time in spite of treatment from a general practitioner. The patient consulted a dermatologist at this stage where a culture for fungal elements and biopsy was done. Culture came to be sterile, and biopsy showed the possibility of mycetoma [Figure 3]. He was prescribed tablet dapsone 100 mg 1 h.s, tablet cotrimoxazole 1 b.d and tablet terbact 250 mg 1 o.d. However, there was no response to the treatment. Swelling over the foot progressed gradually involving the whole of the dorsum, medial malleolus and the lower third of leg with multiple discharging sinuses. Skin became puckered and excoriated due to itching. On pressing the swelling, there was a discharge of purulent and foul-smelling pus. A right nontender inguinal lymphadenopathy also appeared. There was no history of BCG vaccination or any trauma.

Routine investigations were nonsignificant except for mild anemia. Viral markers for HIV, hepatitis C virus, and hepatitis B virus were nonreactive. X-ray foot anteriorposterior and the lateral view were done which showed no involvement of bones. X-ray chest was also within normal limits. Pus was sent for MTB culture from our side that showed growth

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Figure 1: Dorsum of foot showing swelling and discharging sinuses



Figure 2: Lateral view of dorsum of foot showing swelling and discharging sinuses

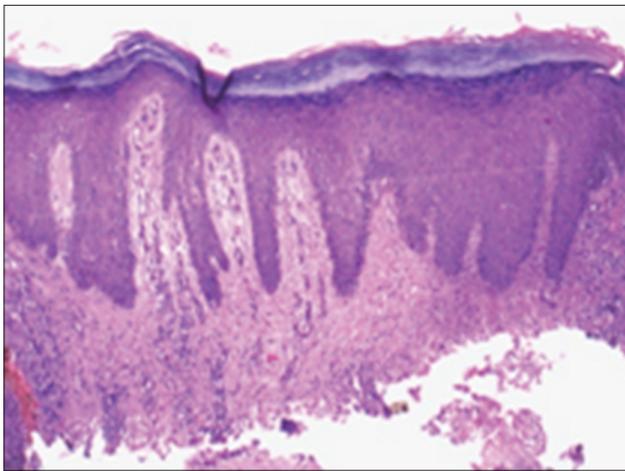


Figure 3: Biopsy showing mycetoma



Figure 4: Dorsum of foot showing healed sinuses and improvement in swelling

of MTB complex. Polymerase chain reaction (PCR) test of the pus showed the presence of MTB complex DNA. As there was no previous history of antitubercular treatment in past patient was started on rifampicin, isoniazid, ethambutol, and pyrazinamide as per weight. He improved gradually as there was a progressive decrease in the size of swelling [Figures 4 and 5]. He is in our regular follow-up and improving day by day.

DISCUSSION

TB remains one of the leading infectious causes of death worldwide.^[1] TB is one of the most common, rampant infectious diseases in underdeveloped countries, and the number of cases in industrialized countries has increased in recent years as a result of the increased incidence of HIV, AIDS, and drug resistance.^[2] CTB describes dermatological manifestations of TB involving the skin, which can be caused by MTB, *M. bovis*, and the BCG vaccination.^[3] These lesions can be acquired exogenously or endogenously, although the former route is significantly less common. Although CTB is reported as <1% of all cases of TB,^[3] it is important for

practitioners to consider this infection when faced with a suggestive clinical picture.

Despite the fact that it can affect any organ or site of the body, the breasts, skeletal muscles, and spleen are considered the most resistant organs to TB.^[4] Isolated cutaneous involvement of TB is rare. Underlying systemic involvement of TB is often seen in CTB, especially in children. Early classification of CTB was based only on lesion morphology. Tappeiner and Wolff proposed the most widely accepted classification based on the route of infection.^[4] An additional classification designed to enhance the Tappeiner and Wolff system allows further distinction using bacterial load. In this classification, CTB is classified into multibacillary and paucibacillary forms. In the multibacillary forms, mycobacteria can easily be identified on histological examination utilizing the Ziehl-Neelsen staining (AFB) method and culture.^[5] In the paucibacillary sparse *Bacilli* are seen on histological examination and culture isolation is rare.^[6]



Figure 5: Lateral view of dorsum of foot revealing healed sinuses and decrease in swelling

Direct exogenous inoculation of MTB into the skin of a susceptible person may lead to TB verrucosa cutis, TB chancre, and in some cases Lymphogranuloma venerum like an infection. Endogenous infection occurs in previously infected person via lymphatic, hematogenous spread, or contiguous extension. Hematogenous spread is seen in acute miliary TB, metastatic TB abscess (gummatous TB), papulonecrotic tuberculid (PNT), and Lymphogranuloma Venerum like infection. Contiguous extension results in scrofuloderma and orificial tuberculoid. CTB can again be classified as true TB or tuberculids.^[7] True CTB comprises tuberculous chancre, miliary TB, lupus vulgaris, scrofuloderma, TB verrucosa cutis, tuberculous metastatic abscess, and orificial TB. Tuberculids are delayed sensitivity reactions to MTB in patients having a strong immune response. Lichen scrofulosorum and PNT are examples of tuberculids. Facultative tuberculids consist of erythema induratum and erythema nodosum. Erythema induratum can be defined as a subcutaneous nodule that is recurrent and painful presenting usually on the posterior aspect of the leg; biopsy of which shows lobular panniculitis with vasculitis and granulomatous inflammation. Erythema nodosum is a painful subcutaneous nodule, occurring mostly over the anterior aspect of the legs and hands. Biopsy shows septal panniculitis with an absence of vasculitis and usually without granuloma. Erythema nodosum occurs in association with a granulomatous disease such as sarcoidosis, TB, and granulomatous colitis. TB remains an important cause of erythema nodosum in endemic countries.

Clinical manifestations of CTB are variable. Constitutional symptoms such as fever, weight loss, night sweats, or a failing of general health are infrequently encountered. Patients usually have a positive tuberculin skin test.

Differential diagnosis most often includes carcinoma. Less common differentials are blastomycosis and actinomycosis.

An accurate diagnosis is usually made on histopathology by demonstrating a classical caseation, AFB within such a lesion and/or by demonstrating epithelioid granulomas,

Langhans giant cells, and lymphocyte aggregates. Though the diagnosis is mainly based on the identification of tubercle *Bacilli*, it has been recognized that an AFB-positive smear is not always sufficient evidence for a definitive diagnosis of MTB.^[8] Differentiation of MTB from mycobacteria other than tuberculosis species is essential. Cultures and AFB staining are negative in most cases. Often failure to demonstrate necrosis on fine needle aspiration cytology does not exclude TB because of the small quantity of the sample examined. Still biopsy is the most reliable test. PCRs are highly sensitive especially in culture-negative specimens from paucibacillary forms of the disease.^[9] Another great advantage of this system is that it does not show cross-reactivity with actinomycetoma species such as *Actinomadura* or *Nocardia*.^[10] Reliable identification of causal agents to the genera *Actinomadura*, *Nocardia*, and *Streptomyces* can be achieved by PCR and sequencing.^[10] However, the identification to the rank of species still cannot be achieved even with PCR.^[10]

Antituberculous chemotherapy is the main treatment for CTB. No specific guidelines are available for its treatment. The disease should be treated as any other form of EPTB. Antituberculous therapy comprise rifampicin, isoniazid, pyrazinamide, and ethambutol for the initial 2 months, which is then followed by rifampicin and isoniazid for another 4 months.

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Conflicts of interest

There are no conflicts of interest.

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Chapter 7

Coronavirus Infection Among Children and Adolescents



Sujita Kumar Kar, Nishant Verma, and Shailendra K. Saxena 

Abstract Coronavirus infection is a global emergency. Over the past few months, there is a rapid increase in the number of cases and deaths due to coronavirus infection. It has been observed that elderly individuals and those with medical co-morbidities are maximally affected. In children and adolescents, coronavirus infection has low mortality as well as the severity of symptoms are less. Children and adolescents with immunocompromised state, malnutrition, medical co-morbidities and poor hygiene are at higher risk of contracting coronavirus infection. Minimizing this risk factors and adopting appropriate prevention measures will be helpful in limiting the spread of infection as there is no specific treatment and immunization available to date to address this serious issue. This chapter highlights the issues and challenges of coronavirus infection in children and adolescents.

Keywords Coronavirus infection · Children · Adolescents · Prevention

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7.1 Introduction

Novel coronavirus (COVID-19) infection, recently declared as a pandemic by the World Health Organization (WHO), is a global threat. According to the situation report of the WHO, by the end of the third week of March 2020, there are more than 266,000 confirmed cases and 11,184 deaths over 182 countries globally (WHO 2020). The above data depict the grievousness of the endemic in the contemporary world. People of all ages are affected with the deadly coronavirus infection, though the risk of infection is higher among older people and those with medical co-morbidities (Wu et al. 2020a). As per the initial report from Wuhan, China, less number of children were affected with coronavirus infection than adult patients (Liu et al. 2020).

7.2 Coronavirus Infection Among Children

As per the WHO report in February 2020, there was no fatality due to coronavirus infection in the 0–9 years age group and the death rate was 0.2% in the age group of 10–19 years; however in the age group of 70–79 years and >80 years the death rates are 8.0% and 14.8%, respectively (World Health Organization 2020; Worldometers 2020). Though children and adolescents have lower death rate, they can be potential agents of transmission. As the degree of mobility is higher in this age group of population, the probability of contracting infection and transmitting to others (particularly the high-risk population of elderly) is high. Children infected with coronavirus often present with fever, cough and breathing difficulties. Many children also report vomiting, diarrhoea and the aforementioned symptoms (Yang et al. 2020). Children born from infected mothers have higher risk of contracting the infection from mother (Yang et al. 2020). The clinical symptoms and investigation findings in children with coronavirus infection often resemble with viral pneumonia (Yang et al. 2020). It has been reported that children often have milder symptoms than adults and the elderly (Chen et al. 2020a; American Academy of Pediatrics 2020; Lu and Shi 2020). The biochemical changes and chest computed tomography (CT) changes of children with coronavirus infection also differ from those of adults (Xia et al. 2020). Children often have more upper respiratory infection than lower respiratory infection, which increases their ability to transmit the infection (American Academy of Pediatrics 2020). A report mentions that even an apparently healthy infant had heavy viral load which indicates that children can even transmit infection without manifesting the illness (Kam et al. 2020).

7.3 Risk Factors Specific to Children and Adolescents

7.3.1 *Immunocompromised State*

Immunocompromised state is a potential risk factor for acquiring highly contagious infections like novel coronavirus infection. Children and adolescents with poor immune function or on immune-suppressant medications need to be cautious. Preterm babies and newborn babies with low birth weight are also at risk due to their immunocompromised state.

7.3.2 *Malnutrition*

Malnutrition is still a common problem in the developing and underdeveloped countries. Children with protein-energy malnutrition (Marasmus and Kwashiorkor) or specific vitamin and micronutrient deficiency are at risk of acquiring infections due to their poor body immunity.

7.3.3 *Medical Co-morbidities*

Specific medical co-morbidities increase the risk of coronavirus infection. Children and adolescents with cardiac disease (mostly congenital heart diseases) and respiratory diseases (bronchial asthma, bronchiectasis) are more vulnerable as coronavirus mostly infects the respiratory system. Patients with haematological disorders like anaemia, leukaemia, etc. also have a compromised immune system, which makes them vulnerable to coronavirus infection.

7.3.4 *Poor Hygiene*

Small children are often dependent on their cares for personal hygiene. Lack of understanding about the importance of personal hygiene makes them vulnerable to acquire infections.

7.3.5 *Lack of Sensitization*

Small children are not aware of the concept of pandemic, its seriousness and importance of all preventive measures recommended. Unfortunately, the sensitization activities run by various government and non-government agencies mostly

target adults and youths. Many parents seldom discuss or explain the issue of coronavirus infection with their children. All the above factors result in improper sensitization of children as a result of which they are at risk of contracting as well as spreading infection.

7.3.6 Age-Specific Issues

Children are often playful. They talk loudly and express themselves without restraints. Evidence suggests that talking loudly and shouting may cause the spread of the infection through droplets (Chen et al. 2020a). Similarly, touching the face, nose and mouth with hand is common during play among children. It also increases the risk of transmission of coronavirus infection (Chen et al. 2020a). Similarly, children often spend a significant proportion of their time out of home (in school, play activities) and may come in contact with individuals with coronavirus infection.

7.4 Prevention of Coronavirus Infection Among Children and Adolescents

There is no specific treatment for coronavirus infection to date. The evidences gathered in favour of certain anti-retroviral agents and antimalarial agents are not robust yet. Patients with coronavirus infection need to be treated symptomatically and monitoring needs to be done for organ failures. As there is no definite treatment to date for this illness, prevention becomes the top priority.

The Centre for Disease Control and Prevention had issued certain instructions in the public interest that intends to create awareness among the public about coronavirus infection and its prevention among children (Centers for Disease Control and Prevention 2020). As small children may not be able to take their own responsibility, parents, teachers and sensitive citizens of this civilized society should take responsibility to prevent the spread of coronavirus infection. They need to monitor the activities of children at home, school and outside the home setting. There is a need to restrict large group activities, limit play time and keep distance during play and interaction. Similarly in the home and school setting, there is a need to keep the surfaces and objects (walls, toilets, chairs, tables, boards, play items, reading materials) sanitized through repeated cleaning as these remain the medium of transfer of pathogens from infected individuals to healthy ones (Centers for Disease Control and Prevention 2020). Choosing outdoor game in small groups may be more beneficial than indoor games as the ventilation is better outside and the possibility of maintaining distance during play is higher in outdoor play. Group travel, picnics and study tours are to be strictly discouraged. Children need to be taught about hygiene regularly, and they need to be monitored for the implementation of hygiene in practice.



Fig. 7.1 Recommended preventive measures against coronavirus infection in children

Healthcare professionals on the other hand have a pivotal role in providing health education to child and parents and conducting awareness camps in schools and community, as well as regular health check-up for the early identification and prompt treatment of health ailments. Figure 7.1 provides a summary of preventive measures against coronavirus infection in children.

It is of paramount importance to ensure that children should properly sanitize themselves before coming in contact with other family members (particularly elderly and those who have medical illnesses) to limit the possible transmission of coronavirus infection.

Older children and adolescents are trainable and educable about the basics of hygiene and its relevance in the context of coronavirus infection. The above recommendations also stand valid for older children and adolescents for the prevention of coronavirus infection transmission.

Additionally children should avoid contact with persons or other children with recent travel history or contact with persons with recent travel history or those with respiratory infections or fever (Chen et al. 2020a). It is important to target various risk factors (predisposing factors, precipitating factors and perpetuating factors) to limit the chances of getting infected (Kar and Tripathy 2019). Table 7.1 summarizes the potential risk factors that can be targets of intervention.

Table 7.1 Potential risk factors, which can be targets of intervention

Nature of risk factors	Examples	Preventive measures
Predisposing factors	<ul style="list-style-type: none"> • Low immunity • Malnutrition • Medical co-morbidity • Poor hygiene 	<ul style="list-style-type: none"> • Dietary supplementation • Adequate treatment of medical co-morbidity • Hygiene
Precipitating factors	<ul style="list-style-type: none"> • Contact with infected persons, contaminated surfaces and objects 	<ul style="list-style-type: none"> • Social distancing • Restricting play, tour, travel, picnic, etc. • Proper sanitation
Perpetuating (maintaining) factors	<ul style="list-style-type: none"> • Low immunity • Malnutrition • Medical co-morbidity • Poor hygiene 	<ul style="list-style-type: none"> • Dietary supplementation • Adequate treatment of medical co-morbidity • Hygiene • Early identification, isolation and prompt treatment

Children and adolescents, who develop fever and respiratory infections, need to consult for evaluation at the nearest health centres with appropriate precautions till coronavirus infection is ruled out.

7.5 Evidence-Based Management Approach

There is no specific treatment for novel coronavirus disease (COVID-19) supported with evidence to date. Patients with coronavirus infection are often given symptomatic treatment and supportive care (Wu et al. 2020a, b). However, probable management approach against coronavirus infection in children has been exhibited in Fig. 7.2. Researchers found the possible roles of hydroxychloroquine, anti-retroviral medications and interferon in the management of coronavirus infection (Yang et al. 2020). Antibiotics are recommended for secondary bacterial infection and pneumonia. Corticosteroids are to be avoided, except exceptional situations like septic shock, rapidly deteriorating chest imaging, and presence of obvious toxic symptoms like encephalitis or encephalopathy (Chen et al. 2020a).

There is no specific vaccine available for the prevention of COVID-19 infection. Many vaccine trials are going on globally; however, it has been recommended that uninfected people and health workers need to get vaccinated for influenza (Zhang and Liu 2020). There is a possible role of convalescent plasma (if available) in the management of COVID-19 infection (Zhang and Liu 2020).

As of now, prevention is the best option for controlling the rapidly spreading infection of coronavirus. It has been recommended that newborn babies of mothers infected with COVID-19 need to be isolated immediately after delivery to prevent them from acquiring infection (Yang et al. 2020). However, there is no evidence that

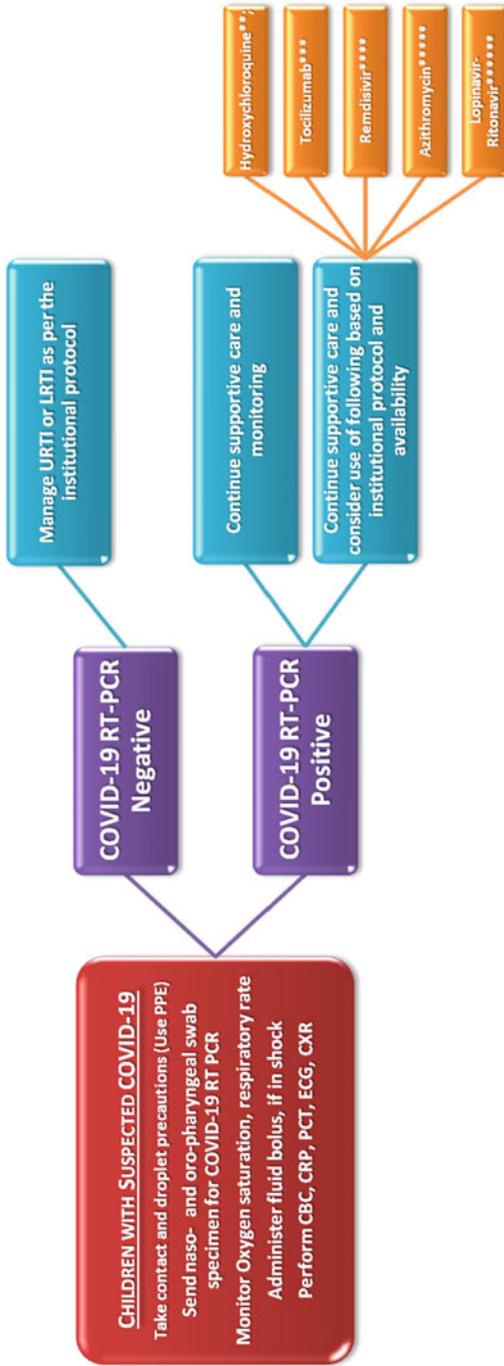


Fig. 7.2 Current probable management approach against coronavirus infection in children. *PPE* personal protective equipment, *CBC* complete blood count, *CRP* C-reactive protein, *PCT* procalcitonin, *ECG* electrocardiogram, *CXR* chest X-ray, *URTI* upper respiratory tract infection, *LRTI* lower respiratory tract infection. *Worsening*: Increasing respiratory distress, worsening gas exchange, hypoxia, radiological deterioration. ****Hydroxychloroquine (HCQ)*: Dose 10–13 mg/kg (max: 600 mg/dose) PO BID x2 (load), then 6.5 mg/kg PO BD (max: 200 mg/dose). Certain guidelines recommend initiation of HCQ for all hospitalized patients with COVID-19. *****Tocilizumab*: Dose 8–12 mg/kg single dose. Interleukin-6 inhibitor; useful for children with rapid deterioration due to COVID-19. *****Remdesivir*: Investigational antiviral drug for COVID-19. *****Azithromycin*: Dose 10 mg/kg/day for 1 day, then 5 mg/kg/day for 4 days. ******Lopinavir-Ritonavir*: Dose 15–25 kg: 200 mg–50 mg; 26–35 kg: 300 mg–75 mg; >35 kg: 400 mg–100 mg PO BID for 5 days

vertical transmission of infection from mother to foetus occurs in the intrauterine environment (Lu and Shi 2020; Chen et al. 2020b). Early isolation is also recommended for children with underlying disease manifestations (Yang et al. 2020).

7.6 Conclusions

Despite low mortality and low infection rate among children and adolescents, they play a crucial role in the spread of infection in this ongoing pandemic of coronavirus disease. Adequate prevention measures, early identification and isolation will be helpful in altering the course of this pandemic.

7.7 Future Perspectives

There is a paucity of research on coronavirus infection in children and adolescents. There is a need to monitor the long-term impact of the virus exposure on the growth, development and other health measures. There is also an intense need to explore treatment options and vaccination for the effective control of coronavirus infection.

Executive Summary

- Children and adolescents with coronavirus infection have milder symptoms.
- Compromised immune function, malnutrition, co-morbid medical illnesses and poor hygiene are potential risk factors for contracting coronavirus infection in children and adolescents.
- Social distancing, limiting group activities, play time, tours, picnics and adequate hygiene training may be beneficial in limiting the chances of getting coronavirus infection in children and adolescents.

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CASE REPORT

Tuberculosis of the thyroid gland

Ajay Kumar Verma, Mayank Mishra, Ved Prakash, Surya Kant, Singh HP¹, Neha Kapoor

ABSTRACT

Thyroid tuberculosis is a very rare condition despite an overall increase in the extrapulmonary forms of tuberculosis. Tuberculous infection spreads to the thyroid by lymphogenous/hematogenous route or directly from adjacent organs. Thyroid tuberculosis does not have any specific symptom. Fine needle aspiration is the mainstay of diagnosis. Antituberculous therapy and surgical removal of affected parts of the thyroid gland are the most common methods of treatment of thyroid tuberculosis. We present a case of a 37-year-old male who presented with a swelling in the neck and was diagnosed as tubercular thyroiditis on cytopathological examination.

Key Words: Extrapulmonary, thyroid, tuberculosis

Introduction

Tuberculosis of the thyroid gland is very rare even in countries with a high prevalence of tuberculosis. The supposed reasons for this are the bactericidal attributes of the thyroid colloid, extensive vascularization, and high levels of iodine in the gland. Thyroid involvement can be symptom-free as seen in generalized miliary spread or may present as a diffuse or localized swelling of the gland. It can also present as thyroid abscess in pulmonary tuberculosis patients.

Case Report

A 37-year-old male came to our outpatient department with chief complaints of swelling on the right side of neck for 1 month. It developed slowly and did not show signs of compression. Swelling was about 2 cm × 2 cm in size, present on the right anterior side of the neck at the level of cricoid cartilage.

An ultrasound inspection of the neck revealed a bulky thyroid, mainly the right lobe, with heterogenous appearance. Cervical lymph nodes of level 2, 3, 4 on the right side and level 2 on the left side were also enlarged. Thyroid profile was suggestive of hyperthyroidism with raised level of T3 and T4 and decreased level of thyroid-stimulating hormone.

Fine needle aspiration of the neck swelling revealed benign follicular cells in small clusters along with well-formed epithelioid granulomas comprising epithelioid cells, histiocytes, lymphocytes, and giant cells in a background of scant colloid, [Figures 1 and 2] suggestive of granulomatous thyroiditis – tubercular pathology. However, acid-fast bacilli (AFB) were not visualized in the specimen examined. A biopsy was planned but not done as the fine needle aspiration cytology report was suggestive of and clinically correlated with tuberculosis and also because the patient did not give consent.

Chest X-ray was normal. Mantoux test was suggestive of tuberculosis with 15 mm induration. A final diagnosis of tubercular thyroiditis with tubercular lymphadenitis was made and the patient was treated with isoniazid,

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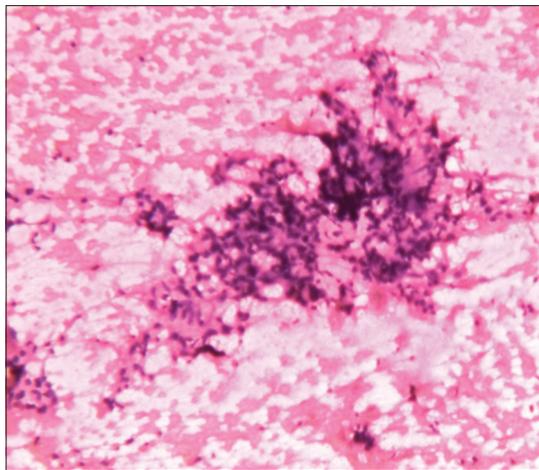


Figure 1: Granulomatous thyroiditis

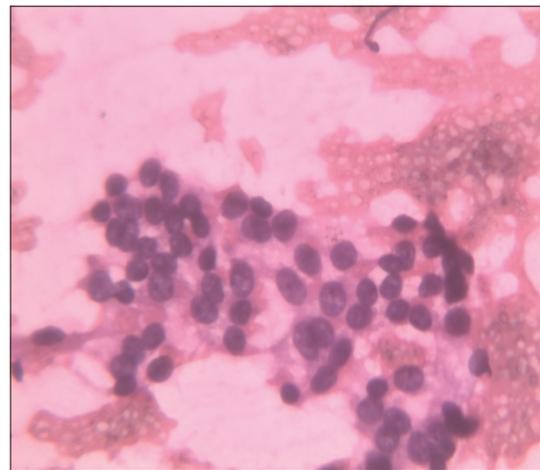


Figure 2: Granulomatous thyroiditis suggestive tubercular pathology

rifampicin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for 4 months as per the Revised National Tuberculosis Control Programme protocol. Clinical signs of regression of the swelling and improvement in thyroid profile started to occur toward the end of intensive phase of treatment and were completely normal by the end of therapy. However, serial ultrasounds were not done in follow-up.

Discussion

Thyroid tuberculosis is rare, with an incidence of <0.4% based on histological analysis of resected thyroid specimens.^[1] Frequently, it is unsuspected because of its rare occurrence; furthermore, it is manifested with a wide array of nonspecific symptoms such as high temperature, weight loss, malaise, night time sweating, or it can even be asymptomatic.

Most frequently, the patients are middle-aged women.^[2] Although dysphagia, dyspnea, and more rarely dysphonia are the main symptoms of the disease, the patient may be asymptomatic.^[3] The most frequent clinical presentation is a solitary thyroid nodule that may present a cystic component.^[2,4,5] The patients are usually euthyroid, but cases of hypothyroidism and hyperthyroidism are described.^[6]

It is observed that certain tissues are relatively resistant to tuberculous infection –so tubercles in heart, striated muscle, thyroid and pancreas are rarely seen.^[7] The ability of thyroid to resist infection is attributed to a number of factors – prosperous lymphatic and vascular supply, well-developed capsule and high iodine content of the gland,^[8] colloid possessing bactericidal action, destruction of tubercle bacilli due to increased physiological activity of phagocytes in hyperthyroidism, and possible antitubercular role of thyroid hormones.^[9]

Tuberculosis may involve thyroid gland in two main forms. One of them is miliary spread to thyroid gland as a part of generalized dissemination. Alternatively, focal caseous tuberculosis of thyroid may occur, presenting as localized swelling mimicking carcinoma or as cold abscess.^[10-13]

Spread of the disease to the thyroid occurs by hematogenous or lymphogenous route or directly from larynx or tubercular cervical lymphadenitis.^[1] Four morphological variations of thyroid tuberculosis are distinguished: (1) Multiple tubercles in case of military tuberculosis, (2) solitary and sometimes merging tubercles, (3) foci of caseation necrosis or cold abscesses, and (4) cicatrized tubercular foci.

Tuberculosis of the thyroid gland is diagnosed on the basis of cytological or histological examination and identification of AFB. Histological demonstration of epithelioid cell granulomas with peripheral lymphocytic cuffing, Langhans giant cells, and central caseation necrosis proves the diagnosis. Ultrasonographic and computed tomography (CT) findings can help in this matter as well: Heterogeneous hypoechoic mass is seen on ultrasonogram and peripheral-enhancing low-density abscess with regional lymphadenopathy is demonstrated on CT scan.

The following prerequisite conditions present for diagnosis of thyroid tuberculosis were described in early 1939: (1) Demonstration of AFB within thyroid, (2) a necrotic or abscessed gland, and (3) demonstration of tuberculous focus outside. Histological and bacteriological confirmation is adequate and fulfillment of the third criterion is not essential.

Tuberculosis is difficult to distinguish from other inflammations of the thyroid gland as well as from its carcinoma mainly because the regional lymphatic nodes

are infiltrated as well. It is particularly vital to distinguish thyroid tuberculosis from thyroid cancer in an attempt to avoid unnecessary surgery. It is very important to differentiate tuberculosis from other granulomatous diseases such as De Quervain's thyroiditis and sarcoidosis. Corticosteroids are used for treatment of these disorders which could worsen the illness of patients with tuberculosis of the thyroid gland. In this case, sarcoidosis was excluded based on the absence of multisystem involvement (presentation only in the form of neck swelling), positive Mantoux test, normal chest X-ray, and cytology report favoring tuberculosis.

The treatment of tuberculosis of the thyroid gland is not much different from the treatment of other forms of tuberculosis. At least 6 months of therapy is required using two or three of the following drugs – rifampicin, isoniazid, pyrazinamide, and ethambutol. Surgical treatment is required, along with the earlier described therapy, when the affected thyroid gland causes mechanical obstruction, when there is a suspected combined malignant process or if hyperthyroidism is present which is unaffected by medical treatment. When surgical treatment has to be undertaken in addition to antituberculous therapy, one must keep in mind possible complications such as local relapse of disease, slow wound recovery, fistula formation, and the occurrence of tuberculous abscess.

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Rehabilitation of a Complex Oro-Facial Defect by Modified Prosthetic Approach

Saumyendra V. Singh, Himanshi Aggarwal, Vinit Shah, Pradeep Kumar and Deeksha Arya

ABSTRACT

Loss of part of the face is associated with physical disability, social isolation and immense psychological trauma. Proper rehabilitation of such a patient is a challenging yet satisfying task for a maxillofacial prosthodontist. Facial prostheses are commonly fabricated of silicone because of many favorable properties, though it predisposes to fungal growth. This report is of a patient with history of uncontrolled diabetes and associated invasive fungal infection, leading to a complex oro-facial defect, which was rehabilitated successfully with a silicone facial prosthesis lined by a material more resistant to fungal growth along with a cast partial obturator. Other design and procedural modifications were also made to suit the needs of the case. Wise selection of materials, keeping in mind the properties of materials, is important in successful rehabilitation.

Key Words: Prosthetic rehabilitation. Oro-facial defect. Silicone. Fungal infection. Uncontrolled diabetes.

INTRODUCTION

Face is associated with a person's identity and individuality. Loss of part of the face is associated with physical disability, social isolation and psychological trauma. Depending on the extent of defect and time of presentation, it may be possible to use a surgical reconstructive approach for congenital facial defects. However, those resulting from trauma or oncological surgical excision are mainly restored using a prosthetic approach.¹

Among the facial defects, the loss of an eye causes profound functional and psychosocial disability.² Orbital exenteration is a radical surgery which involves removal of the entire contents of the orbit and associated periorbital structures, leaving the patient with a devastating functional and cosmetic state. Fabrication of an orbital prosthesis is demanding because of the complexity of replicating contours of tissues and accurate positioning of the iris.

Since the first mention of facial prosthesis in literature by Ambroise Pare in 1575 to the present, methods of fabrication and choice of prosthetic materials have evolved a lot. At present, silicone elastomers are the commonly preferred prosthetic material for fabrication of a facial prosthesis, though it has several undesirable properties, including proneness of fungal growth.³

This case report is about the prosthetic rehabilitation, using silicone prostheses lined by vacuum formed

polyvinyl chloride and a cast-metallic obturator. The defect involving left orbit and maxilla resulted from road-side accident in a patient complicated with uncontrolled diabetes and associated invasive fungal infection.

CASE REPORT

A 47-year female with mid-facial fractures (due to road traffic accident) 2 years back was referred to the Unit of Maxillofacial Prosthetic Rehabilitation. At that time, the patient developed soft tissue necrosis with discharge oozing from left facial region, followed by loss of vision from left eye. Culture of discharge had confirmed fungal infection secondary to bone necrosis. Orbital exenteration had to be performed along with excision of all necrotic tissues, leaving the patient with a complex defect. No reconstruction of the defect was performed because of the patient's systemic condition.

On examination, the patient presented with an oro-facial defect (Figures 1 and 2), classified as Class III Subclass F according to Okay *et al.*⁴ On evaluation, the orbital defect was lined by healthy tissue and presented with moderate tissue undercuts. It was decided to rehabilitate the patient with a cast partial removable prosthesis for the intraoral defect and an orbital prosthesis after taking patient consent.

Impressions, surveying, mouth preparation and metal framework designing of the intraoral defect (Aramany class II) was done conventionally.⁵ The cast partial denture had an antero-posterior palatal strap type of major connector, with occlusal rests and minor connectors planned in a quadrilateral design configuration (Figure 3). Effectiveness of obturation of defect was confirmed by asking the patient to sip water with no leakage noted from the nasal cavity. Maintenance and care instructions were reinforced and prosthesis reevaluated at post insertion appointments.

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Figure 1: Intraoral defect communicating with the sinus in the maxillary left 2nd premolar-1st molar region.



Figure 2: Orbital defect.



Figure 3: Cast removable partial denture to obturate the intraoral defect.



Figure 4: Clay pattern.



Figure 5: Final orbital prosthesis, camouflaged with large spectacle frame and tinted glasses.

The orbital defect impression was made after blocking undesirable undercuts with damp gauze, using addition silicone putty relined by light body impression material and poured in type III stone (Orthokal, Kalabhai Karsons Pvt Ltd, Mumbai, India). A 1mm thick polyvinyl chloride (PVC) sheet (Softray sheets; Ultradent Products Inc.) was adapted to the model using a vacuum former (Model P105-U02; Ultradent Products Inc.) as a base for pattern fabrication. For ocular part of the prosthesis, a stock eye matching in contour and colour of contralateral eye was selected and positioned on the PVC base. The orbital pattern was then carved in modeling clay (Funclay, Nara Factory Co., Ltd, Bangkok, Thailand) onto the PVC base and skin creases were sculpted to mimic the contralateral region. Clay offered advantage of easy manipulation over usage of wax for the purpose. Finally, eyelids were carved in modeling clay. The pattern was tried on the patient for adequacy of fit, proper positioning of prosthesis margins and accurate reproduction of contours and creases in harmony with adjacent and contralateral structures (Figure 4). A spectacle frame, wide enough to camouflage the margins of the prosthesis, was selected at this stage. The finalized pattern was invested in stone after ensuring that the margins of the prosthesis were feathered and merged with surrounding tissues. This was followed by heating the clamped mold in a water bath to remove the clay. The PVC base was retained in the mold with the intention to retain it as the base of the final silicone prosthesis. Maxillofacial prosthetic silicone material (Maxillofacial Rubber M511, Technovent Limited, South Wales, U.K) was intrinsically pigmented and packed in the de-waxed mold, which was then cured at 100°C in the oven. After curing, the prosthesis was carefully retrieved and tried on the patient. The prosthesis was further characterized using external stains. The finalized prosthesis was delivered to the patient. Edge adhesive (G604, Technovent Limited, South Wales, U.K) was used at the margins of the prosthesis. Tinted glasses were placed in the spectacles to camouflage the prosthesis (Figure 5). The patient was educated in maintenance and care of prosthesis and importance of periodic follow-up. The patient was satisfied with the esthetics, though some looseness of the prosthesis was noted after 1 year, probably because of tissue remodelling.

DISCUSSION

Oro-facial defects are difficult to rehabilitate with a constant dilemma between reconstructive surgery and prosthetic rehabilitation options. Albeit, in certain cases, reconstructive surgery may be less feasible like in the present case, as the patient may be predisposed to risk of infection and/or graft rejection/failure. Also, some lesions have a high recurrence rate and need to be left uncovered for regular examination to rule out recurrence.

Oro-facial defect can be restored by fabricating a conjoint prosthesis. However, such prosthesis is difficult to fabricate and demands increased manual dexterity from the patient in insertion and removal of the prosthesis. We, therefore, preferred to restore the oral and facial defects separately to simplify the manipulation and maintenance of both prostheses, by utilizing intraoral and extraoral tissue undercuts separately, eliminating the need of complex and expensive attachment systems or demanding fabrication procedures.

The orbital prosthesis was fabricated adapting a PVC sheet as the base of the pattern, providing a more durable foundation which would adapt to the undercuts meant to be used for the retention of the final prosthesis.⁶ A wax base is rigid and would, therefore, have to be relined in the undercut areas. The PVC base gave an estimate of the retentiveness of the prosthesis at the trial stage itself. The pattern for orbital prosthesis was carved in modeling clay as it offers the advantage of ease of sculpting, eliminating the need of using a flame and providing superior replication of skin creases. In this case, we preferred the stock eye for ocular component of the prosthesis as it simplified the procedure. As favorable tissue undercuts were present, only edge adhesive was used to camouflage the margins of the prosthesis.

PVC sheet complies with the ideal biological properties of non-irritating, non-allergic, non-toxic; and most importantly, for this case, non-supportive to microbial/fungal growth.⁷ The patient was followed up at 1 year for a fungal culture. The orbital prosthesis was satisfactorily

camouflaged using tinted glasses with wide frame, carefully chosen for the purpose.

The restoration of an oro-facial defect is often the toughest challenge to the prosthodontist. On the other hand, rehabilitating the patient on social front is immensely satisfying. Careful modification of basic principles and skillful selection of materials and techniques can render satisfactory results, restoring the patient's appearance and confidence significantly.

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DENTAL TECHNIQUE

Technique to prevent fracture of a partial auricular prosthesis mold

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Partial auricular defects are a result of certain congenital disorders, trauma, or tumors. The loss of an ear, an organ aiding in acoustics and esthetics, affects social behavior and psychology.¹ Management of such defects can be either surgical or prosthetic, depending on the patient's age, medical and financial circumstances, and the condition of the residual tissue. When surgical reconstruction is not indicated, a prosthesis is the best management option. The procedure for fabricating a complete silicone auricular prosthesis normally involves a 3-piece stone mold to facilitate characterization, prevent prosthesis tearing on retrieval, and prevent mold fracture.² Direct printing of a virtually designed prosthesis by using a high-resolution 3D silicone printer has been described.³ The technique reproduces major and minor anatomic surfaces of the prosthesis and has also been applied to nasal prosthesis fabrication.⁴ However, the current scope of characterization is restricted with these techniques, limiting the esthetics of the prosthesis. The initial cost associated with digital equipment is another disadvantage, and the accuracy and applicability of digital technology for facial prosthesis fabrication is still unclear.⁵

One of the difficulties faced during fabrication of a partial auricular prosthesis with the 3-piece stone mold technique is fracture of the elevated part of the mold, which fits into the natural concha and triangular fossa

ABSTRACT

One of the difficulties faced during the essential and demanding step of fabricating a mold for a partial auricular prosthesis is the fracture of its most elevated part, which engages the remnant concha and triangular fossa region, because of the presence of excessive convolutions and undercuts. This technique describes a 4-part mold for a partial auricular prosthesis in which the most elevated portion is poured separately, thereby preventing mold fracture. (J Prosthet Dent 2019;■:■-■)



Figure 1. Partial auricular defect.

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Figure 2. Partial auricular pattern.

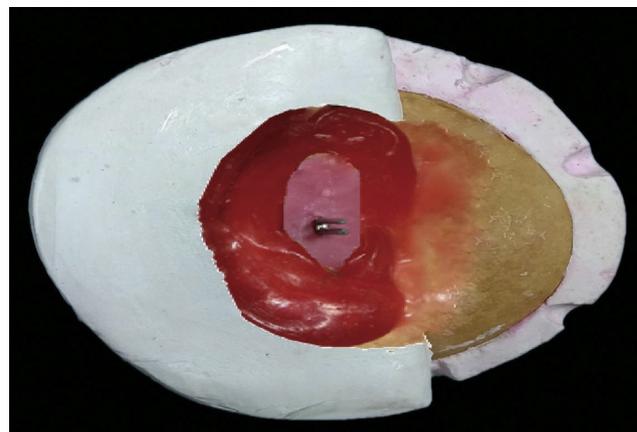


Figure 3. First, second, and third parts of mold poured.



Figure 4. Four-part mold separated.



Figure 5. Separated acrylic resin third part of mold with dowel pin.

region. The region has extreme convolutions and undercuts that are susceptible to fracture. The technique developed provides a straightforward and rapid method of preventing mold fracture and uses materials available in a dental laboratory.

TECHNIQUE

1. Make an impression of the residual auricle (Fig. 1) with the surrounding tissue by following conventional methods and pour it in die stone (Kaldent; Kalabhai Karson Pvt Ltd). Fabricate the pattern by following conventional steps (G-120; Factor II Inc) (Fig. 2).
2. Create the first 2 parts of the mold in the conventional manner using white die stone (Orthokal; Kalabhai Karson Pvt Ltd), involving the base and helix region of the wax pattern.
3. Apply a thin layer of separating medium on the first 2 parts of the mold and any portion of the partial ear model which is not to be covered by silicone.
4. Mix autopolymerizing resin (Rapid Repair Cold Cure; DPI) in the advised ratio and allow it to reach

the doughy consistency. Pack this material into the concha and triangular fossa region to form the third part of the mold.

5. Place a double dowel pin with a single head (Dental Die Pin; Nebula Industries Co, Ltd) in the doughy acrylic resin such that only the head of the pin is in the resin (Fig. 3).
6. Make the fourth and final pour with white die stone (Orthokal; Kalabhai Karson Pvt Ltd), covering the protruding sleeve of the dowel pin, the remaining wax pattern, and the first, second, and third parts of the mold to the requisite thickness.
7. Follow the regular dewaxing protocol and separate the parts of the mold (Fig. 4). The acrylic resin third pour will have the dowel pin (Fig. 5), while the sleeve will be encased in the fourth part of the mold. This allows accurate duplication of the concha region in acrylic resin without the risk of fracture of a stone mold. The acrylic resin can be easily positioned in its designated place and indexed to the fourth pour by the dowel pin.



Figure 6. Prosthesis in place.

8. Proceed with packing and polymerization, separating and joining the third and fourth mold parts as required (Fig. 6).

DISCUSSION

This article details a technique for facilitating the fabrication of a 4-part partial auricular prosthesis mold. Part of the mold engaging the concha region is fabricated in autopolymerizing resin. The advantage of using autopolymerizing resin lies in providing rigidity and strength in the vulnerable concha region of the mold, thus preventing the fracture of the mold in this area and facilitating the retrieval of an intact prosthesis. Preservation of the mold is ensured for future prosthesis remakes. The dowel pins allow accurate positioning of the fourth part of the mold to the acrylic resin index.

Limitations of this technique include an increase in the number of steps and the additional time and armamentarium required to fabricate the mold.

SUMMARY

The article describes a time-efficient and convenient method for preventing the fracture of a partial auricular prosthesis mold by pouring the conchal and triangular fossa portion in autopolymerizing resin, thereby converting the conventional 3-part auricular prosthesis mold into a 4-part mold.

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Medknow

Mechanically retained functional prosthetic rehabilitation of partial lip necrosis: A rare clinical report

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Abstract

Prosthetic rehabilitation plays a crucial role in restoring patients with facial defects to normalcy. Although comprising a small proportion, lip defect plays a pivotal role in drastically diminishing the quality of life of the patient, both functionally and socially, with dwindling confidence and self-esteem. Patients may experience speech impairment, uncontrolled drooling, and unesthetic appearance. In addition, constant exposure of tissues to air leads to drying and crusting of lips. This rare case report of a patient with partial lip necrosis describes her functional, mechanically retained prosthetic rehabilitation, which improved phonetics, esthetics, and function without the need of additional retentive features, increasing convenience and ease of use by the patient and at the same time cutting down cost.

Keywords: Functional rehabilitation, lip necrosis, mechanically retained, silicone

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INTRODUCTION

Prosthetic rehabilitation plays a crucial role in restoring patients with facial defects to normalcy. Although comprising a small proportion, lip defect plays a pivotal role in drastically diminishing the quality of life of patients, both functionally and socially, with dwindling confidence and self-esteem. Lip defects could be of congenital, surgical, or traumatic etiology. Lip cancers constitute 1.4% of oral cancers.^[1] Cases of loss of lip due to necrosis are hardly reported. Normally, surgical reconstruction is the primary treatment rendered for lip defects. Vascularized pedicle flaps from the iliac crest, scapula, fibula, radial forearm, and temporalis are utilized for reconstruction.^[2,3] Surgical rehabilitations, though desirable, are not always feasible for reasons such as compromised tissue bed and risk of

tumor recurrence. In such cases, prosthetic rehabilitation plays a fundamental role in rehabilitation.^[4]

Importance of lower lip defects in speech disarticulation has been elucidated by Robinson and Niiranin.^[5] Other problems experienced include uncontrolled drooling, unesthetic appearance, and constant exposure of tissues to air, leading to drying and crusting. As lips play a fundamental role in consonant phonemic production, reduction in speech intelligibility occurs, especially with bilabial and labiodental phonemes.^[6] Comparatively favorable prosthetic outcome is impeded by tissue resiliency, continuous lip movement, limitations of fabrication material, paucity and inadequacy of anatomical undercuts, and variable patient compliance. Various modes of retention include use of adhesives,

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implants, or intraoral prosthetic attachment with magnets. This report discusses the fabrication of mechanically retained silicone inferior lip prosthesis.

CASE REPORT

A 35-year-old female patient was diagnosed with central hemangioma of the mandible about a year back [Figure 1], for which, sodium tetradecyl sulfate was injected into the lesion thrice. Although the lesion subsided, posttreatment necrosis developed involving the right part of the lower lip with some involvement of the upper lip extending up to the ala of the nose. Surgical reconstruction was not immediately advisable because of questionable vascularity of recipient site, and the patient was referred to the department of prosthodontics for prosthetic management. The chief complaint of the patient was unesthetic appearance and drooling of saliva due to partially absent lower lip [Figure 2].

A preliminary combined intraoral and lower lip impression was made with irreversible hydrocolloid impression material (Zelgan; Dentsply, Gurgaon, Haryana, India)

and poured in type III stone (Keldent; Kalabhai, Mumbai, Maharashtra, India), taking care to record the lip without distortion or displacement. This was achieved by increasing the flowability of alginate and loosely confining the lip part of the impression. This was followed by fabrication of a custom tray in acrylic resin (Pyrax; Pyrax Polymers, Roorkee, Uttarakhand, India) with a double spacer. This tray was used for secondary intraoral impression [Figure 3] in addition silicone (Elite HD; Zhermack, Badia Palesine, Italy) and poured in white die stone (Orthokal, Kalabhai, Mumbai, Maharashtra, India) [Figure 4]. One-millimeter thick polyvinyl chloride (PVC) thermoplastic sheet (Soft-tray sheets; Ultradent, South Jordan, Utah) was adapted on the remnant lower lip model to aid in the retention of the trial pattern, which was sculpted in wax on the model and evaluated on the patient in subsequent appointments. The PVC thermoplastic sheet was extended over the entire lower lip till the commissures on either side, till the shadow of mentolabial sulcus externally, and upto the labial vestibule internally, to aid in mechanical retention. This would also facilitate camouflage of future prosthesis margin in areas which are less remarkable.

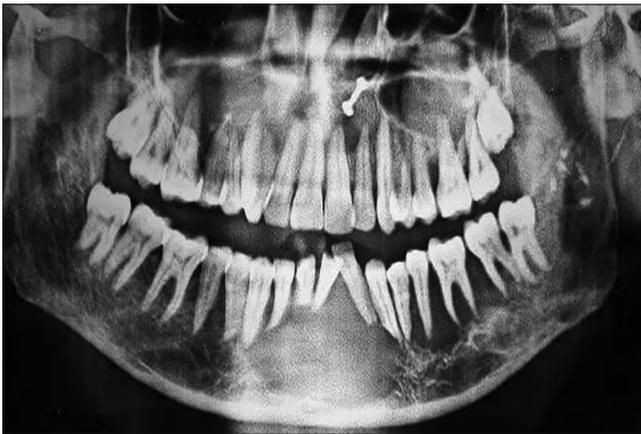


Figure 1: Central hemangioma of the mandible



Figure 2: Postoperative view after lower lip necrosis



Figure 3: Combined intra- and extraoral secondary impression



Figure 4: Model of lip defect

The wax pattern was modified to develop profile, shape and merge margins of prosthesis with natural tissue, and imitate wrinkles, skin creases, etc. [Figure 5]. To further improve the adaptation and retention, a wash impression was made in light body addition silicone (Elite HD; Zhermack, Badia Palesine, Italy) on the wax pattern itself. This relined wax pattern was again poured in white die stone (Orthokal, Kalabhai, Mumbai, Maharashtra, India) followed by marginal sealing, thinning, and merging with adjacent tissues [Figure 6]. This pour formed the first part of the mold into which keys were made for indexing. A three-part mold was necessary to achieve better characterization of different lip parts and removal of prosthesis without tearing. The second and third pours were preceded by careful application of separating media. For second pour, the boxed 1st part of mold was poured up to the inner lip line; keys were again made in this pour, followed by the third pour which was made to cover both previous pours. Dewaxing was carried out at 100°C for 5 min. The mold was cleaned properly [Figure 7]. Shade matching was done with the help of a digital spectrophotometer (Orthokal, Kalabhai, Mumbai, Maharashtra, India), and an appropriately colored

matched silicone (Technovent M511; Technovent Ltd.) was placed on to the different parts of the mold after applying a silicone-releasing agent (Orthokal, Kalabhai, Mumbai, Maharashtra, India) and polymerized as per instructions. Prosthesis was removed from investment [Figure 8] and finished and extrinsic staining was done, where required. Prosthesis was delivered to the patient 18 months back [Figure 9], who was satisfied by improved esthetics, lessened drooling, and enhanced speech intelligibility and retention, as recorded on the 3-monthly recall appointments. However, interruption of seal between prosthesis and movable soft tissues of the lip and cheek, sometimes resulted in margin show-through. Furthermore, extension of the prosthesis over the entire lip slightly increased the contour of the remaining natural portion of the lower lip.

DISCUSSION

Lip is a tactile organ which contributes not only to the process of articulation but also in creating oral seal. Its importance in attractiveness, identification of an individual,



Figure 5: Pattern: frontal and profile views

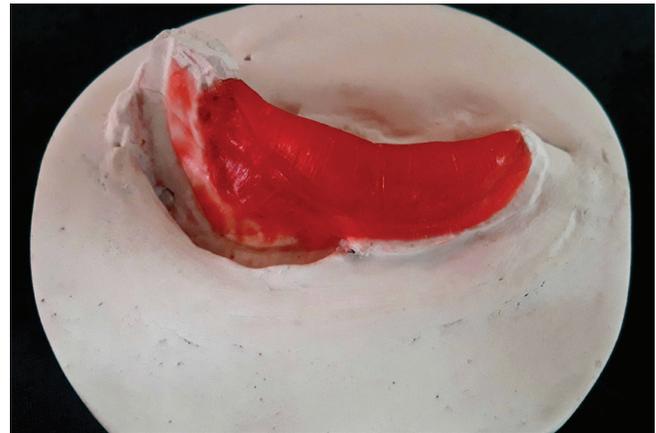


Figure 6: First part of the mold



Figure 7: Three-piece mold



Figure 8: Retrieved prosthesis from the mold



Figure 9: Final prosthesis after extrinsic coloring: frontal and profile views

and communication is undeniable. Any lip deficiency naturally leads to speech impairment and drooling of food and saliva.^[6] The prominent location makes it impossible to be missed by the eye. Therefore, a meticulous and swift correction of the defect is imperative to the patient's psychological well-being.

Restoration of such a defect poses a challenge in obtaining proper coloration, texture, and masking the margins of the prosthesis. Mobility of the tissues neighboring the defect compounds the problem. Engaging anatomical undercuts is not always feasible. Possible methods to mask margins include extending border beyond the midline, placement of margins in natural depressions, and thinning the margin. As described earlier, this prosthesis covered the entire lower lip to use the commissures and mentolabial sulcus for margin masking, increasing the retention of the prosthesis. However, the risk of making a bulky lip with this technique cannot be denied.

Another possible complication is salivary influx, breaking prosthetic seal, as well as causing show-through of margin while speaking, sucking, and smiling. Some methods utilized for retention of lip prosthesis include resin-retentive elements bonded to anterior mandibular teeth – Cheng *et al.*,^[7] placement of ball attachments on obturator's labial surface for retaining the upper lip – Oki *et al.*,^[8] and use of magnets and micro extracoronary resilient attachment (ERA) attachments – Zeno *et al.*^[4,9] Mukohyama *et al.*^[10] used lip plumper-like intraoral devices to correct mandibular lip posture skewed by marginal mandibulectomy.

Use of attachments is justifiable when no other retentive mean remains as these would have their own set of complications on the hard tissue to which the lip is anchored, make insertion and use complicated, and be

more feasible for the upper lip which is less mobile than the lower one. Gaining retention by increasing prosthesis surface area to intraoral sulcus and mentolabial sulci and extending coverage over the entire lip can be explored. Any deficiencies in retention experienced due to tissue mobility and salivary ingress may be supplemented by adhesives, though this was not done here, as a matter of patient preference (she wanted to avoid the added expenditure involved).^[11] However, such prosthesis can only be possible if about half of the lower lip is present.

CONCLUSION

Prosthetic rehabilitation plays a crucial role in the correction of lip defects where surgical reconstruction is not feasible, particularly in the rare case of necrosis described in this report. The prosthesis enhanced esthetics and aided functional and psychological recovery of the patient. This clinical report describes step-wise fabrication of the prosthesis, which was solely mechanically retained, was convenient to use, was economical, and was easy to fabricate.

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Conflicts of interest

There are no conflicts of interest.

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Dental Implant Supported Thumb Prosthesis with Friction Fit Retention System

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ABSTRACT

Introduction: An amputated thumb causes aesthetic deficit and functional loss. Reconstruction can be surgical or prosthetic. A small residuum leaves little scope for rehabilitation with suction-retained prosthesis. Prosthetic management requires implant placement or distraction osteogenesis to be successful.

This report presents the use of bone-anchored dental implants to support a prosthesis for rehabilitation of an amputated thumb.

Case Description: Satisfactory osseointegration of a dental implant placed in the amputated right pollex of a 24-year-old woman was achieved, after a two-stage surgical procedure. A healing abutment, which is normally placed transitionally after second-stage surgery, was modified to create a permanent friction fit coping. This was used to retain the silicone thumb.

Discussion and Conclusions: The study to some extent established off-the-label use of dental implants in rehabilitating amputated digits. Also, the friction fit retention system proved to be a cost- and armamentarium-effective method of retaining thumb prosthesis for cases with small residuum.

Clinical Relevance: This report describes a procedure for two-stage surgical placement of an osseointegrated dental implant in an amputated thumb with fabrication of prosthesis, which was effectively retained by a modified healing abutment. (*J Prosthet Orthot.* 2022;34:e103–e108)

KEY INDEXING TERMS: amputation, CAD-CAM, cost-effective, healing abutment, silicone

Digit amputation is one of the more common injuries of the upper limbs.^{1,2} Aesthetic embarrassment to the patient is immense, with psychosocial implications. Impairment in hand function can occur, leading to decreased grip and inability to perform precise movements and engage in certain tasks.^{3,4}

There are several reconstructive and rehabilitative techniques available for such patients, varying from adhesive retained silicone prosthesis, transplantation surgeries, and bionic fingers.^{5,6} Each technique has its own attendant advantages and disadvantages.

With the advancement of microsurgical techniques, many centers offer autologous reconstruction of the digit and replantation. However, when this fails or when replantation is not an option due to the mechanism of injury, techniques such as finger pollicization or toe-to-hand transfer offer good reconstructive alternatives. Manrique et al.⁷ reported that, in circumstances when these options are not feasible and patients desire improved

digit functionality and aesthetics, an osseointegrated implant-supported finger prosthesis is an option.

Li et al.⁸ wrote that implantation of an osseointegrated percutaneous prosthesis provides a reconstruction alternative for thumb amputation without sacrificing donor tissues. The concept of osseointegration can be defined as direct anchorage of an implant into the skeleton by induction of bone healing at the implant surface.⁸

One of the first such reported cases was a two-stage reconstruction aimed at support of thumb prosthesis from the first metacarpal through an osseointegrated titanium implant described by Lundborg et al.⁹ Thus, the successful use of osseointegrated implants with differently designed abutments for anchorage of prosthesis has been frequently reported.

The purpose of this case report is to describe the rehabilitation of an individual with a thumb amputation, using staged surgical placement of an osseointegrated dental implant and a simple but innovative friction fit design for prosthesis retention.

CASE DESCRIPTION

A 24-year-old unemployed woman reported to the department to have a new thumb prosthesis made. A history of trauma from a chaff cutting machine during childhood, which led to right thumb amputation, was elicited. The patient reported getting a suction fit thumb prosthesis made 2 years back, which was aesthetic but unretentive. As a result, the patient stated a clear desire for a snug-fitting new prosthesis.

Clinical examination revealed constant flexion of proximal interphalangeal joint of the right index finger, probably caused

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by the same trauma (Figure 1A). Skin over the residuum was thickened, firm, and sensate. Radiographic examination revealed that the thumb was amputated through the first metacarpal with a tiny piece of proximal phalanx. Metacarpophalangeal joint was preserved and functional.

The patient was right-handed. Functional deficit involved reduced ability to grasp objects and pinch. Adduction, opposition, extension, and abduction of the pollex were affected. However, as the trauma had occurred a long time ago, the patient had adapted to these deficits. The primary goal for which the patient had reported was aesthetic rehabilitation with a well-fitting prosthesis. She had no history of any systemic disorder.

The case was planned in coordination with Department of Plastic Surgery. All available treatment options were explained to the patient. She refused any treatment that would cause donor site deficit. Considering her desire, opinion, and the small residuum, an implant-retained thumb prosthesis was decided upon as the treatment of choice. Written informed consent was obtained from the patient. The possibility of aesthetic and functional deficit remaining after rehabilitation was explained. Possible complications of the procedure were communicated. Her blood investigations were normal.

The plan was to place a titanium dental implant in the metacarpal for prosthesis retention. Cone beam computed tomography (CBCT) revealed that the bone was 39.1 mm in length and



Figure 1. A, Amputated thumb. B, Cone beam computed tomography of amputated thumb.

10.5 mm in width (at the widest region, Figure 1B). Considering the topography of the metacarpal (it shows a definite taper from base upwards), a 4.5-mm diameter \times 14-mm length Cowell SLA-SH dental implant (Seoul, South Korea) was selected. Two-stage implant surgical procedure was planned and explained to the patient. Although this would lengthen the duration of treatment compared with the single stage, chances of osseointegration of the submerged fixture were higher.

TECHNIQUE

Surgery was performed in operatory with strict asepsis under local anesthesia. The right thumb digital nerve was anesthetized with 2% lignocaine without epinephrine. Skin incision was made at the implant site, and full thickness flap was elevated. The position and angulation of osteotomy was guided by radiographs to ensure parallelism to the long axis of the metacarpal. Sequential drilling with progressively larger drill sizes was done at low speed in the presence of a coolant to create an appropriately sized osteotomy. Next, the implant was manually torqued into a marginally subcrestal position. A satisfactory torque of 40 N-cm was attained following which cover screw was placed (Figure 2).

Radiographs were taken in palmar and lateral views to verify correct placement of implant. Peri-implant connective tissues were reduced to a thickness of approximately 2 mm to prevent implant movement, and flaps were repositioned. Nylon sutures were placed with pressure dressing, which was repeated after a week. Postoperative medication consisted of an anti-inflammatory analgesic (ibuprofen) and an antibiotic (amoxicillin and clavulanic acid) regimen for 7 days. Healing was uneventful, and sutures were removed after 2 weeks. Instructions were given for operated site hygiene, cold fomentation, and watching out for warning signs such as pain, oozing, or wound dehiscence.

At the 4-month follow-up, radiographs revealed satisfactory osseointegration of implant. There was no inflammation, pain, or other complication (Figure 3A). Second-stage surgery was scheduled. An incision was given in the region of the cover screw. The cover screw was located, removed, and replaced with a healing abutment (2HS4572; Cowell Dental Implant, Seoul, South Korea) of 4.5-mm diameter and 12-mm length. The dimension

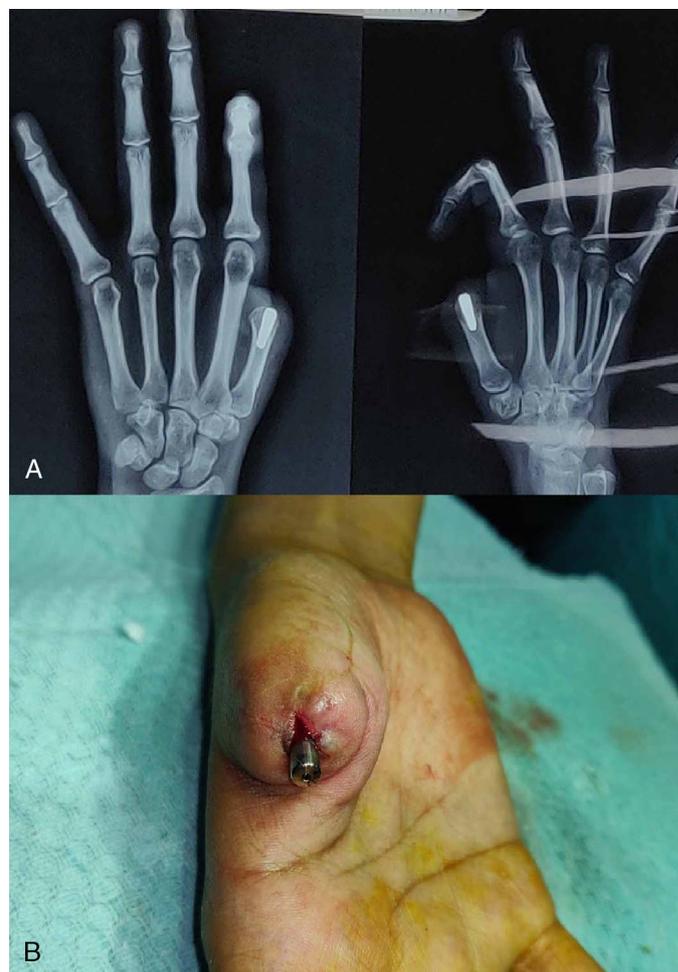


Figure 3. A, Radiograph at 4 months, lateral and palmar view. B, Second stage surgery, healing abutment placed.

of the slightly tapered abutment was chosen so as to project clearly out of the residuum for utilization in retaining the prosthesis. A shorter abutment would have been less retentive for the prosthesis, and a longer one would have created an unfavorable implant prosthesis ratio. Sutures were placed and patient instructed to avoid contact with the operated area until their removal after a week (Figure 3B).

The patient was recalled for making an impression of the residuum (implant-level impression) after 3 days of suture removal. A special tray was made in the shape of a cylinder with the help of modeling wax (Pyrex Modeling Wax, Pyrex Polykem). A transfer coping was connected to the implant, and an open-tray impression was made with additional silicone impression material (3M ESPE, St Paul, MN). An implant analog was connected to the transfer coping, and a model poured in type 4 die stone (Kalrock; Kalabhai, Mumbai, India).

Then, the healing abutment was modified to be used as an attachment for friction fit prosthesis. Its undercuts and taper were removed with the help of highly compressed, fine-grain carbide burs and finish achieved with the help of silicon rubbers (Vitality Laboratory Rotary Instruments Kit). A metal alloy coping designed with friction fit over the altered healing abutment was fabricated



Figure 2. Implant with cover screw.

(Figure 4). A white, heat-polymerized acrylic housing was prepared over the coping as an interface between the metal coping and silicone thumb. Several fins were made in the housing to make it mechanically retentive to the prosthesis (Figure 5). A properly textured and characterized wax pattern of the right thumb was sculpted in modeling wax (Pyrex Modeling Wax; Pyrex Polykem) over the acrylic housing on the residuum model. Then, the modified abutment was connected in situ for trial of the wax thumb on the patient.

After some minor modifications, the pattern—acrylic housing—metal coping assembly was again seated on the residuum model (on the healing abutment), invested and dewaxed to create a two-part mold (superior and inferior). The acrylic housing was cleaned thoroughly, and the platinum primer (G611; Technovent Ltd, South Wales, United Kingdom) was applied to improve its adhesion to silicone. Separating media was applied; the mold space was packed with intrinsically colored medical grade silicone (Technovent Ltd, South Wales, United Kingdom), which was processed conventionally. Extrinsic characterization helped achieve lifelike appearance of the prosthesis.

OUTCOME

A well-retained and stable prosthesis was obtained. The range of movement as assessed by Kapandji rule of 10, wherein the patient was asked to touch 10 specific finger areas with the tip of the thumb, was 8.¹⁰ The ability of the patient to pinch and grasp objects was improved, with limited improvement in overall mobility. Patient-assessed aesthetic outcome was 9 on a visual analog scale of 10 (Figure 6). However, on greater abduction, a slight opening at the prosthesis margin could be seen.

Maintaining proper hygiene of the peri-implant tissues with a soft brush, lukewarm water, and soap at least once a day was emphasized.¹¹ Follow-up was done on day 7 and day 30 of delivering the prosthesis. From then on, the patient has been followed up uneventfully at 3-month intervals. More than a year has elapsed since delivering the prosthesis. Radiograph taken at 12 months of baseline revealed no significant changes in implant-bone interface.

DISCUSSION

Digit amputations may be caused by work-related accidents, road traffic accidents, animal bites, and systemic diseases including



Figure 4. Coping over altered healing abutment.



Figure 5. Acrylic housing incorporating coping in (A) lateral and (B) superior views.

diabetes. The thumb is an important part of the hand used to perform daily tasks including pinch, grip, grasp, and precision handling. From a functional standpoint, it is the most important digit, performing the movements of opposition and apposition.

Amputation of the first digit can have a negative functional, aesthetic, and psychological impact. Reconstruction or rehabilitation is definitely desirable. Surgical replantation is most desirable but not always possible. Autologous transplantation or reconstruction is often complex, financially demanding, and comprises multiple procedures.¹² Such digits can be compromised in shape and size and therefore lead to dissatisfaction.¹³ Distraction osteogenesis can effectively increase functional length of the amputated digit, but apart from a long treatment procedure, possible sequelae include joint stiffness and nerve injury.¹⁴

It has been established that patients benefit from socket type of prostheses based on suctional retention. However, such prosthetic digits are not always stable, especially when the residuum

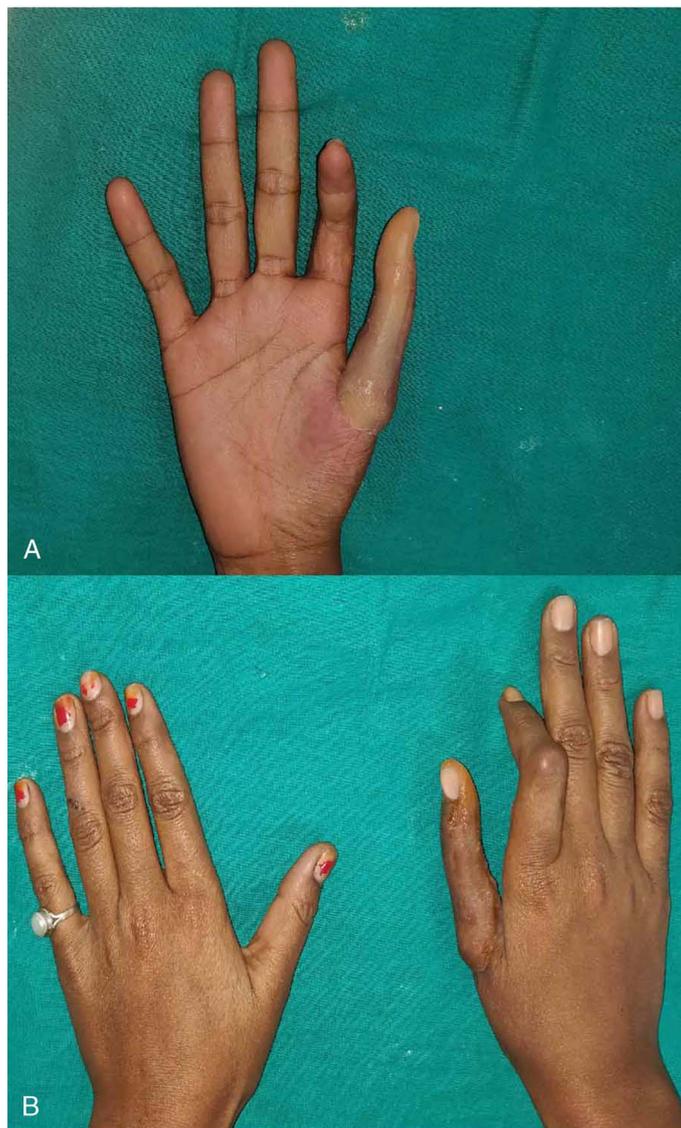


Figure 6. Finished prosthesis: (A) ventral and (B) dorsal view.

is small. A split ring is sometimes added to the socket-type thumb prosthesis at prosthesis-residuum junction to gain added retention and camouflage margin, but retention achieved is questionable, especially when the residuum is compromised in size.¹⁵ Prosthesis retention by means of osseointegrated titanium fixtures has been established as a viable solution in such cases.¹⁶

The concept of osseointegration has been applied in craniofacial reconstruction for many years, with few studies reporting prosthetic implant use for hand reconstruction. Osseointegration has also been defined as direct attachment of an implant to the bony residuum by formation of bony tissue around the implant, without growth of fibrous tissue at bone-implant interface. This allows reconstruction of the missing digit(s) when autologous tissue is not available, or when the patient desires to undergo a less complicated and invasive surgical intervention. High grip and pinch strengths, with good Jebsen Hand Function Test scores, have been reported with implant-supported prosthesis.⁷

Manurangsee et al.⁴ reported a two-stage reconstruction procedure with osseointegrated titanium implants in three patients fixing a finger prosthesis to the proximal phalanx. The first stage included implantation of the titanium fixture into the medullary canal of the proximal phalanx. After a 3-month rest period to allow the fixture to firmly osseointegrate, a skin-penetrating abutment was connected to the fixture, to which the prosthesis was attached. They reported minimal skin problems, some tactile sensibility, improved motor function, better comfort, and good cosmetic results as outcomes of the rehabilitation.⁴

Data published by Li et al.⁸ showed that osseointegrated thumb prostheses wearers achieved 66% grip strength and 71% lateral pinch strength when compared with hand function of the unaffected side. These results were comparable to great toe-to-thumb transfers, which had grip strength of 77% and pinch strength of 67%, compared with the normal side. The osseointegrated implant-retained thumb prosthesis has been reported to offer better aesthetic and functional results compared with adhesive or suction-retained prosthesis, and allow some pressure perception and tactile sensation, facilitating surface and texture distinction.¹⁷

Specific titanium fixtures are in use for retaining finger and toe prostheses.⁹ However, these are costly and difficult to obtain, in contrast to dental titanium counterparts. Further, the shape and dimensions of the metacarpal is suitable for placing a dental implant. The Cowell sand-blasted, large grit-etched, super hydrophilicity activated surface treatment (SLA-SH) dental implants were selected for this off-the-label purpose because this surface design has been reported to accelerate osseointegration and maximize bone implant interface.¹⁸

Retention is a deciding factor in the success of any prosthesis, and various mechanisms have been used to retain the artificial digit. O ring attachment systems have been used, but they add to the cost of treatment.¹⁹ A cast silver palladium two-bar system screwed to the implant body was used to retain an osseointegrated thumb prosthesis. Clips in an acrylic substructure were incorporated in the prosthesis. The clips had a snap fit on the bar. However, this system was bulky and not cost-effective.²⁰

Friction fit retention has been defined as a form of fastening between two tight-fitting mating parts that produce a joint by friction after the parts are pushed together. It was used in this study because of being cost-effective, by virtue of the healing abutment being modified as the friction fit component for retaining the coping. The healing abutment is an essential part of the armamentarium needed for rehabilitating any dental implant patient, as it aids in proper healing and attachment of peri-implant soft tissues. Costly retentive systems such as the O ring, bar, and clip were not needed. Fins were created in the acrylic substructure to provide added retention to the silicone toe, preventing accidental separation.

Areas of concern for such prosthesis include hygiene maintenance of the peri-implant area, where it is common to observe accumulation of debris and exfoliated cells. If cleaned improperly, this may lead to inflammation, infection, and implant failure. Further, the response of dental implants to a foreign environment and different sets of microorganisms needs further study.

Other issues can include failure of implant osseointegration, mechanical implant failure, implant failure due to overload, and cost compared with suction-retained thumb prosthesis. Persons with diabetes, smokers, and individuals who perform major heavy manual labor may not be good candidates for such rehabilitation. Silicone prostheses are subject to wear and tear, needing replacement.¹³

CONCLUSIONS

Dental implant-supported friction fit retained thumb prosthesis offers a retentive, functional, cost-effective, and convenient outcome.

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Spectacle Cord-retained Oculo-Orbital Prosthesis

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ABSTRACT

Retention of an orbital prosthesis plays a key role in treatment success and patient acceptance as does aesthetics. Though numerous retentive aids are available such as implants, adhesives, etc, the cost, surgical aspect, difficulty of use and allergic potential may compromise efficiency. This report describes the case of an 11-year post-enucleation poor retinoblastoma patient, in whom an unfavourable defect leads to a major prosthetic challenge (from point of view of retention and camouflage). This report describes a simple, economical, and user-friendly approach to obtain satisfactory retention and camouflage for such patients with spectacle cords and customised spectacles.

Key Words: *Oculo-orbital prosthesis, Spectacle, Cord.*

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INTRODUCTION

A facial defect compromises an individual's life by introduction of elements like facial disfigurement, social stigma, psychological strain, and economical predicament. Hence, successful rehabilitation plays an integral role in acclimatisation of patient to a more normal life. An inconspicuous prosthesis plays a major role in restoring aesthetics; and equally significant is the achievement of retention. Inadequate retention is associated with patient distress, prosthesis neglect, and discardment. Multiple methods have been described in literature to achieve adequate retention for orbital prosthesis including use of adhesives, magnets, stud attachments, and implants.¹⁻⁶ While some methods have expense as a limitation; for others, surgical intervention is the major pitfall.

In childhood, retinoblastoma is one of the most frequently encountered tumors.⁷ It is managed predominantly with the help of enucleation and adjunctive radiotherapy and chemotherapy. Enucleation creates a volume deficit, which is managed with the placement of both implant and prosthesis.⁸ Failure of early prosthesis wear can contribute to development of socket contracture, which constitutes an integral component of the post-enucleation socket syndrome (PESS).⁹ Management of socket contracture depends on severity of the condition including techniques like anterior lamellar repositioning, mucous membrane grafting, and free vascularised radial forearm flap.^{9,10}

CASE REPORT

An 11-year male patient reported to the Department of Prosthodontics with the chief complaint of unaesthetic facial appearance, due to loss of left eye. He had been diagnosed with retinoblastoma of left eye about two years back, which was managed by enucleation surgery and chemotherapy. At post-surgery, as a result of not wearing an ocular prosthesis/conformer, patient developed PESS and presented with fused upper and lower eyelids for prosthesis fabrication. He was referred to the Department of Plastic Surgery for creation of a favourably sized defect for prosthesis retention and aesthetics. Unfortunately, the surgeon removed both upper and lower eyelids, and covered the socket defect with a split thickness graft, leading to a large unaesthetic non-retentive defect (Figure 1a). For the lack of existing terminology, the prosthesis thus fabricated, and has been termed an oculo-orbital prosthesis.

A conventional impression of the defect and surrounding tissues was made with irreversible hydrocolloid impression material (Zelgan; Dentsply Pvt. Ltd.) and poured in type IV stone (Kalstone; Kalabhai). This was followed by adaptation of a 2 mm thick PVC thermoplastic sheet (Sof-tray sheets; Ultradent Products Inc) on the model to facilitate process of pattern trial by enhancing adaptability. A stock ocular prosthesis matching to the contralateral eye in terms of colour, shape and size of sclera and iris, was selected. Its position was adjusted anteroposteriorly, mediolaterally, and superioinferiorly with respect to normal gaze of the contralateral eye. Pattern was fabricated in clay and sculpted in accordance to the normal contralateral eye with subsequent modifications to obtain desired life-like contour and skin texturing by creating skin folds and stippling.

This was followed by thinning and merging of the margins with adjacent tissues.

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Investing of the pattern was done with addition of acrylic stump (Pyrax; Pyrax Polymers Ltd.) on the iris to avoid displacement of the ocular component of the orbital prosthesis, as displacement often leads to altered gaze of the prosthetic eye after processing. Dewaxing procedure was carried out at 100°C for 5 minutes. A digital spectrophotometer (e-skin; Spectromatch Ltd.) was utilised for shade matching. Colour-matched Room Temperature Vulcanising (RTV) medical-graded silicone material (Technovent M511; Technovent Ltd) was packed in the investment mould. Post-polymerisation, the prosthesis was deflasked, retrieved, and finished. Extrinsic staining was done for correction of any deficiencies and natural hair were stitched over upper and lower eyelids of the silicone prosthesis using 23 gauge syringe needle.

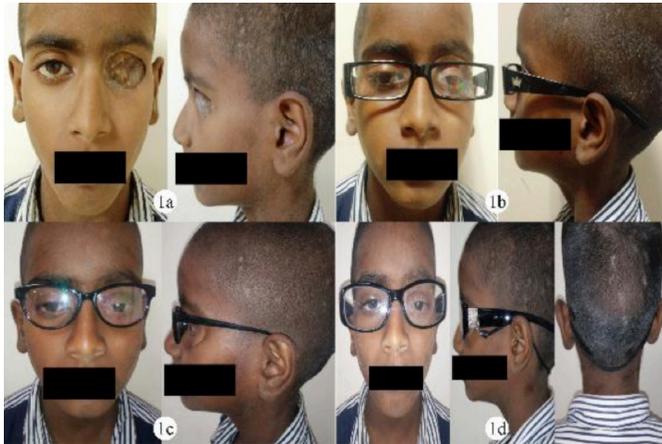


Figure 1: (a) Pre-rehabilitation frontal and profile views. (b) Mismatched spectacle 1 frontal and profile views. (c) Mismatched spectacle 2 frontal and profile views. (d) Matched spectacle with cord and prosthesis *in situ*: frontal, profile and back views.

To obtain optimum camouflage and retention, customised spectacles with elastic black nylon spectacle cord were utilised (Cord diameter was 0.3 cm and length 58.5 cm). The cord was fastened in proportion to the pressure needed to obtain a stable retentive comfortable prosthesis. For camouflage of the defect prosthesis margins (unfavourable surgical outcome left little place for their concealment), spectacles were used for the patient with wide rimmed frames. The importance of spectacle design in camouflage can be appreciated from Figures 1a through 1d. While spectacles in Figure 1b lead to lateral margin show through, the ones in Figure 1c revealed superior margin of the prosthesis. Spectacles in Figure 1d concealed the margins from all aspects. The spectacle shape was chosen to coincide with prosthesis shape, with its bridge as close as possible to the nose. The spectacle temple was chosen to be wide enough to create camouflage in lateral view. Photochromatic lenses were used for obscuring the prosthesis in daylight (Figure 1d).

Prosthesis was delivered to the patient. At the subsequent follow-up visits (now 1 year), patient and guardian expressed satisfaction with improved aesthetics, adequate retention and ease of wear.

DISCUSSION

Inter-disciplinary communication plays a major role in successful prosthesis rehabilitation. Proper case planning with involve-

ment of both the surgeon and prosthodontist is needed. Clear communication and understanding of factors, such as creation/preservation of undercuts for prosthesis retention, partial/split thickness flap coverage of denuded areas, minimum size and shape of defect necessary for satisfactory prosthetic rehabilitation and/or need of extra retentive mechanisms such as implant placement, is essential. Selection of mode of retention of a prosthesis is dependent on a multitude of factors like defect size and undercut presence, patient's economic status, and aesthetic prominence of the site. Retention for an orbital prosthesis can be obtained through inclusion of anatomical undercuts with conformer/acrylic resin template relined by a resilient denture liner, spectacle retained prosthesis, use of stud attachment, magnets, adhesives and implants.¹⁻⁶

In this patient, no functional undercuts were present, which could be utilised to obtain retention. Since the patient was from poor economic strata and had already undergone debilitating surgeries, implants were not a feasible option. Literature has delineated increased incidences of soft tissue infections and higher hygiene maintenance requirements with implant placement.^{5,6}

Adhesive serves as an expensive alternative, which require frequent applications and good manual dexterity on the part of the patient, which becomes more problematic in a paediatric patient. Routine adhesive usage is conducive to allergic responses and may simultaneously also impair prosthesis external pigmentation.^{3,4}

In conventional spectacle retained prosthesis, an acrylic shim is utilised to obtain anchorage from the spectacle due to absence of direct bond of silicone with it.⁹ This can hamper the aesthetics due to increased visibility of acrylic shim. In addition, it can introduce an element of difficulty in prosthesis insertion and removal, due to varying path of insertion of the prosthesis and spectacle. Further, the shim takes up additional space, which the concerned defect could not accommodate. Above difficulties can be ameliorated by the use of magnets or studs in the spectacle.^{3,4} However, due to limited depth of this defect and cost, these were not feasible options. In addition, magnets exhibit loss of attraction over time and corrosion.³

In this report, positive pressure created by the spectacle and elastic cord, was used for prosthesis retention. Eye-wear cords are nylon extensions with adjustable plastic loops at their end. They are readily available and are an economical retentive aid, affordable even by impoverished patients. The aesthetics of the prosthesis is not compromised by black cords, being camouflaged within scalp hair. They do not demand great manual dexterity from the patient and, therefore, can be used by the very young or old. They can be removed at any desired time and there is negligible likelihood of any allergic reaction.

Aesthetics and retention are two fundamental elements for a successful facial prosthesis, which needs good team-work between the surgeon and prosthodontist. Surgically created

unfavourable defects such as the one presented, pose a major prosthodontics challenge. This report describes the fabrication of an oculo-orbital prosthesis with spectacle and cord aided camouflage as well as retention, to meet this challenge in an economical and patient-friendly manner.

PATIENT'S CONSENT:

The written informed consent has been obtained from the guardian of the patient.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SG, SVS: Contributed to prosthesis design, fabrication and manuscript preparation.

NS: Contributed to manuscript preparation.

DA, PC: Contributed to literature review.

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Improving the Prognosis for Phthisis Bulbi Patients

Sir,

Prosthetic rehabilitation of patients with phthisis bulbi is challenging, primarily due to reduced prosthetic space and corneal sensitivity. Sensitivity can cause difficulty in prosthesis fabrication; and inability of the patient to wear the prosthesis¹ (Figure 1a). Surgical techniques to minimise sensitivity have their own complications.^{2,3} Therefore, a prosthetic technique, aimed at gradual desensitisation, and improving the esthetic outcome in cases of phthisis bulbi has been being discussed.

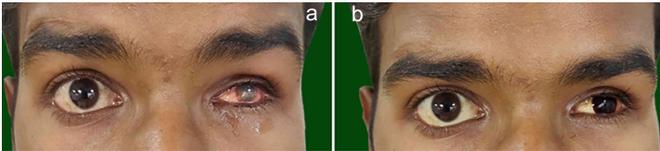


Figure 1: (a) Excessive corneal sensitivity associated with the phthisical eye. (b) Contact lens given to the patient for gradual desensitisation.

A 24-year male patient was referred for left prosthetic eye fabrication, who had presented with a history of trauma resulting in phthisis bulbi. Testing with a cotton wisp showed that the patient had sensitivity in this eye. To start with, a coloured rigid glass permeable (RGP) contact lens (Elite, Everclear) matching patient's contralateral iris colour (Figure 1b) was selected. Patient was told to wear the contact lens for brief time periods initially. The time of wear was increased gradually until two weeks.

After this, patient's affected eye was examined again for sensitivity. As the tolerance had improved, an ocular impression was made after anaesthetising the affected eye. Had excessive sensitivity been persistent, patient would have been instructed to increase lens wearing time for another two weeks. Impression was poured in type III dental stone (Kalabhai Kalstone, Karson Pvt. Ltd., Mumbai), to create a two-half mold, then wax was poured in this mold to fabricate a wax pattern for the prosthesis. Carving and contouring of the wax pattern was done to simulate the lost eye. After this, try-in was done to assess for fit, contour, comfort, size, support and movement. Acrylisation of the wax pattern was done in heat-cured tooth coloured acrylic resin (Heat Cure, Pyrax Polymers, India), matching the shade with the sclera of unaffected eye.

Margins were ascertained to be thin to avoid an over-bulging prosthesis. Prosthesis was checked for fit and contour, following which it was relined with permanent heat-cured soft reliner (Molloplast B, Detax, Germany) after reducing 1 mm

circumferentially to improve retention and reduce discomfort (Figure 2a). Iris position was determined on scleral shell according to conventional techniques (Figure 2b). This portion of the prosthesis was formed with the initially used contact lens, which was adhered with cyanoacrylate to the shell, in previously determined position. Monopoly syrup was used to protect the surface and contact lens. After this, the final prosthesis was delivered (Figure 2c).



Figure 2: (a) Margins of the prosthesis trimmed and relined with a permanent soft liner. (b) Iris positioning. (c) Final prosthesis with contact lens as the iris.

Use of contact lens introduced an inceptive stimulus to gradually desensitise the patient. Using same contact lens as iris in the prosthesis, provided superior esthetics by minimising risk of a bulging over-contoured prosthesis, pre-empting excessive thinning of scleral shell, which can lead to fragility and show through. Use of permanent soft liner at the margins of the prosthesis, reduced discomfort and aided retention. However, this approach is technique-sensitive and time-consuming, with additional cost of the lens.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

NS: Conceptualisation, investigation, writing the original draft.

SVS: Formal analysis, methodology, writing, reviewing and editing.

DA: Supervision, validation, and visualisation.

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Association of interleukin-1 gene polymorphism and early crestal bone loss around submerged dental implants: A systematic review and meta-analysis

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Abstract

Aim: Early crestal bone loss (ECBL) has been observed regardless of the absence of possible etiologic factors for bone loss during the healing phase and before the second-stage implant surgery. The purpose of this systematic review and meta-analysis was to correlate the possible association of interleukin-1 (IL-1) gene polymorphisms and ECBL (bone loss before the second-stage surgery) around dental implants.

Settings and Design: Systematic review and meta-analysis following PRISMA guidelines.

Materials and Methods: Considering the inclusion criteria, an electronic search by using specific keywords of three databases PubMed [("Dental" OR "oral") AND ("Implants*") AND ("gene polymorphism" OR "genotype" AND ("IL-1" OR "interleukins")), Cochrane library [implant AND (biomarker or cytokine), interleukin-1 or IL-1 AND implants], and EMBASE [("gene polymorphisms"/de OR "interleukins"/cytokine exp OR "biomarker":ti,ab,kw) AND ("dental implantation"/de OR "oral implant")] and manual search from 1995 till March 2020 was made by 2 independently calibrated reviewers. ACROBAT-NRSI, Version 1.0.0 and Review Manager, Version 5.3, computer software were used for the risk of bias assessment and to conduct the meta-analysis respectively.

Statistical Analysis Used: Cochran's Q test and I² statistics.

Results: Of 38 articles which were found eligible for full-text screening, two articles fulfilled the inclusion criteria and hence were included in the meta-analysis. The I² statistic and Q-test values of the included studies revealed acceptable homogeneity for studied three IL-1 gene polymorphisms (IL-1A-889: I² = 0%, IL-1B-511: I² = 0%, IL-1B+3954: I² = 24%). Forest plot of association between IL-1B-511 gene and ECBL revealed a significant association between 2/2 genotype of IL-1B-511 gene and an increased risk of ECBL (OR = 0.23, 95% CI = 0.09-0.58, P_{heterogeneity} = 0.68, I² = 0%, and P = 0.002). Results of the IL-1A-889 and IL-1B+3954 gene revealed no significant associations between any genotype of these genes with risk of ECBL.

Conclusions: There is an evidence of the association of IL-1B-511 (2/2) genetic polymorphisms and increased ECBL in the individuals of Asian ethnicity (OR = 0.23, P = 0.002).

Keywords: Dental implant, implant failure, marginal bone loss, single nucleotide polymorphism

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INTRODUCTION

Endosseous implants provide the most predictable and successful restoration technique for the aesthetic and functional replacement of missing teeth.^[1] The longevity and success of these implants depend primarily on the phenomenon known as osseointegration which could be elaborated as a direct functional and structural union between synthetic implants and living bone tissues.^[2] The crestal bone level encircling the dental implants plays a pivoted role for successful implant integration, as early breakdown or failure of implant-tissue junction instigate at the alveolar crest region.^[1,2] The success and survival of implant rehabilitations have not attained 100%, failures do observed.^[3,4] Bone loss around implants has been the leading reason for implant failure.^[3-5] Factors contribute to peri-implant bone loss are infection, smoking, bone quality, mechanical overloading, surgical trauma, menopause, and metabolic diseases.^[1,4-6] However, these factors play a role subsequent to the second-stage surgery. Majority of the researchers believe that in the absence of any underlying metabolic disease and other risk factors during the healing phase (4–6 months), bone loss should not occur.^[3,7-10] Nonetheless, early crestal bone loss (ECBL) has been frequently observed during the healing period of submerged dental implants.^[3,7-9] Probable etiologic factor behind this ECBL could be the genetic variations or polymorphisms of a particular gene as bone formation and resorption have been continuously under the control of cytokine production.^[3,7,8,11] Evidence has suggested that peri-implant complications including bone loss and failures have been clustered in specific high-risk patients and in those patients if the failure of one implant occurs, there was the likelihood of further failures.^[12,13] This prospective link has triggered a series of researches that attempted to categorize, both at the site and patient levels, distinct risk factors disrupting the host-parasite harmony and propagating to the development of implant complications.^[14-16]

Interleukin (IL)-1 had been the frequently explored pro-inflammatory cytokine in several bone diseases and conditions as polymorphisms in the promoter region of this cytokine has been associated with the stimulated differentiation of osteoclast precursors leading to altered regulation of bone mineral density and accelerated bone loss.^[3,7,17,18] These IL-1 gene polymorphisms have been illustrated in various studies to be linked with peri-implantitis,^[19-24] periodontitis,^[25-31] low bone mineral density,^[32] and peri-implant bone loss^[3,7,9,10,19,33,34] leading to implant failures and loosening of teeth as well. Most of the bone loss studies were related to the bone loss

after second-stage surgery and in association with either peri-implantitis or periodontitis. Although there was an evidence for the association of the IL-1 gene with peri-implant bone loss, association studies related to IL-gene polymorphisms and ECBL (bone loss before second-stage implant surgery) are scarce. Thus, the aim of this systematic review and meta-analysis was to evaluate whether polymorphisms of the IL-1 gene (IL-1A-889, IL-1B-511, and IL-1B+3954) are associated with increased rates of crestal bone loss before the second-stage implant surgery (ECBL). The null hypothesis was that the IL-1 gene polymorphism might influence the crestal bone loss before the second stage surgery.

MATERIALS AND METHODS

The study design followed the criteria recommended by the Cochrane collaboration for reporting the systematic review and meta-analysis.^[35] Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines have been pursued to report the article.^[36]

The patient, intervention, comparator, and outcome question index designed for the present study was as follows:

- Systemically healthy patients who received dental implant rehabilitation (P)
- Effects of IL-1 gene polymorphism on bone loss around the implants (I)
- Patient group that exhibited ECBL versus group that does not (C)
- Potential association between IL-1 gene polymorphism and ECBL/implant failure (O).

Eligibility criteria

Inclusion criteria:

1. Literature published in English
2. Prospective, cross-sectional, retrospective, and randomized control trial studies on peri-implantitis, dental implant loss, or peri-implant marginal bone loss before second-stage surgery in association with IL-1 gene polymorphism
3. Minimum follow-up period of 6 months and adult patients (≥ 18 years)
4. The included studies should report ECBL that is from the day of implant placement and before second-stage surgery during the bone healing period.

Exclusion criteria:

1. Studies reported in medically compromised patients such as uncontrolled/controlled diabetes mellitus, malignancy, and osteoporosis

2. Studies on immediate extraction and immediate loading
3. Case reports, review of literature, and studies on animals.

Information sources

An electronic search from inception to March 2020 was carried out in the following databases by two independently calibrated reviewers (C. G., M. A.): PubMed (Medline), Cochrane Library, and EMBASE.

Search strategy

Boolean operators based on Medical Subject Headings terms and PubMed included the following: (“Dental” OR “oral”) AND (“Implants*”) AND (“gene polymorphism” OR “genotype” AND (“IL-1” OR “ILs”). Search headings in the title, abstract, and keywords applied in the Cochrane Library were: implant AND (biomarker or cytokine), interleukin-1 or IL-1 AND implants. For EMBASE following keywords were used, (“gene polymorphisms”/de OR “interleukins”/cytokine exp OR “biomarker”:ti,ab,kw) AND (“dental implantation”/de OR “oral implant”).

In addition, manual searching of the reference lists of the following identified journals were carried out from 1995 up to March 2020: (*Clinical Implant Dentistry and Related Research, Oral Surgery Oral Medicine Oral Radiology Oral Pathology and Endodontics, Genes, Clinical Oral Implant Research, Implant Dentistry, European Journal of Oral Implantology, International Journal of Periodontics and Restorative Dentistry, International Journal of Oral and Maxillofacial Implants, Journal of Periodontal Research, Journal of Clinical Periodontology, Journal of Oral and Maxillofacial Surgery, Journal of Indian Prosthodontic Society, Journal of Dental Research, Journal of Periodontal and Implant Science, and the Journal of Periodontology*).

Validity assessment

Quality assessments of studies to be included were independently executed by two competent authors (P. C., K. K. A.) as a part of extraction process. Abstracts and titles of the search results were screened as per the selection criteria, and then full texts of selected articles were assessed and screened. Search methodology of databases involves a three-stage screening process by reviewers. First-stage screening involves screening of titles of searched articles. Second-stage involves the assessment of the abstract followed by full-text articles at the third stage. At each stage, a discussion was done to resolve discrepancies (if any) and if consensus was not reached, expert consultation was taken with an experienced third author (S. V. S). The k (kappa) statistics^[37] was calculated for potentially relevant articles at the second and third stages of screening to assess the level of compliance between the authors concerning study inclusion.

Data collection

Data were extracted and analyzed from the eligible studies and the following predesigned and standardized information was obtained: publication year, authors, country of origin of study, participants characteristics (mean age, number, intervention received, etc.), sites and number of implants placed, follow-up period, study variables, and data of ECBL. Wherever possible, contacts with the corresponding authors were made, whenever data were found out to be missing, incomplete, or ambiguous. Studies with incomplete data (even after contacting corresponding authors and/or contacts not made) were excluded from the meta-analysis. The extracted data related to various characteristics were stratified and arranged in chronological order in the form of evidence tables, and finally, a descriptive summary was generated to facilitate the data synthesis process.

Risk of bias assessment

A Cochrane risk of bias assessment tool for nonrandomized studies of interventions (ACROBAT-NRSI), Version 1.0.0 (riskofbiastools.info), dated September 22, 2014, “ACROBAT-NRSI”^[38] was used for assessment of risk of bias (ROB) for the observational studies of interventions.

A funnel plot was drawn to ensure asymmetry, if any, owing to ROB in the included studies. Any asymmetry observed in obtained funnel plot for included studies may point toward publication bias and other biases associated with sample size.^[35]

Statistical analysis

Heterogeneity variations between included studies were determined by means of Cochran’s Q -test (χ^2) and I^2 statistics. An I^2 value of $>50\%$ and $\alpha = 0.05$ for Q -test were considered statistically significant. Mantel–Haenszel method or fixed-effect model for meta-analysis was applied to draw the forest plot and to calculate the summary odd ratios (ORs) and 95% confidence intervals (CIs) ($\alpha = 0.05$). RevMan (Review Manager v5.3; Cochrane Collaboration) computer software, which is freely available on Cochran’s site, was used to conduct the meta-analysis.

RESULTS

Figure 1 displays the study selection procedure through the PRISMA flowchart. Electronic search from various databases yielded 297 articles, while manual searching provided 21 articles. Two hundred and ten articles remained subsequent to the elimination of overlapping articles. One hundred seventy-two articles were eligible for screening of title and abstract. One hundred thirty-four articles were excluded after reading the “title and abstracts.” Altogether, 38 articles were eligible for full-text screening. After initial full-text screening of 38 eligible articles, 33 articles^[20-24,27-31,33,39-60] [Table 1]

were not included as they did not compare the IL-1 gene association with crestal bone loss, leaving five potentially eligible articles.^[3,7,10,19,34] Full-text articles were obtained from these five articles, of them three articles^[10,19,34] were further excluded following third-stage screening with reasons listed in Table 2. Thus, a total of two published articles^[3,7] were included in the present meta-analysis.

Study characteristics

The κ -value (kappa) for inter-reviewer (P. C., K. K. A.) harmony for “titles and abstracts” was 0.82, whereas for “full text articles,” its value was 0.72, indicating “nearly perfect” score for interobserver agreement as criteria established by Landis and Koch.^[37] Cases and controls in both the included studies were dental implant patients. Studies were hospital based at separate geographical locations with the same ethnicity (Asian population). Detailed characteristics of included studies are revealed in Table 3.

Meta-analysis

The meta-analysis was carried out by pooled outcomes of included studies. The I^2 statistic and Q -test values of included studies revealed acceptable homogeneity

for studied 3 IL-1 gene polymorphisms (IL-1A-889: $I^2 = 0\%$ and Q -test $P = 0.99$, IL-1B-511: $I^2 = 0\%$ and Q -test $P = 0.68$, IL-1B+3954: $I^2=24\%$ and Q -test $P=0.20$) [Figures 2-4]. Therefore, a fixed-effect model was used to draw forest plots and to carry out the meta-analysis.

Association of IL-1 gene polymorphisms (IL-1A-889, IL-1B-511, and IL-1B+3954) and risk of ECBL using occurrences of dominant genotypes (1/1, 1/2, and 2/2) in a particular gene in each study are depicted by results of pooled fixed-model meta-analysis [Figures 2-4].

Forest plot of association between IL-1B-511 gene and ECBL [Figure 2] had revealed a significant association between 2/2 genotype of IL-1B-511 gene and an increased risk of ECBL (Pooled OR = 0.23, 95% CI = 0.09–0.58, $P_{\text{heterogeneity}} = 0.68$, $I^2 = 0\%$, and test for overall effect $P = 0.002$). The results of IL-1A-889 [Figure 3] and IL-1B+3954 [Figure 4] gene revealed no significant associations between any genotype of these genes with risk of ECBL (IL-1A-889 gene: Pooled OR = 0.96, 95% CI = 0.3–62.53, $P_{\text{heterogeneity}} = 0.99$, $I^2 = 0\%$, and test for overall effect $P = 0.93$; IL-1B+3954 gene: Pooled OR = 0.41, 95% CI = 0.11–1.46, $P_{\text{heterogeneity}} = 0.20$, $I^2 = 39\%$, and test for overall effect $P = 0.17$).

The possible risk of publication bias was carried out for included nonrandomized (case-control) studies, as illustrated in Table 4 and Figure 5. Both the included studies depict low ROB. A visual assessment of the shape of the funnel plots of the meta-analysis [Figure 5] revealed clear symmetry and none of the included studies extend beyond the limits of 95% CI, demonstrating the probable absence of bias related to publications.

DISCUSSION

Genetic polymorphism, which is primarily a result of mutations, is a term used to describe the co-existence of different variants of a gene in nature.^[43] Variations of the IL-1 gene cluster, especially in the IL- α and IL- β genes, have been the most frequently investigated functional polymorphisms for implant loss.^[58] Several

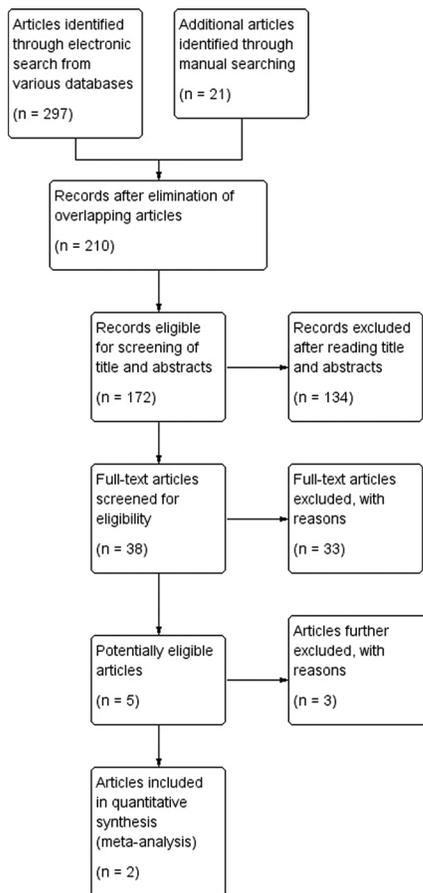


Figure 1: Preferred reporting items for systematic reviews and meta-analysis flowchart for meta-analysis

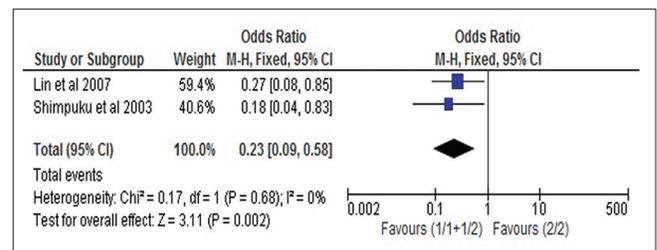


Figure 2: Forest plot of comparison: IL-1B-511 gene

Table 1: Full-text articles after second-stage screening

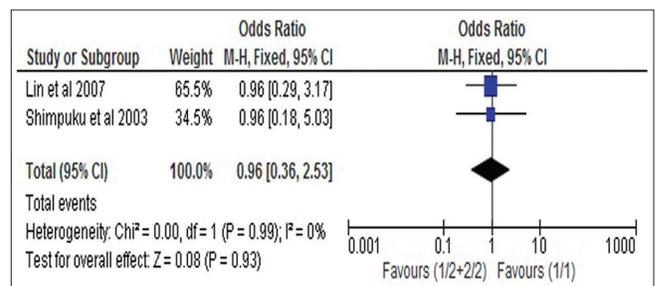
Selected study	Gene polymorphism studied	Complications
Petkovic-Curcin <i>et al.</i> , 2017 ^[33]	CD14, TNF α , IL-1, IL-6, IL-1ra	Delayed bone loss
Sampaio Fernandes <i>et al.</i> , 2017 ^[41]	IL1A, IL1B, IL1RN	Peri-implant success
Liao <i>et al.</i> , 2014 ^[42]	IL-1A (-889) and IL-1B (+3954)	Implant loss
Cosyn <i>et al.</i> , 2016 ^[43]	IL-1A (-889), IL-1B (-511), and IL-1B (+3954)	Early implant loss
Melo <i>et al.</i> , 2012 ^[20]	IL-1B, IL-6	Peri-implantitis
Rogers <i>et al.</i> , 2002 ^[44]	IL-1A (-889), IL-1B (+3953), IL-6, IFN γ	Implant loss
Campos <i>et al.</i> , 2005 ^[45]	IL-1 (-889) and IL-1B (+3953), IL-6	Early implant loss
Antoszewska <i>et al.</i> , 2010 ^[46]	IL-1B	Data on mini-implants
Andrioteilli <i>et al.</i> , 2008 ^[47]	IL-1	Peri-implantitis, Review article
Jacobi-Gresser <i>et al.</i> , 2013 ^[48]	IL1A (-889), IL1B (+3954), IL1RN (+2018), TNFA (-308)	<i>In vitro</i> study
Huynh-Ba G <i>et al.</i> , 2008 ^[49]	IL-1	Peri-implantitis-Review article
Wilson and Nunn, 1999 ^[50]	IL-1	Implant loss
Hamdy and Ebrahim, 2011 ^[51]	IL-1A (-889) and IL-1B (+3954)	Peri-implantitis
Hwang and Wang, 2007 ^[52]	IL-1	Review article
Dereka <i>et al.</i> , 2012 ^[53]		Systemic review article
Bormann <i>et al.</i> , 2010 ^[21]		Review article
Laine <i>et al.</i> , 2006 ^[22]	IL-1A (-889), IL-1B (+3953), IL-1B (-511)	Peri-implantitis
Greenstein G <i>et al.</i> , 2002 ^[27]	IL1A+4845 and IL1B+3954	Periodontitis
Greenstein and Hart, 2002 ^[28]	IL-1A+4845 and IL-1B+3954	Chronic periodontitis
Petkovic <i>et al.</i> , 2010 ^[23]	IL-1 β , TNF- α , IL-8, MIP-1 α	Peri-implantitis
Dirschnabel <i>et al.</i> , 2011 ^[39]	IL1B (C-511T)	Implant loss
Hao <i>et al.</i> , 2013 ^[29]	IL-1 α , IL-1 β and IL-1RN	Chronic periodontitis
Jansson <i>et al.</i> , 2005 ^[54]	IL-1	Early implant loss in patient under periodontal therapy
Rabel and Köhler, 2006 ^[55]	IL-1	Implant loss in periodontally compromised patients
Montes CC <i>et al.</i> , 2009 ^[40]	IL1B (C+3954T) and IL1RN	Implant loss
De Boever and De Boever, 2006 ^[30]	IL-1	Peri-implantitis, peri-mucocitis in patients with aggressive periodontitis
Lachmann <i>et al.</i> , 2007 ^[24]	IL-1 (-889), IL-1B (3954)	Peri-implantitis
Perala <i>et al.</i> , 1992 ^[56]	IL-1 β , TNF- α	Implant loss
Baradaran-Rahimi <i>et al.</i> , 2010 ^[31]	IL-1	Periodontitis
Santiago Junior <i>et al.</i> , 2018 ^[57]	IL-1B, IL-1 γ , TNF α	Review article
Alvim-Pereira <i>et al.</i> , 2008 ^[58]	IL-1A, IL-1B, IL-2, IL-6, BMP, MMP, TNF- α	Review article
Ghassib <i>et al.</i> , 2018 ^[59]	IL-1 β , IL-6, TNF- α , MMP-8	Review article
Schultze-Mosgau <i>et al.</i> , 2006 ^[60]	IL-1B, TGF β 1	Study on soft tissues

IL: Interleukin, MMP: Matrix metalloproteinase, BMP: Bone morphogenetic protein, TNF: Tumor necrosis factor, TGF: Transforming growth factor, MIP: Macrophage inflammatory protein, TNFA: Tumor necrosis factor-alpha

Table 2: Excluded studies and the reason of exclusion

Authors	Reasons for exclusion of full text articles
Grucia <i>et al.</i> , 2004 ^[34]	Bone loss was evaluated after 8-15 years and subjects were smokers
Feloutzis <i>et al.</i> , 2003 ^[10]	Bone loss was evaluated after the prosthetic rehabilitation and 5.6 years average thereafter
Al-Askar <i>et al.</i> , 2018 ^[19]	Study on diabetics, follow-up information missing

studies^[10,19,20,22-24,27-31,33,34,51,54-56] in the available literature reported that individuals carrying a particular genotype of IL-1 gene have been linked “directly or indirectly” to increased susceptibility to crestal bone loss around the natural teeth and/or dental implants. Most of the studies^[20,22-24,27-31,51,54-56] were related to bone loss as a feature of the progression of periodontitis or peri-implantitis and hence were omitted from the present meta-analysis. Some studies^[10,19,33,34] were excluded from the present review because of the chances of co-existence of multiple risks or confounding factors for bone loss, as in them, bone loss measurements were carried out after prosthetic loading. Only two studies,^[3,7] fulfilling the eligibility criteria of the

**Figure 3: Forest plot of comparison: IL-1A-889 gene**

present review, which have had evaluated the association of IL-1 gene polymorphisms and ECBL were thereby included.

Included studies in the present analysis were observational studies with statistically homogenized ($P > 0.05$) samples for known risk factors for bone loss such as age, gender, and menopausal status as well as bone quality. Thus, these variables did not influence the outcome of the present meta-analysis. Heterogeneity was acceptable and a random effect model was followed for meta-analysis.

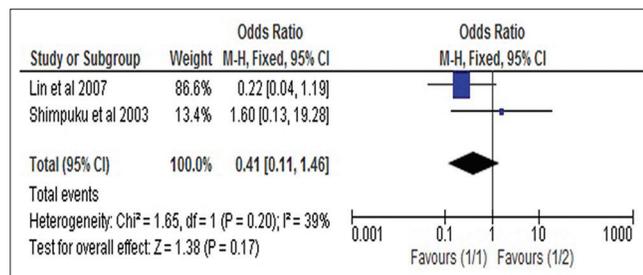
Table 3: Characteristics of the included studies

Characteristics	Lin <i>et al.</i> ^[7]	Shimpuku <i>et al.</i> ^[3]
Publication year	2007	2003
Study design	Prospective	Prospective
Country of origin	China	Japan
Ethnicity	Asian	Asian
Age range (years)	18-67	29-74
Mean age (years) (cases/controls)	44.24±12.114/41.30±13.376	54.2±12.2/55.9±6.6
Gender distribution (male/female) (cases/controls)	(19/10)/(13/17)	(5/12)/(10/12)
Postmenopausal women (yes/no) (cases/controls)	(3/7)/(11/6)	(8/4)/(8/4)
Bone quality (Type 3/Type 2) (cases/controls)	(17/12)/(15/15)	(4/13)/(6/16)
Number of patients at the beginning of the study	59	39
Drop out	0	0
Number of implants placed	143	251
Mean healing period (maxillary/mandibular)	Not reported	6.8/4.1 months
Implant failed	0	0
Outcome	Marginal bone loss	Marginal bone loss
Implants with bone loss	32	36
Patients with/without bone loss (cases/controls)	29/30	17/22
Baseline radiograph	After implant placement	After implant placement
Follow-up radiograph	Before second-stage surgery	Before second-stage surgery
Standardized radiograph	Panoramic	Unclear
Gene polymorphism studied	IL-1A-889, IL-1B-511, IL-1B+3954	IL-1A-889, IL-1B-511, IL-1B+3954
Examiner blinding for genotypes	Yes	Yes
Calibration of examiners	Not reported	Not reported
Result-gene polymorphism associated with bone loss	Significant association of IL-1B-511 (2/2)	Significant association of IL-1B-511 (2/2)

IL: Interleukin

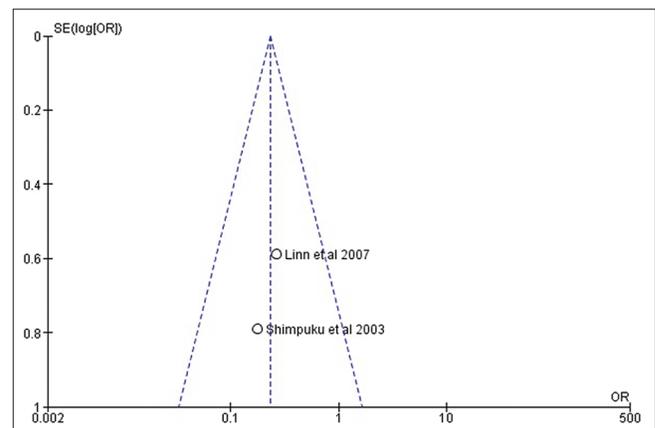
Table 4: A Cochrane risk of bias assessment tool for nonrandomized studies of interventions

Study	Bias due to confounding	Bias in selection of participants	Bias in intervention measurements	Bias due to intervention departures	Missing data bias	Bias in measuring outcomes	Reported results bias	Other bias	Pooled bias
Shimpuku H <i>et al.</i>	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Linn YH <i>et al.</i>	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk

**Figure 4: Forest plot of comparison: IL-1B+3954 gene**

The null hypothesis was accepted since forest plots of an association indicate that there has been a significant association of IL-1 gene and ECBL as evident through pooled results of the included studies. The presence of IL-1B-511 (2/2) genotype has been identified as a risk factor independent of age, gender, menopausal status, and bone quality for the occurrence of marginal bone loss around dental implants before stage-two surgery (OR = 0.23, 95% CI = 0.09–0.58, $P = 0.002$).

There was no significant association found among other (IL-1A-889 and IL-1B+3954) genetic variations of the IL-1 gene (IL-1A-889 gene: OR = 0.96, 95% CI = 0.36–2.53, $P = 0.93$; IL-1B+3954 gene: OR = 0.41,

**Figure 5: Funnel plot for risk of bias assessment**

95% CI = 0.11–1.46, $P = 0.17$). In fact IL-1A-889 (2/2) and IL-1B+3954 (2/2) genotype was not detected in any participant of both the included studies.

Kornman *et al.*^[17] suggested for the first time the genetic susceptibility of the composite genotype of IL-1A-889 and IL-1B+3954 as a genetic vulnerability marker linked with an elevated risk for severe chronic periodontitis. Thereafter, studies on the association of

IL-1 gene biomarker and crestal bone loss have come into existence.^[3,7,10,19,34] Three systematic reviews and two meta-analyses studies assessed the possible involvement of the genotypic variations of IL-1 gene in various peri-implant diseases.^[21,42,47,49,53] Contrasting opinion exists among these reviews regarding inclusion criteria, search strategies, and focused questionnaires. A systematic review by Dereka *et al.*^[53] was focused on the genetic predisposition of the implant biological complications including peri-implantitis and implant failures. They concluded that there was no significant association between genetic polymorphisms and implant loss mediated through biological complications; perhaps, they reported some link toward occurrences of peri-implantitis and IL-1 genotype. Other reviews by Andreiotelli *et al.*^[47] and Bormann *et al.*^[21] and meta-analysis by Huynh-Ba *et al.*^[49] and Liao *et al.*^[42] were based on genetic associations with peri-implantitis only. Two systematic reviews^[21,47] on peri-implantitis only found insufficient evidence regarding these associations with IL-1 gene polymorphisms. Huynh-Ba *et al.*^[49] included two observational studies in their meta-analysis and found an insignificant association between annual crestal bone loss (a surrogate biomarker of peri-implantitis) and the IL-1 composite genotypes (IL-1A-889 and IL-1B+3954). Included studies (Gruica *et al.*^[34] and Feloutzis *et al.*^[10]) in the above-mentioned review were confounded by factors such as sex distribution, follow-up period, smoking status, blinding procedure, lack of a control group for comparison, and had measured bone loss after second-stage implant surgery and hence were excluded from the present meta-analysis. The meta-analysis results by Liao *et al.*^[42] were similar to the present meta-analysis results. However, their study was related to the association of IL-1 composite genotypes with peri-implant disease. They found a significant association of IL-1B-511 allele T carrier with peri-implant disease in Asian descents, while no significant association was identified for other composite genotypes of IL-1 gene (IL-1A-889 and IL-1B+3954) in Asian as well as European descents.

A recent meta-analysis on the use of IL-1B, IL-6, tumor necrosis factor- α , and MMP-8 gene polymorphisms to differentiate healthy implants, peri-implant mucositis, and peri-implantitis by Ghassib *et al.*^[59] observed that the mucositis group exhibited a significantly greater IL-1B level than the healthy implant group (standardized mean difference = 1.94, 95% CI = 0.87–3.35 and $P < 0.001$). They also found that in meta-analysis of four included studies, IL-1B level in mucositis site was comparable to that in peri-implantitis site (standardized mean difference = 1.52, 95% CI = -0.03–3.07 and $P = 0.055$). They concluded that in addition to other cytokines, IL-1B cytokines could

be used to differentiate healthy implants, peri-implant mucositis, and peri-implantitis.

Findings of the present review may help in the identification of individuals (through preoperative genetic screening) with greater risk for the ECBL and subsequently the implant failure, thereby assisting the health-care workers in developing customized treatment plans and prevention strategies so as to improve the success and survival rates of implants.

Limitations

The limitations of the study are following:

1. Included studies in the present review had a case-control design, meaning a particular characteristic was observed in two groups of subjects at one point in time
2. Although funnel plot and ACROBAT-NRSI tool showed low publication bias, there has been possibility of study biases because of the presence of confounding factors. For example, in the included studies, exact location (anterior or posterior) and length of edentulous span (single tooth gap or multiple tooth gaps) for implant placements were not specified, both maxillary and mandibular implants were included, minimum required available bone height and width for implant placement were not clear, and torque value range of inserted implants was not described in inclusion criteria. These are confounding factors for bone loss
3. The number of included studies in the meta-analysis is limited which contributes to the low power of the statistical test for publication bias
4. Lack of sample size and/or statistical power calculation. Small sample sizes and limited number of included studies, limits the author's ability to perform definitive stratification analysis to explore the multiple sources of heterogeneity. As reported by Ioannidis *et al.*,^[61] at least a couple thousand participants would have been needed in any study to draw a definite conclusion regarding involvement of the genetic risk factors for a particular characteristic or a disease
5. Since bone formation and resorption have been under the control of multiple factors, it is desirable to investigate, in subsequent studies, other genetic factors involved in bone metabolism
6. Finally, selection bias in the English language literature cannot be excluded.

CONCLUSIONS

Within the limitations of the present meta-analysis, the following conclusions were drawn:

1. There was an evidence of association of IL-1B-511 (2/2) genetic polymorphisms and increased ECBL in individuals of Asian ethnicity
2. No significant influences of other genetic polymorphisms of IL-1 gene (IL-1A-889, IL-1B+3954) were found with ECBL
3. The limited number of included studies and the presence of confounding factors restrict the author's ability to draw any definite conclusion
4. Well-designed observational studies based on the following parameters: adequately powered sample sizes, the inclusion of patients with different ethnicities, avoidance of potential sources of bias, and consideration of all possible confounding factors and its adjustment in the final analysis is required to support our findings.

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Conflicts of interest

There are no conflicts of interest.

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Acquired partial auricular defect rehabilitation aided by four-part mold technique and spectrophotometer

ABSTRACT

Patients with auricular defects benefit greatly by an ear prosthesis. However, during the fabrication of auricular prosthesis, difficulties can be faced in obtaining a satisfactory outcome, such as tearing of the prosthesis, fracture of the mold and poor color matching. An 18 year old male lost part of his left auricle in an assault and battery because of which the patient was suffering from adverse psychosocial impact. Surgical reconstruction was ruled out because of patient's desire and financial constraints. Partial auricular prosthesis using four part mold technique and spectrophotometer was fabricated leading to a desirable outcome. Four part mold technique prevented fracture of mold and made retrieval of prosthesis easier. Spectrophotometer reduced the duration of patient visit and the artistic skill required for colour matching in trial and error method.

Keywords: Acquired partial auricular defect, four-part mold technique, spectrophotometer

INTRODUCTION

Auricular defects can be briefly classified as congenital or acquired deformities. Acquired type usually occurs due to blunt trauma, thermal injuries, bite injuries in a battery and assault or due to dog bite, road traffic accidents, or surgical removal of tumoral lesions.^[1-4] Such patients usually face functional as well as psychological problems which in turn affects their social life. Being considerate in such aspects, reconstruction of these acquired defects should be performed to ensure a better quality of life.

Among various reconstructive options available either surgically or prosthetically, the choice usually depends on factors such as location, size, type of the defect, systemic or local health status, and preferences of the patient.^[5-7] Surgical reconstruction of the human ear is an extremely complex procedure. However, it has certain advantages over prosthetic options such as more stability, enhanced psychological benefit to patient, and elimination of defect site. In certain cases, where, surgical reconstruction is not considered suitable for reconstructing the defect, due to systemic, financial, or psychological causes or because

of recurrent failures, provision of prosthesis may be a better option for rehabilitation of ear defects.^[8,9] Unlike surgical reconstruction, usually, prosthetic rehabilitation has excellent esthetics as the prosthesis can be made to resemble the contralateral ear to maximum extent by sculpting.

Conventionally, three-part mold technique is performed during fabrication of the partial auricular prosthesis. One major problem faced with this three-part mold technique is

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the fracture of the elevated part of the mold, which fits into the natural concha and triangular fossa.^[10] The traditional method of color mixing involves trial and error method of mixing different pigments and dyes to the base with the disadvantage being unable to compensate for metamerism. The recent advancement, spectrophotometer compensates for metamerism making it superior choice for accurate, repeatable color measurement and reduces the patient's visit. This article gives insight in the fabrication of auricular silicone prosthesis using a four-part mold technique aided by spectrophotometer.

CASE REPORT

An 18-year-old male patient reported to the Department of Prosthodontics with the chief complaint of bad appearance of the face due to partial missing left ear. The patient had lost part of his auricle in an assault and battery 1 year back. On examination, the patient had normal hearing in both ears and partial left ear defect with missing helix, antihelix, scapha, concha cyma, and helix crus. Tragus, antitragus, and lobus of the left ear were retained [Figure 1]. Patient was informed of all possible options for reconstruction and their merits and demerits and consent for prosthetic rehabilitation was obtained.

A partial auricular prosthesis was fabricated with technique described in following manner.

1. Initially, petroleum jelly was applied around the surrounding area and hair to prevent the alginate from sticking to the tissues and for the easy removal of the impression. The patient's head was tilted with the auricular area parallel to the floor. External acoustic meatus was blocked with the cotton pellet to prevent the flow of impression material into the auditory canal. The modeling wax was shaped around the defect

to support the impression material. Impressions of both ears were made using irreversible hydrocolloid. (Zelgan, Dentsply India Pvt. Ltd., Delhi, India) The models were poured with Type-III gypsum product (Kalabhai Karson Pvt. Ltd., Mumbai, Maharashtra, India) [Figure 2a]

2. Donor impression was taken which resembled more or less with the patient's ear and modeling wax was poured into it. Further changes in the wax pattern over the adapted Poly Vinyl Chloride sheet were made comparing the patient's contralateral ear model. Try-in of the wax pattern was done to confirm symmetry in vertical and horizontal planes and marginal integrity with surrounding tissues. The projection of the ear in relation to the side of the head was also checked [Figure 2b]. The wax pattern was extended to cover the remnant ear as well so that it aided in additional retention with extended margins and better camouflage. Stippling was done on the wax pattern using gauze piece to mimic natural appearance. The wax prosthesis was sealed to the model, and the leading edge was thinned, to allow the silicone edges to feather out to the natural skin
3. To prevent mold fracture and aid easy retrieval of silicone material, a four-part mold was prepared. The base of the mold along with wax pattern merged to the cast was the first pour. Over the first pour, separating medium was applied, and the orientation grooves were made above and on the posterior part of the helix of the wax pattern in the first pour [Figure 2c]. The second pour was made with white dental stone (Orthokal, Kalabhai Karson, India) and allowed to set. For easy retrieval of the prosthesis, third pour with die stone was made in the center of the ear which had many depressed parts such as cyma and cavum. A die pin was placed in the third pour and allowed to



Figure 1: Patient's partial left ear defect

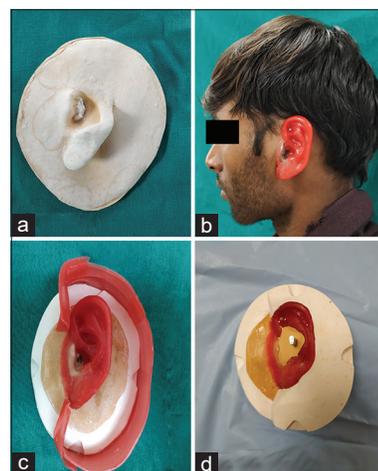


Figure 2: (a) Model of the defect. (b) Wax pattern try in. (c) Preparation for second part of mold to be poured. (d) Third pour in situ

set [Figure 2d]. Orientation grooves were placed in the second pour and separating media was applied over it. The fourth pour was made with white dental stone over it

4. Dewaxing was done leaving behind a four-part mold which could be packed with silicone [Figure 3a] Spectrophotometer (e-Skin) was used to match the color of patient's skin [Figure 3b]. According to quantity and coloration obtained from spectrophotometer readings, silicone mixing was done and packed into the four-part mold. Then, the mold with packed silicone was kept in the oven for 1 h at 100°C. Cured prosthesis was retrieved from the mold. Excess silicone was trimmed from the margins. Extrinsic coloration was done to match the exact patient's skin shade. Thereafter, the fit of the prosthesis was checked in place. The esthetics of the prosthesis was evaluated using visual analog scale and was scored to be excellent
5. For optimum retention of the prosthesis, the patient was advised to apply a thin coating of the adhesive (G609 Probond Adhesive) to the tissue side of the prosthesis and allowed to dry for 2 to 3 min until it cleared, before sticking [Figure 4a and b]. The patient was instructed to avoid excessive sun/dust exposure to increase life of prosthesis.^[11] The patient was recalled initially 1 week after prosthesis insertion and further at 1 month intervals for periodic evaluation and was found to be satisfied during the follow-up visit at 12 months.

DISCUSSION

In the traditional three-part mold technique, first pour was made with the mold in plaster up to the leading edge. Indentations were made in the helix area of the mold to allow the second pour of the mold to fit into the first mold precisely. After the second pour sets, third pour was made

to cover the wax pattern and the remaining second pour with indentations made on first and second pour. One major concern for this technique was probability of the fracture of the elevated portion of three pour mold could happen whenever the molds were being separated from each other. To overcome it, a four-piece mold fabrication was done with the extra pour being added as a third pour which filled up the depressed portions of the ear. The die pin placement in the third pour helped to accurately orient the fourth pour into the third pour. This four pour technique helped in retrieving the silicone from mold without tearing the prosthesis.

The third pour in this four-part mold technique may be made by different materials such as resin, putty, die stone, or dental stone. Here, preference of die stone was given over the resin, dental stone, and putty as the resin in dough stage when placed over the wax pattern of prosthesis could distort the carving done earlier, putty can inhibit the curing of silicone prosthesis and the die stone exhibits more rigidity than the dental stone. The exothermic reaction when compared between acrylic resin and gypsum products liberates heat of about 50–70 KJ/mol and 3900 cal/gmol (16.3 KJ/mol), respectively, making it obvious that gypsum products were less likely to distort wax pattern.

The spectrophotometer, being able to measure the amount of light absorbed by the skin, helped get instant readings and the exact quantity of different colored silicone to be mixed in appropriate amounts in contrast to traditional mixing. Thus, the usage of spectrophotometer gives an appreciable color matching, with minimum time consumption and reducing the patient's visit. The repeatability, accuracy, and recordability (aiding future prosthesis refabrication without repeat color matching) of



Figure 3: (a) Four-part mold. (b) Spectrophotometer showing readings



Figure 4: (a) Auricular prosthesis (lateral view). (b) Auricular prosthesis (profile view)

the spectrophotometer ensures its continued applicability in maxillofacial prosthetics in future as well. However, the extrinsic staining is required even after the usage of spectrophotometer for better results.

The retention of auricular prosthesis can be obtained either by the use of natural anatomical undercut, mechanical retention, adhesives, or extraoral implants. Various systems have been used to attach the prosthesis to the implant such as bar and clip retention, magnetic retention, bar splint/magnet retention, and ball attachment.^[12] The retention from the adequate anatomical structure allowed for the fabrication of prosthesis and further retention was obtained from adhesive.

Although the usage of adhesives is quite advantageous, there are certain limitations such as limited retention, potential for tissue irritation, and difficulty in orientation of the prosthesis, especially in patients with compromised manual dexterity.

CONCLUSION

Four-part mold technique helped to prevent fracture of mold and provided ease in retrieval of silicone prosthesis from the mold. Usage of spectrophotometer makes it easy for the prosthodontist to get an appreciable color matching with life-like appearance of the prosthesis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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CLINICAL RESEARCH

Association of interleukin-1, interleukin-6, collagen type I alpha 1, and osteocalcin gene polymorphisms with early crestal bone loss around submerged dental implants: A nested case control study

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ABSTRACT

Statement of problem. The reason for variations in peri-implant early crestal bone loss is unclear but may be due to genetic differences among individuals.

Purpose. The purpose of this nested case control study was to investigate the association of single-nucleotide polymorphisms of interleukin-1, interleukin-6, collagen type I alpha1, and osteocalcin genes to early crestal bone loss around submerged dental implants.

Material and methods. Dental implants were placed in the mandibular posterior region (single edentulous space) of 135 participants selected according to predetermined selection criteria. Bone mineral density measurement by using dual energy X-ray absorptiometry, cone beam computed tomography scans at the baseline and after 6 months, and interleukin-1A-889 A/G (rs1800587), interleukin-1B-511 G/A (rs16944), interleukin-1B+3954 (rs1143634), interleukin-6-572 C/G (rs1800796), collagen type I alpha1 A/C (rs1800012), and osteocalcin C/T (rs1800247) genotyping were performed in all participants. Early crestal bone loss measured around dental implants was used to group participants into clinically significant bone loss (BL)>0.5 mm and clinically nonsignificant bone loss (NBL)≤0.5 mm. Early crestal bone loss was calculated as the mean of the difference of bone levels at the baseline and bone levels after 6 months as measured with cone beam computed tomography scans. The obtained data for basic characteristics, early crestal bone loss, and genotyping were tabulated and compared by using a statistical software program ($\alpha=0.05$).

Results. AA genotype and the A allele frequency of interleukin-1B-511 and GG genotype and the G allele frequency of interleukin-6-572 were significantly higher in BL than in NBL ($P<0.05$). Multiple logistic analysis suggested that interleukin-1B-511 AA/GG+AG and interleukin-6-572 GG/CC+CG genotype expression were significantly associated with early crestal bone loss (AA/GG+AG; $P=0.014$, GG/CC+CG; $P=0.047$) around dental implants. Other risk factors were not significantly different ($P>0.05$).

Conclusions. Of the genes studied, individuals with interleukin-1B-511 AA (rs16944) or interleukin-6-572 GG (rs1800796) genotype had higher susceptibility to early crestal bone loss around dental implants. (J Prosthet Dent 2021;■:■-■)

Crestal bone loss (CBL) is typically identified around successfully osseointegrated dental implants regardless of the surgical approach (flap or flapless), placement (submerged or nonsubmerged), or loading protocols

(immediate or delayed). CBL in the range of 0.9 to 1.6 mm has been reported around submerged dental implants by the end of the first year in function, while CBL of only 0.05 to 0.13 mm has been reported after the first

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Clinical Implications

Genetic differences among individuals could explain the variation in peri-implant crestal bone loss. This study encourages dentists to consider the polymorphisms of the genes controlling proinflammatory cytokine production after dental implant installation as a screening tool for individuals needing dental implant treatment so that prevention strategies can be adopted or treatment procedures altered to optimize the prosthetic rehabilitation.

year; thus, CBL may affect the long-term outcome of dental implants and contribute to implant failure.^{1,2} Etiological factors for CBL may include surgical trauma, bone quality, biologic width, implant design, implant material, biomechanical loading, smoking, infection, metabolic diseases, and medications affecting bone metabolism.²⁻⁶ These appreciable causes for peri-implant bone loss have been reported to be invariable, absent, or minimal during the healing period (4 to 6 months) of submerged dental implants, although variable or higher peri-implant early crestal bone loss (ECBL) (before stage II surgery) among individuals has been observed. Probably, differences in the genes involved in the bone remodeling of individuals contribute to the occurrence and variation in ECBL.

The interleukin-1 (IL1) gene present on chromosome 2 and the interleukin-6 (IL6) gene located on chromosome 7 encode proinflammatory cytokines IL1 (IL1A and 1 B) and IL6, respectively, which function as mediators in various inflammatory responses (also after implant placement), as well as in bone metabolism.⁷⁻¹⁰ Polymorphisms in IL1A-889, IL1B-511, IL1B+3954, and IL6-572G/C have been associated with the increased production of cytokines, leading to increased susceptibility to periodontitis and osteoporosis.^{7,11-15} Studies of IL1A-889, IL1B-511, and IL1B+3954 polymorphisms have reported contradictory results for implant failure, periimplantitis, or crestal bone loss.^{11,16-18} Most of these studies had a small sample size with undefined inclusion and exclusion criteria.⁴ A significant effect of IL1B-511 on CBL has been revealed in Chinese and Japanese populations, but not in participants of European descent, indicating variability with different ethnicity.⁴

Polymorphisms of collagen type I alpha1 (COL1A1) and osteocalcin (BGP) genes encoding major osseous proteins of bone have been correlated with low bone mineral density (BMD) and systemic bone loss, as well as with periodontitis and alveolar bone loss.¹⁹⁻²³ COL1A1 polymorphism has also been identified as a marker for

increased bone fragility rather than low BMD.²⁰ BGP-298 C>T polymorphism regulates the expression of the osteocalcin gene and has been associated with osteoporosis and periodontitis.^{24,25} Overall data suggest that COL1A1 and BGP gene polymorphisms affect the bone metabolism and might therefore be of interest as a susceptibility marker for CBL around dental implants.

Studies that identified the causes of the occurrence and variation of ECBL and determined the mechanism of peri-implant ECBL are lacking, and the authors are unaware of any studies into the peri-implant ECBL and single-nucleotide polymorphisms (SNPs) of the IL6, COL1A1, and BGP genes. Therefore, the purpose of the present study was to investigate the association of SNPs in the IL1, IL6, COL1A1, and BGP genes involved in bone remodeling and the extent of ECBL around submerged dental implants. The null hypothesis was that no association of gene polymorphisms and ECBL would be found around dental implants.

MATERIAL AND METHODS

This nested case control study was conducted in King George Medical University, Lucknow, India, from June 2017 to September 2020 in accordance with the ethical principles recommended by the present version of the Declaration of Helsinki, the ICH-GCP, or ISO EN 1415 and was approved by the Institutional Review Board of Office of Research Cell (reg. no. ECR/262/Ins/UP/2013). As logistic regression analysis would be conducted to determine the association between ECBL around dental implants and genetic polymorphisms, a sample size of 133 was estimated assuming bone loss (50%) with an odds ratio of 3.00 and at a 5% level of significance and power of 80%.⁹ Therefore, a cohort of 135 healthy individuals requiring dental implant treatment for a single missing mandibular posterior tooth and fulfilling the predefined eligibility criteria were recruited. The criteria for inclusion were age between 18 and 65 years, sufficient bone volume at edentulous sites (more than 11.0 mm in height and 8.0 mm in width) as evident on preoperative cone beam computed tomography (CBCT) scans, fully healed bone sites (at least 6 months after extraction), with a mucosal thickness >2 mm, along with sufficient width of keratinized gingiva at implant sites, no medical contraindication for implant surgery, signed informed consent for participation, and permission to use obtained data for research purposes. The exclusion criteria were poor general or oral health, known genetic disorder or syndrome, medications affecting bone metabolism, previous history of radiotherapy or chemotherapy, and signs of acute infection around alveolar bone or bone defects (severe bony concavity or lack of bone due to infection, trauma, or tumor at planned implant site) as determined by CBCT.



Figure 1. Osteotomy at edentulous site. A, Preoperative edentulous site. B, Bone exposure after full-thickness flap reflection and osteotomy.

The age, sex, body weight, body mass index, smoking status, menstruation status, bone quality at implant sites,²⁶ and BMD and T-score (measured through dual energy X-ray absorptiometry) of right femoral neck of participants were recorded. Participants were categorized based on their T-score values according to World Health Organization (WHO) criteria: osteoporosis, ≤ -2.5 ; osteopenia, -1 to -2.5 ; and normal, ≥ -1 standard deviations.^{27,28}

Bone-level dental implants (Myriad plus; Equinox Technologies) of $\text{\O}4.5\text{-mm}$ and 9.5-mm or 11-mm length (according to available bone volume) were placed with the standard flap approach of traditional 2-stage implant surgery.²⁹ After the administration of local anesthesia (Xicaine; ICPA Health Products), an incision along the crest of the ridge with releasing incisions (away from the site) was made at the implant site to raise a full-thickness mucoperiosteal flap to expose the bone. A surgical template was used to guide the placement of the dental implant. The implant site osteotomy was begun with a 2-mm end-cutting pilot drill, and then sequentially increasing diameter bone drills were used to enlarge the osteotomy site to a diameter similar to that of the implant (Fig. 1). The implant was inserted with a low-speed, high-torque hand piece (X-SG20L; NSK) or a torque ratchet with a torque value of at least 30 Ncm . The cover screw was tightened, and flaps were closed with $3\text{-}0$ silk sutures (Ethicon; Johnson & Johnson) (Fig. 2). Peri-implant crestal bone thickness was more than 1.5 mm , and no soft tissue or bone augmentation procedure was performed during or after the implant surgery. Standard postoperative and oral hygiene instructions, which included the use of ice packs, the avoidance of brushing and trauma on the surgical site, a soft diet for 7 postoperative days, and a 0.2% chlorohexidine mouthwash twice daily for 10 postoperative days, were given to all participants.

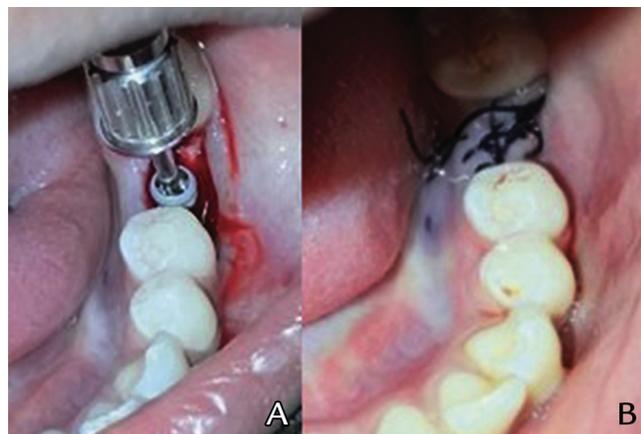


Figure 2. Dental implant insertion and flap closure. A, Dental implant insertion in prepared osteotomy site. B, Flap closure with suture.

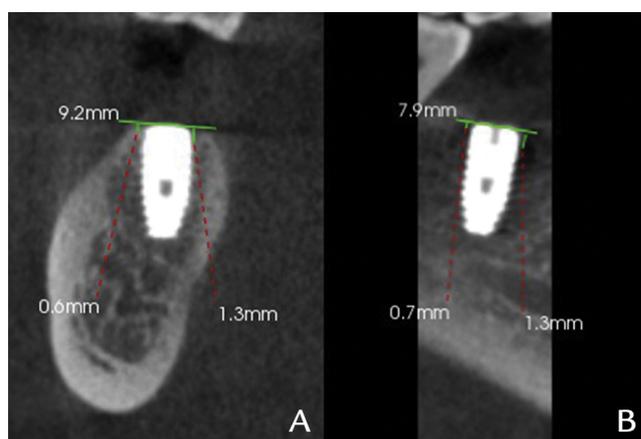


Figure 3. Bone level measurement around dental implant. A, Buccal and lingual side. B, Mesial and distal side.

Change in crestal bone levels were evaluated from CBCT scans made immediately (baseline) after stage I surgery and before stage II surgery (6 months). The digital imaging and communication in medicine (DICOM) files captured with the CBCT scan were evaluated on a computer screen by 2 observers (A.C., M.A.) at different times on the reformatted sagittal and coronal planes by using a software application (CS9300; Carestream). Lines were drawn from the top of the implant along the collar surface of each implant on the buccal, lingual, mesial, and distal sides to measure the first crestal bone to implant contact level (Fig. 3).^{30,31} When intrarater or interrater differences were greater than 0.1 mm , both observers examined the scans together to reach a consensus on the position of the first bone-to-implant contact. Subsequently, measurements were repeated independently. The ECBL of each participant was calculated as a mean of the difference in bone levels at the baseline and after 6 months, and participants were grouped under BL, clinically significant ECBL ($>0.5\text{ mm}$); or NBL, clinically nonsignificant ECBL ($\leq 0.5\text{ mm}$).¹¹

Table 1. TaqMan real-time PCR conditions for SNP genotyping

S.No	SNP	Gene	Gene Name	Context Sequence	Taq-Man Real Time PCR Condition
1.	rs1800012	COL1A1	Collagen type I alpha 1	GGGAGGTCCAGCCCTCATCCGCCACCATTCCTGGGCAGGTGGGTGGCG	Pre-PCR read holding stage: 60 °C for 1 min; holding stage: at 95 °C for 10 min; cycling stage: 40 cycles at 95 °C for 15 s and 60 °C for 1 min; post-PCR holding at 60 °C for 1 min.
2.	rs1800587	IL1A-889	Interleukin-1-alpha	GATTTTACATATGAGCCTCAATGAGTGTTCCTGGTACTATTATTAAAG	Pre-PCR read holding stage: 60 °C for 1 min; holding stage: at 95 °C for 10 min; cycling stage: 40 cycles at 95 °C for 15 s and 60 °C for 1 min; post-PCR holding at 60 °C for 1 min.
3.	rs1800796	IL6-572	Interleukin 6	ATGGCCAGGCAGTTCTACAACAGCCCGCTCACAGGGAGAGCCAGAACACAGA	Pre-PCR read holding stage: 60 °C for 1 min; holding stage: at 95 °C for 10 min; cycling stage: 40 cycles at 95 °C for 15 s and 60 °C for 1 min; post-PCR holding at 60 °C for 1 min.
4.	rs16944	IL1B-511	Interleukin 1 beta	CTACCTTGGGTGCTGTCTCTGCTCAGGAGCTCTCTGTCAATTGCAGGAGC	Pre-PCR read holding stage: 60 °C for 1 min; holding stage: at 95 °C for 10 min; cycling stage: 40 cycles at 95 °C for 15 s and 60 °C for 1 min; post-PCR holding at 60 °C for 1 min.
5.	rs1800247	BGLAP	Bone-gamma carboxylglutamate protein (osteocalcin)	CCGCAGCTCCCAACCACAATATCTCTTGGGGTTTGGCCTACGGAGCTGGGG	Pre-PCR read holding stage: 60 °C for 1 min; holding stage: at 95 °C for 10 min; cycling stage: 40 cycles at 95 °C for 15 s and 60 °C for 1 min; post-PCR holding at 60 °C for 1 min.
6.	rs1143634	IL1B+3954	Interleukin 1 beta	AGGACCACTCATTGCCTGATGTGCTGAAGAGATCGTTCTGGGC	Pre-PCR read holding stage: 60 °C for 1 min; holding stage: at 95 °C for 10 min; cycling stage: 40 cycles at 95 °C for 15 s and 60 °C for 1 min; post-PCR holding at 60 °C for 1 min.

PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism.

A single blood draw (5 mL) of all participants was done and collected in ethylenediaminetetraacetic acid (EDTA) vials. Deoxyribonucleic acid (DNA) was isolated from the blood of all participants by using a DNA isolation kit (QIAamp; Qiagen, Hilden) according to the manufacturer's instructions. The quality and concentration of DNA were evaluated by using 0.8% agarose gel electrophoresis with a spectrophotometer (Quawell; Quawell Technology Inc) and a fluorimeter (QbitBR; Agilent). DNA having an absorption ratio A₂₆₀/A₂₈₀ greater than or equal to 1.8 was considered for TaqMan SNP genotyping assays for reference SNP cluster identification rs1800012, rs1800587, rs1800796, rs16944, rs1800247, and rs1143634 according to the manufacturer's instructions. The designed unlabeled polymerase chain reaction (PCR) primers and TaqMan minor groove binder (MGB) probes (FAM and VIC dye-labeled to detect alleles sequence) in a 40×TaqMan SNP genotyping assay mix (Applied Biosystems; Thermo Fisher Scientific) were used to genotype all reference SNP cluster identifications. Alleles were scored in each well by using TaqMan genotyping master mix (Applied Biosystems; Thermo Fisher Scientific) and 20 ng of specific genomic DNA and following the universal thermal cycling parameters according to the recommended protocol (Table 1). Each sample was processed in triplicate, and a negative control was also processed for real-time analysis with every 96-well format assay. The raw data were obtained by using the step one plus real-time PCR system

(Applied Biosystems; Thermo Fisher Scientific) and were analyzed with a TaqMan genotyper software program (Applied Biosystems; Thermo Fisher Scientific). The genotype call was evaluated with a threshold quality value=0.94.

The data were statistically analyzed by using a statistical software program (IBM SPSS Statistics, v21.0; IBM Corp). Continuous variables were denoted as mean ±standard deviation (SD) and compared by using the student *t* test, while categorical variables were analyzed with the chi-square test (χ^2). Odds ratios were calculated to determine the association of BL and NBL with genetic polymorphisms. Multiple logistic regression analysis was performed for variables of ECBL and IL1B-511 and IL6-572 genotypes ($\alpha=.05$).

RESULTS

Dental implants were placed in 135 participants between June 2017 and March 2020. Data were recorded until September 2020. A total of 131 participants (3 dropped out and 1 implant failure because of healing complication) were grouped according to the calculated ECBL (BL [>0.05]=68, NBL [≤ 0.05]=63), and gene polymorphism analysis was performed (Fig. 4). On comparison, both groups were statistically similar in age, sex, body weight category, smoking status, BMD, BMD category, T-score, torque value of the implant placement, and bone quality at implant site ($P>.05$), but the mean difference was

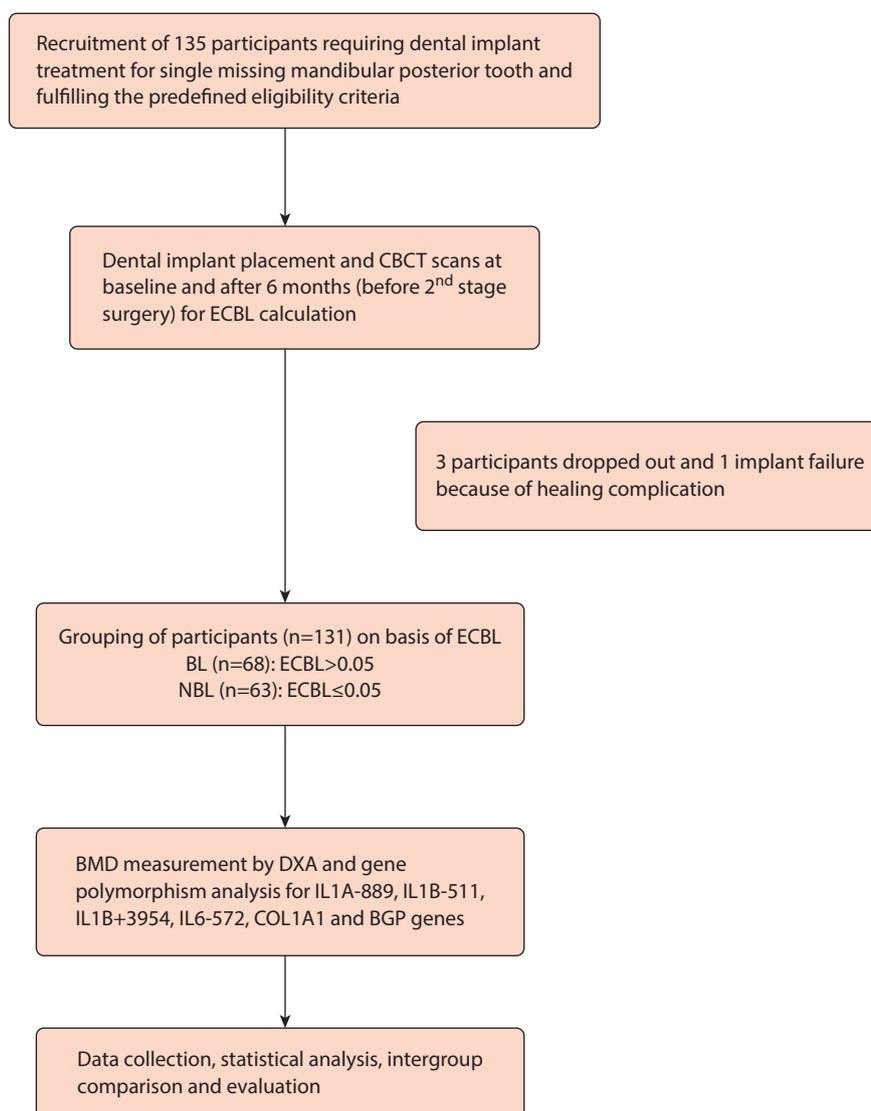


Figure 4. Study flow chart summarizing group allocation and methodology. BGP, osteocalcin; BL, clinically significant early crestal bone loss; BMD, bone mineral density; CBCT, cone beam computed tomography; COL1A1, collagen type 1 alpha 1; DEXA, dual energy X-ray absorptiometry; IL1A-889, interleukin 1A-889; IL1B-511, interleukin 1B-511; IL1B +3954, interleukin 1B +3954; IL6-572, interleukin 6-572; NBL, clinically nonsignificant early crestal bone loss.

statistically significant for several menopausal women ($\chi^2=7.67$; $P=.006$) (Table 2).

Table 3 showed the association of BL and NBL with different genotypic and allelic frequencies. For IL1B-511, AA genotypes were associated with significantly higher odds of ECBL than AG ($P=.007$; OR=3.14 [95% CI=0.43 to 6.92]) and GG genotypes ($P=.015$; OR=4.3 [95% CI=1.44 to 13.02]). The frequency of allele A as compared with allele G was associated with significantly higher odds of ECBL ($P=.002$; OR=2.252 [95% CI=1.355 to 3.744]). Similarly, CC genotypes of IL6-572 were associated with significantly lower odds of ECBL than GG genotypes ($P=.003$; OR=0.15 [95% CI=0.05 to 0.49]). The frequency of allele C was associated with significantly lower odds of ECBL than allele G ($P=.002$; OR=0.39 [95% CI=1.550 to 4.336]). No significant association of IL1A-

889, IL1B+3954, COL1A1, and BGP genotypic or allelic frequencies with ECBL was found. The multiple logistic regression analysis was performed to determine the odds ratios of variables of ECBL and IL1B-511 and IL6-572 genotypes (Tables 4 and 5). IL1B-511 AA versus GG+AG and IL6-572 GG versus CC+CG genotypic expression were found to be significantly associated with outcome ECBL (AA versus GG+AG; AOR=0.658; 95% CI=0.126 to 0.024; $P=.014$, GG versus CC+CG; AOR=0.211; 95% CI=0.045 to 0.979; $P=.047$).

DISCUSSION

The authors are unaware of previous investigations that suggested an association of IL1, IL 6, COL1A1, and BGP gene polymorphisms with peri-implant ECBL with

Table 2. Basic characteristics of participants of both groups

S. No.	Characteristic	BL (ECBL>0.5) (n=68)		NBL (ECBL≤0.5) (n=63)		Statistical Significance
1.	Age (mean, SD)	49.13	16.12	44.22	14.80	$t=-1.81$; $P=.073$
2.	Sex					
	Male (n, %)	34	47.9	37	52.1	$\chi^2=1.04$; $P=.316$
	Female (n, %)	34	56.7	26	43.3	
3.	BMI (mean, SD) in Kg/m ²	24.85	3.61	24.57	5.26	$t=-0.36$; $P=.720$
4.	Weight category (WHO criteria)					
	Normal (n, %)	32	52.5	29	47.5	$\chi^2=8.58$; $P=.035$
	Overweight (n, %)	32	61.5	20	38.5	
	Obese (n, %)	1	14.3	6	85.7	
	Underweight (n, %)	3	27.3	8	72.7	
5.	T-score (mean, SD)	-1.18	1.08	-.83	1.02	$t=1.89$; $P=.061$
6.	BMD (mean, SD)	.89	.16	.95	.15	$t=1.88$; $P=.062$
7.	BMD category (WHO criteria)					
	Normal (n, %)	31	48.4	33	51.6	$\chi^2=0.604$; $P=.437$
	Osteopenia+osteoporosis (n, %)	37	54.4	30	55.6	
8.	Torque (mean, SD)	34.93	6.94	34.84	6.47	$t=-0.73$; $P=.942$
9.	Smoking					
	Yes (n, %)	6	33.3	12	66.7	$\chi^2=2.88$; $P=.089$
	No (n, %)	62	54.9	51	45.1	
10.	Menopausal status					
	Yes (n, %)	20	76.9	6	23.1	$\chi^2=7.67$; $P=.006$
	No (n, %)	14	41.2	20	58.8	
11.	Bone quality					
	I (n, %)	0	0	3	100.0	$\chi^2=5.282$; $P=.0712$
	II (n, %)	47	49.5	48	50.5	
	III (n, %)	21	67.7	12	36.3	

BL, clinically significant early crestal bone loss; BMD, bone mineral density; BMI, body mass index; ECBL, early crestal bone loss; NBL, clinically nonsignificant early crestal bone loss; SD, standard deviation; WHO, world health organization.

appropriate sample size calculation and clearly pre-defined inclusion and exclusion criteria, bone mineral density measurement, particular edentulous site for implant placement, and 3-dimensional measurement of ECBL with CBCT. As a result, the outcomes of this research may be more precise, suggesting a true impact of genetic traits on ECBL. The results indicated the association of IL1B-511 and IL6-572 gene polymorphisms with peri-implant ECBL; therefore, the null hypothesis was rejected.

In the present study, both groups were homogeneous regarding age, sex, body weight category, T-score, mean BMD, and smoking habit, as well as type of implant, surgical method for dental implant placement, and torque value, and several confounders were controlled to minimize bias. Only participants of Indian ethnicity were included as the ethnicity and race affect the frequency of gene polymorphisms and susceptibility to a specific disease.¹⁶ Therefore, the genotypic frequency in a specific ethnic group should be identified, and the result obtained

Table 3. Association of crestal bone loss groups with gene frequency and allele frequency of different genetic polymorphisms

Gene (rs number)	Genotype	Crestal Bone Loss Group				OR (95% CI)	P
		BL (>0.5)		NBL (≤0.5)			
		n	%	n	%		
IL1A-889 (rs1800587)	AA	7	10.3	6	9.5	Ref.	—
	AG	24	35.3	25	39.7	1.22 (0.36-4.14)	.755
	GG	37	54.4	32	50.8	1.01 (0.31-3.31)	.988
	A	38	27.9	37	29.7	0.93 (0.55-1.59)	.906
IL1B-511 (rs16944)	G	98	72.1	89	70.3	—	—
	AA	35	51.5	15	23.8	Ref.	—
	AG	26	38.2	35	55.6	3.14 (0.43-6.92)	.007
	GG	7	10.3	13	20.6	4.33 (1.44-13.02)	.015
	A	96	70.6	65	51.9	2.25 (1.36-3.74)	.002
IL1B +3954 (rs1143634)	G	40	29.4	61	48.1	—	—
	CC	37	54.4	34	54.0	Ref.	—
	CT	27	39.7	26	41.3	1.04 (0.51-2.14)	.897
	TT	4	5.9	3	4.8	0.82 (0.17-3.92)	.799
	C	101	74.3	94	74.6	0.98 (0.56-1.73)	.950
IL6-572 (rs1800796)	T	35	25.7	32	25.4	—	—
	CC	5	7.4	13	20.6	Ref.	—
	CG	27	39.7	36	57.1	0.51 (0.16-1.61)	.378
	GG	36	52.9	14	22.2	0.15 (0.05-0.49)	.003
	C	37	27.2	62	49.2	0.39 (0.23-0.65)	.004
COL1A1 (rs1800012)	G	99	72.8	64	50.8	—	—
	CC	54	79.4	50	79.4	Ref.	—
	AC	14	20.6	13	20.6	1.003 (0.43-2.34)	.994
	C	122	89.7	113	89.6	1.002 (0.44-2.29)	.996
BGP (rs1800247)	A	14	10.3	13	10.4	—	—
	CC	9	13.2	6	9.5	Ref.	—
	CT	15	22.1	22	34.9	2.20 (0.65-7.48)	.333
	TT	44	64.7	35	55.6	1.19 (0.39-3.67)	.981
	C	33	24.3	34	26.7	0.867 (0.49-1.51)	.717
T	103	75.7	92	73.3	—	—	

BGP, osteocalcin; BL, clinically significant early crestal bone loss; CI, Confidence interval; COL1A1, collagen type 1 alpha 1; IL1A-889, interleukin 1A-889; IL1B-511, interleukin 1B-511; IL1B +3954, interleukin 1B +3954; IL6-572, interleukin 6-572; NBL, clinically nonsignificant early crestal bone loss; OR, odd ratio.

from 1 ethnic group should not be generalized to another.¹⁶

Changes in crestal bone levels were evaluated from CBCT scans and bone mineral density from DEXA. CBCT scans can evaluate the bone quantity with precision because of their 3-dimensional nature, ensuring the buccal and lingual peri-implant bone level measurements along with mesial and distal measurements were sensitive enough to quantify 1 mm or less of bone loss.^{30,31} However, artifacts can lower the image quality of CBCT scans.³¹ Previous studies were limited by the use of conventional radiographs.^{11,17} However, CBCT imaging is a reliable diagnostic tool and has been used in previous studies to measure bone loss in the vicinity of titanium dental implants in spite of the associated artifacts.³¹ DEXA is the standard technique for estimating bone mineral density because of its reproducibility, large

Table 4. Multiple logistic regression analysis for variables of ECBL and IL1B-511

Variable	P	AOR	95.0% CI for AOR	
			Lower	Upper
Age (y)	.356	1.043	0.954	1.141
Sex (male/female)	1.000	0.000	0.000	0.000
BMI	.270	0.906	0.759	1.080
T-score	.403	2.671	0.267	26.749
BMD	.499	0.003	0.000	8.216E4
Smoking (yes/no)	.862	1.260	0.093	17.014
Meno pause (yes/no)	.261	0.249	0.022	2.810
Bone Quality	.677	1.546	0.200	11.964
Torque	.119	1.105	0.974	1.253
IL1B-511 (AA/GA+GG)	.014	0.126	0.024	0.658
Constant	.999	2.373E11	–	–

AOR, adjusted odd ratio; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; ECBL, early crestal bone loss; IL1B-511, interleukin1B-511.

normative data, noninvasive nature, short procedure time, and minimal radiation exposure.²⁸ The total radiation exposure (CBCT: 5 to 38.3 μ Sv, DEXA: 0.1 to 0.4 μ Sv) did not exceed the recommended annual dose limit (1 mSv).³² Radiation exposure from CBCT and DEXA scans were minimized.

Smoking has been documented as a risk factor for increased CBL because of poor bone healing and the increased risk of peri-implantitis.^{5,6} In the present study, the number of smokers and nonsmokers in both groups was not statistically significantly different ($P=.089$). The crestal bone levels were measured at 6 months before the dental implants were exposed in the oral environment, thus minimizing the chance of infection.

In the present study, AA genotypes of IL1B-511 were significantly associated with increased susceptibility to ECBL as compared with AG ($P=.007$) and GG genotypes ($P=.015$). However, no significant association of ECBL with IL1A-889 and ILB+3984 genotypes was found. These results were consistent with 2 previous studies of Asian populations.^{11,17} IL1B-511 gene polymorphism has been identified as a genetic marker for noninfectious alveolar bone loss before connection of the abutments because of increased IL1B production in individuals carrying A alleles compared with that in those with G alleles.¹⁷ Kornman et al¹² suggested that peri-implant CBL after abutment connection can be associated with IL1A-889 and IL1B+3954 polymorphism. Cosyn et al¹⁸ established a significant effect of the IL1A-889 and the IL1B+3954 but not the IL1B-511 gene on early implant failure in white individuals. Their study was performed with a limited sample size (14 participants) and had a retrospective study design. Therefore, the full retrieval of reliable information on possible confounders was not possible.

The present study also revealed increased susceptibility to ECBL in individuals having an IL6-572 G allele or

Table 5. Multiple logistic regression analysis for variables of ECBL and IL6-572

Variable	P	AOR	95.0% CI for AOR	
			Lower	Upper
Age (y)	.109	1.074	0.984	1.171
Sex (male/female)	1.000	0.000	0.000	0.000
BMI	.166	0.876	0.726	1.057
T-score	.173	4.561	0.513	40.520
BMD	.316	0.000	0.000	2.797E3
Smoking (yes/no)	.478	2.474	0.203	30.209
Meno pause (yes/no)	.544	0.512	0.059	4.461
Bone Quality	.941	0.929	0.132	6.551
Torque	.052	1.130	0.999	1.279
IL6-572 (GG/CC+CG)	.047	0.211	0.045	0.979
Constant	.999	4.685E11	–	–

AOR, adjusted odd ratio; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; ECBL, early crestal bone loss; IL6-572, interleukin6-572.

GG genotype. The authors are unaware of a direct explanation for this significant association in the current literature, but increased risk of chronic periodontal disease has been reported in participants with IL6-572 GG genotype in studies and meta-analyses because of its role in periodontal inflammation and alveolar bone metabolism.¹³⁻¹⁵ The possible mechanism of increased susceptibility to peri-implant ECBL in IL6-572 GG genotypes may be the overexpression of IL-6 cytokine-mediated inflammatory response after implant placement. The promoter region of the IL-6 gene controls the IL6 transcription through a complex pathway which is regulated by these polymorphisms.¹³

The present study also investigated the polymorphisms of genes (COLIA1 and BGP) encoding the structural proteins of the bone and found no significant association with the severity of ECBL. The association between periodontitis and COLIA1 and BGP gene polymorphisms has been identified, but the study results were contradictory.^{22,23,25} Suzuki et al²² reported a positive correlation between aggressive periodontitis and SNPs of the COLIA1 gene. However, Sakellari et al²³ observed no differences in the distribution and frequencies of COLIA1 genotypes between individuals with or without periodontitis (chronic or aggressive) in participants of Greek origin. Kaulika et al²⁵ reported no significant association between the severity of periodontitis and BGP gene polymorphisms in an Indonesian population.

Limitations of this observational study included that selection bias was unavoidable because this study was single-centered, enrolled participants who visited a single hospital, and included participants of only Indian ethnicity. Additionally, the study was observational, and the comparison was cross-sectional, not providing the highest level of evidence. Therefore, further studies with a large sample size and the random allocation of

participants into experimental groups are required to confirm these results. Furthermore, more studies are needed to evaluate an association between other cytokine genes involved in bone formation (eg, IL-10) and bone resorption, for example, IL-2, TNF- α , and MMP, during the healing period of dental implants.

CONCLUSIONS

Based on findings of this clinical research, following conclusions were drawn:

1. Individuals with IL1B-511 AA genotype and IL-6 572GG genotype were found to be associated with increased susceptibility of early crestal bone loss around dental implants.
2. No association was found between early crestal bone loss around dental implants and single-nucleotide polymorphism of IL1A-889(rs1800587), IL 1B+3954 (rs1143634), COL1A1 (rs1800012), and osteocalcin gene (rs1800247).

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K.K.A., P.C., N.S., and R.K.G. contributed to framing the concept/design of the study. K.K.A., S.V.S., N.S., P.G., A.C., M.A., and A.K. contributed to data acquisition. K.K.A., P.G., M.A., and A.K. contributed to data analysis/interpretation. K.K.A. approved the final article. P.C. and S.V.S. drafted the article. P.C., S.V.S., R.K.G., and A.C. contributed to supervision.

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Novel technique for fabrication of pneumatic ocular prosthesis

Reasons for loss of an eye include irreparable trauma, intraocular malignancy and prevention of sympathetic ophthalmia. Other indications include phthisis, microphthalmia, and improvement of cosmesis [1]. Surgical procedures in the removal of an eye are classified into 3 general categories: evisceration, enucleation, and exenteration, which is followed by fabrication of an ocular prosthesis.

The goal of any ocular prosthetic procedure is to facilitate return of the patient to society with a more acceptable appearance. Often surgical treatment might leave an ocular socket with enormous volume for rehabilitation. An ocular prosthesis of such a large size has enhanced weight, which may lead to ectropion and sagging with decreased prosthesis mobility. It might also cause discomfort to the patient. Various techniques have been proposed for fabrication of light weight/pneumatic prosthesis using lost-wax technique [2] or styrofoam [3]. In this article, an alternative procedure for fabrication of pneumatic prosthesis, using an acrylic shim, has been detailed.

Following impressions, iris-disk placement and final wax pattern try-in, invest and de-wax the wax pattern in the usual manner. Adapt a layer of baseplate wax (Modelling Wax, DPI) on the mold surface in both halves of the flask (Fig. 1). Make 2–3 4 × 4 mm slots holes in the baseplate wax in each half, taking care to locate stops on flat surfaces rather than undulating ones. Pack autopolymerising resin (RR Cold Cure, DPI) in between the baseplate wax and close flask to let acrylic set. After about 30 mins, separate the flask and remove the resin shim with stops (for accurate repositioning) (Fig. 2). Remove baseplate wax layers.

Apply separating media (Cold Mould Seal, DPI) onto the mold. Mix appropriate color matched heat polymerising resin (Heat Cure, DPI) with iris and place in respective flask halves, in dough stage. Place



Fig. 1. Baseplate wax adapted on both halves of flask and slots created for acrylic stop for acrylic shim fabrication.



Fig. 2. Acrylic shim fabricated.



Fig. 3. Two halves of the prosthesis obtained after polymerization.

cellophane sheets as separating media on top of each half of dough. Place resin shim in between cellophane sheets and close flask halves. Acrylize, remove cured halves (Fig. 3) and approximate them with thin layer of autopolymerising resin after removing the shim. Finish, polish and deliver final prosthesis conventionally.

The technique suggested here is a relatively easy, simple and cost-effective method of fabrication of custom pneumatic ocular prosthesis. It helps in controlling the amount of hollowing achieved. The weight of the ocular prosthesis fabricated by this technique is much less. In this instance reduction of weight was about 2.79 gm or 24% [Fig. 4] than conventional solid ocular prosthesis. However, this technique has



Fig. 4. Weight difference between pneumatic and solid prosthesis.

certain drawbacks as well. It is technique sensitive with increased number of steps, making it time consuming. The approximated margins may be a potential source of leakage, discolouration and irritation.

A simplified, accurate method of fabrication of a hollow, light-weighted ocular prosthesis for patients with large ocular defects or sagging lower eyelids is presented.

Source of support

None

Conflicts of interest

None

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CLINICAL RESEARCH

Effect of mucostatic and selective pressure impression techniques on residual ridge resorption in individuals with different bone mineral densities: A prospective clinical pilot study

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Edentulism is an important public health issue for the elderly.¹ Although the prevalence of edentulism is decreasing in developed countries, many individuals still need prosthodontic treatment worldwide. In India, an estimated 11.7% are edentulous.² These patients are normally rehabilitated with complete dentures supported by residual ridges. Masticatory function with dentures generates forces which are transmitted through the denture base onto the underlying residual ridge.^{3,4} The inherent capacity of the bone to bear these transmitted stresses depends on its quantity and quality (constitution and microarchitecture), which varies in different regions of the jaws.⁵

Peak bone mass is usually attained by the age of 35 to 40 years in healthy humans, after which bone mass depletion occurs with varying intensity, accelerating in women after menopause, but less so in men of a similar age. Bone mass is decreased in individuals diagnosed

with conditions such as osteoporosis. Most individuals seeking prosthodontic rehabilitation, especially those requiring complete dentures are of an age where bone mass depletion has started, which further diminishes the ability of the bone to withstand masticatory forces.^{6,7}

ABSTRACT

Statement of problem. Although different impression techniques have been advocated for complete denture prosthodontics, objective studies that predict their effect on alveolar bone resorption are lacking.

Purpose. The purpose of this prospective clinical pilot study was to objectively evaluate the effect of complete dentures fabricated by different impression techniques on mandibular residual ridge resorption in individuals with different bone mineral density.

Material and methods. Ninety-six participants with edentulism, selected according to inclusion criteria, underwent bone mineral density assessment and were divided into normal, osteopenic, and osteoporotic groups. Half of the participants in each group were provided with dentures fabricated by selective pressure impression technique (subgroup SIT), and the other half were provided with dentures fabricated by mucostatic impression technique (subgroup MIT). Computed tomographic scans of the mandible were made at denture delivery and 1 year after prosthesis use to assess alveolar bone height and width difference at marked locations at and after denture delivery. The data obtained were analyzed with the Student t test ($\alpha=.05$).

Results. Significantly less reduction in mandibular ridge height and width was found in the MIT versus the SIT subgroups in both osteopenic and osteoporotic participants ($P<.05$). No significant subgroup difference was found for normal bone mineral density group, although resorption increased in height and width for the SIT subgroup.

Conclusions. Mandibular residual ridge resorption was reduced for dentures fabricated using the mucostatic impression technique compared with the selective pressure impression technique in individuals with diminished bone density. (J Prosthet Dent 2018;■:■-■)

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Clinical Implications

Complete dentures for patients with osteopenia or osteoporosis could be fabricated using a minimal pressure impression technique to decrease residual ridge resorption, thereby improving the overall prognosis and quality of life.

Therefore, knowing the condition of the bone before planning a prosthetic rehabilitation is essential. Altered hormonal status, sex, vitamin metabolism, systemic disorders, and pathological and congenital conditions play an important role in determining the quality of the alveolar ridge,⁸ along with bone mineral density (BMD), which is an independent factor that can be associated with the rate of residual ridge resorption (RRR).⁹⁻¹¹

Three techniques have been described for making impressions of edentulous arches in relation to the pressures applied to anatomic areas: the mucostatic impression technique (minimal pressure technique), functional impression technique (pressure technique), and semi-functional impression technique (selective pressure technique).¹² Each technique has its advantages and disadvantages. The selective pressure impression technique, as advocated by Boucher,¹³ has been commonly used and records predefined stress-bearing areas under pressure and nonstress bearing areas under minimum pressure. Relief is provided in nonstress bearing areas to maintain tissue health.¹³ In the mucostatic, nonpressure, or minimal pressure technique, all denture bearing areas are recorded in a nondisplaced, passive state under minimal pressure, either by providing consistent relief or by using a fluid impression material. This technique captures only nonmovable tissues and the denture relies on interfacial surface tension for retention.^{13,14} Proponents of different techniques have reported varying degrees of RRR.¹³

The authors are unaware of a study that has objectively determined the effect of different impression techniques on RRR in patients with different BMD status. Therefore, this study was conducted to determine the effect of complete dentures fabricated using different impression techniques on mandibular RRR in participants with different BMD status. The null hypothesis was that no difference will be found in mandibular RRR with selective pressure or mucostatic impression techniques in different BMD groups.

MATERIAL AND METHODS

This prospective 2-year study was carried out in the Department of Prosthodontics of Saraswati Dental College, Lucknow after obtaining the approval of the institutional ethical committee. The inclusion criterion was edentulous men between 40 and 70 years.⁷ The exclusion

criteria included participants with a history of smoking or alcohol dependence, oral, metabolic, skeletal, hepatic, renal, or endocrine disease, or medications for these disorders. Based on these criteria, 102 participants were included in the study. Six participants were lost to follow-up. Informed consent was obtained from each participant.

All participants were assessed for BMD with a bone densitometry system (Lunar DPX DXA System analysis v11.40; GE Healthcare). Participants were divided on the basis of T scores (as per World Health Organization guidelines) as follows: group NO (normal): edentulous participants with BMD values/T score greater than -1 (n=36); group ON (osteopenic): edentulous participants having BMD values/T score between -1 to -2.5 T score (n=32); and group OR (osteoporotic): edentulous participants having BMD values/T score less than -2.5 T score (n=28).¹⁵

In each group, the participants were randomly (software generated 1:1 sequence) divided into 2 subgroups. For subgroup SIT, dentures were fabricated using the selective pressure impression technique¹³ and for subgroup MIT, the mucostatic impression technique was used. To make preliminary impressions for the SIT subgroup, rimmed edentulous metal stock trays (Rim-Lock Impression Trays; Dentsply Sirona) were selected that allowed for an approximately 6 mm thickness of impression material and impressions made with irreversible hydrocolloid (Zelgan; Dentsply Sirona). A 1-mm-thick wax spacer (MAARC Spacer Wax; Shiva Products) was placed on the entire mandibular basal seat area on the preliminary cast, except the buccal shelf area and retromylohyoid spaces,¹³ and custom trays were made with autopolymerizing resin (RR Cold Cure; DPI). Border molding was done with low-fusing modeling plastic impression compound (DPI Pinnacle Tracing sticks; DPI), and definitive impressions were made with zinc oxide eugenol impression paste (DPI Impression Paste; DPI).

Preliminary impressions for the MIT subgroup were similar to those for the SIT subgroup. A 2-mm-thick wax spacer (MAARC Spacer Wax; Shiva Products) was placed on the entire mandibular basal seat area of the preliminary cast and custom trays made with autopolymerizing resin (RR Cold Cure; DPI). No border molding was done, and definitive impressions were made with irreversible hydrocolloid (Zelgan; Dentsply Sirona) after complete spacer removal.

A traditional method¹⁶ of denture fabrication was used for all participants by the same clinicians (T.A., G.A.). The method included a facebow record and horizontal and vertical jaw relation records to mount casts on a semiadjustable articulator (Hanau Wide-Vue; Whip Mix Corp), semi-anatomic polymethyl methacrylate resin teeth (Ruthinium Dental teeth set-Acryrock; Deccan Dental Depot Pvt Ltd) arranged in a balanced occlusion,

compression molding polymerization, and conventional delivery and follow-up appointments. Radiopaque markers were incorporated in the mandibular dentures between the central incisors and inferior to the first molars (Fig. 1). At the time of denture delivery, high resolution panoramic computed tomographic scans (SOMATOM Definition AS; Siemens Healthcare GmbH) of the mandible were obtained with the participant in a supine position. The position of the gantry was standardized for all scans.

After 1 year of denture use, a new computed tomographic scan was made. Alveolar bone height and width was assessed tomographically at baseline and after 1 year of denture use at the marked locations (at same slice number for a particular participant). Mean values of residual ridge height and width resorption for each subgroup were calculated from the 3 readings obtained at the interincisor and molar areas (where the radiopaque markers had been placed). The values were combined, calculated, and analyzed for the 2 subgroups in each group. Before and after comparisons were made with statistical software (IBM SPSS Statistics v23.0; IBM Corp). The Student *t* test was used to make intragroup comparisons for this single-factor study ($\alpha=.05$).

RESULTS

The data are presented in Table 1. No statistically significant differences ($P>.05$) in mandibular residual ridge height or width were found between subgroups MIT and SIT for all 3BMD groups (NO, ON, and OR). Also, the reduction in mandibular height and width for subgroup MIT versus SIT in the NO group was not significant ($P>.05$). However, mandibular height and width reduction was significantly greater for SIT subgroup compared with the MIT subgroup in ON ($P<.001$ for both height and width) and OR participants ($P=.014$ for height, $P<.001$ for width).

DISCUSSION

The results obtained from this study led to rejection of the null hypothesis as a difference was found in mandibular RRR with different impression techniques in individuals with different BMDs.

Considerable individual variation in the degree of RRR has confounded studies on factors that may influence the progress of such resorption.¹⁷ The etiology of RRR is still not fully understood; however, studies have described a correlation of 63 different factors and ridge resorption.¹⁸ Despite the listing of many factors responsible for RRR, a single dominant factor has not yet been determined.

In the absence of teeth, masticatory forces transferred to residual ridges either directly or indirectly by removable prostheses accelerate RRR. Whatever the etiological

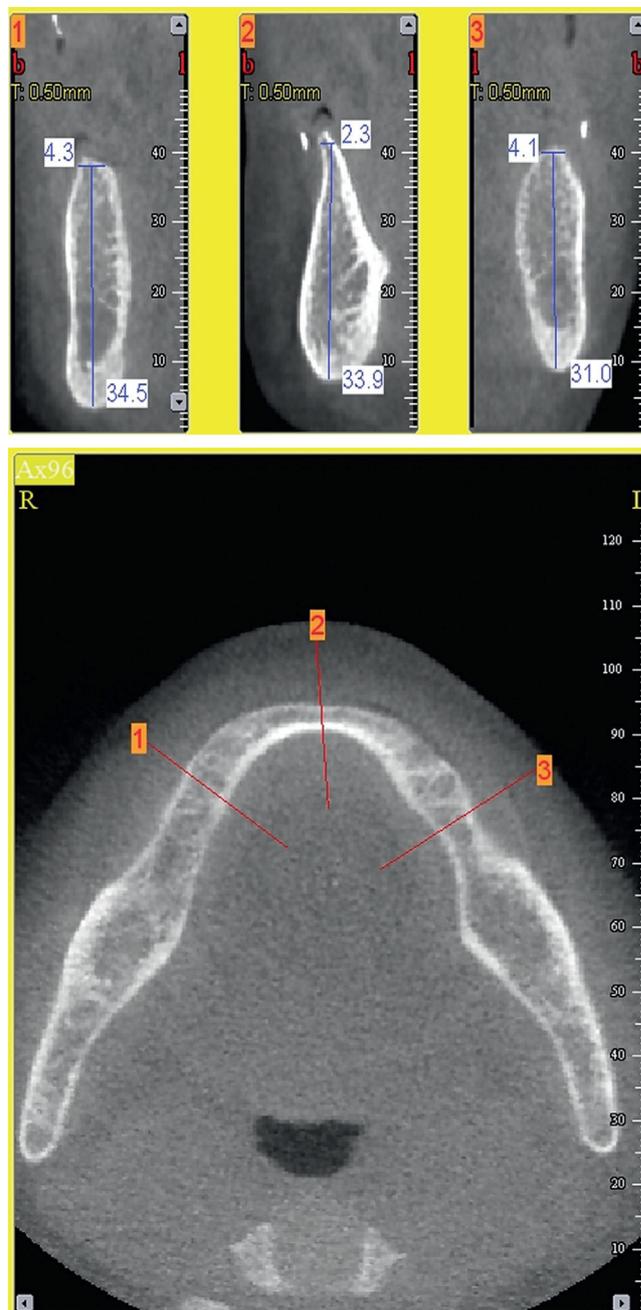


Figure 1. Top, Representative mandibular residual ridge computed tomographic scan. Bottom, Denture radiopaque inserts for site specific height and width measurement.

factor responsible for RRR, its effect on the prognosis of complete dentures is always detrimental. Some studies have shown that denture wearing is one of the factors associated with increased residual alveolar bone loss.^{17,18} The number of mandibular dentures worn can be correlated to the severity of alveolar bone loss.¹² Continuous RRR results in irreversible progressive loss of bone volume, causing poor denture fit, appearance, mastication, and health.

Table 1. Total and percentage reduction in mandibular residual bone height and width at 1 year

Characteristic	Group NO (N=36)		Group ON (N=32)		Group OR (N=28)		Total (N=96)	
	% Reduction	Mean Reduction \pm SD (mm)	% Reduction	Mean Reduction \pm SD (mm)	% Reduction	Mean Reduction \pm SD (mm)	% Reduction	Mean Reduction \pm SD (mm)
Mandibular Height								
MIT	1.08	0.21 \pm 0.86	1.27	0.25 \pm 0.50	4.01	0.76 \pm 1.39	2.12	0.41 \pm 1.68
SIT	1.60	0.30 \pm 1.13	2.71	0.53 \pm 1.43	5.48	0.94 \pm 1.48	3.19	0.59 \pm 2.06
T score		1.578		4.164		2.629		3.020
P		.126		<.001		.014		.003
Mandibular Width								
MIT	1.39	0.17 \pm 1.06	1.21	0.16 \pm 0.63	4.96	0.62 \pm 2.00	2.45	0.31 \pm 2.27
SIT	2.07	0.34 \pm 1.67	3.62	0.46 \pm 1.35	8.02	0.92 \pm 2.36	4.65	0.57 \pm 3.06
T score		2.764		6.856		4.126		4.304
P		.010		<.001		<.001		<.001

MIT, mucostatic impression technique; NO, normal; ON, osteopenic; OR, osteoporotic; SIT, selective pressure impression technique.

That an individual's BMD status affects RRR has been well established.^{7,19} The deleterious effect of RRR on bone increase in patients with low BMD because of depleted bone, deteriorated bony architecture, and alteration in the physiology of osseous proteins makes the bone more prone to injury from mechanical forces.¹⁹

Although RRR continues throughout the life of a denture wearer; the quality of life for patients with edentulism is improved by optimally supported, stable, and well-retained complete dentures. Factors related to complete denture fabrication and method of use may also affect RRR. Different methods have been introduced for making impressions of edentulous ridges, and their proponents have claimed varying degrees of RRR.¹³

However, the authors are unaware of a study that has objectively illustrated the effect of different impression techniques on RRR in patients with different BMD status. Therefore, this study was conducted to determine the effect of complete dentures fabricated by different impression techniques on mandibular RRR in patients with different BMD status.

In the present study, only men were recruited to exclude the possible variation due to menopausal factors in women. Participants between 40 and 70 years were selected as most of the patients seeking complete denture prosthodontic rehabilitation services in our institution fall in this age range. Upper extremes of age were excluded because of the possible effect of general systemic compromised RRR.

The gold standard noninvasive diagnostic modality for determining skeletal mineral density, energy x-ray absorptiometry (DXA), was used in the present study. Computerized tomography scans (Dentascans) were used for quantitative analysis (residual ridge dimension in mm) of mandibular bone, as it is the best method of visualizing anatomic structures and bone borders.²⁰

The results of this study indicate that dentures made with the minimal pressure impression technique decrease residual alveolar ridge resorption in patients with compromised BMD compared with the conventional

technique. Hence, strategizing denture fabrication in deference to the quality and quantity of available bone by suitably altering the impression technique is one way to slow bone loss under function and to improve the long-term prognosis of the complete denture service. The conventional selective impression technique may be preferred for participants with normal BMD to improve retention. In patients with osteopenia or osteoporosis, the minimal pressure technique may be a better treatment choice.

To our knowledge, this study is the first to objectively evaluate the effect of 2 different impression techniques on RRR. Limitations of this study include the short observation period of 1 year. Future studies involving a larger sample size and longer follow-up are required to substantiate the results of this pilot study.

CONCLUSIONS

Based on the findings of this prospective clinical pilot study, the following conclusion was drawn:

1. RRR is reduced for dentures fabricated using mucostatic impression technique compared with the selective pressure impression technique in patients with diminished bone density.

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Research Article

Circulating Serum Levels of Fox P3, GATA-3 and IL-17 A as Potential Biomarkers in Patients with Symptomatic Asthma

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A B S T R A C T

Background: The lack of information on the association of certain factors in the pathophysiology of the chronic inflammatory disorder, Asthma limits its early detection and therapy. Keeping these facts in view, an endeavour was made to investigate the roles, if any, such as IL-17A, FoxP3 and GATA-3 in the occurrence and intensity of asthma in north Indian population.

Objective: The study was conducted to evaluate the level of FoxP3, GATA-3 and IL-17A in symptomatic asthma patients as compared to healthy controls.

Methods: In the study we had taken 125 cases and 125 controls. Levels of total interleukin 17A, transcription factors FoxP3 and GATA-3 were measured by ELISA in serum of asthmatic patients. Student's T-test and ANOVA test was applied for quantitative variables. The qualitative variables analyzed using Chi-Square test /Fisher's exact test.

Results: Clinical symptoms like breathlessness, cough, headache, disturbed sleep, congestion, and wheezing were found significantly elevated in asthmatics as compared to the controls. Except haemoglobin; in the cases the levels of blood eosinophils, Absolute Eosinophil Count (AEC), Total Leukocyte Count (TLC) and serum Immunoglobulin E (IgE) were observed higher as compared to the controls and also the higher serum levels of IL-17A and GATA-3 were found in the cases. Contrary to IL-17A and GATA-3; the levels of FoxP3 was increased in the control, and was lower in the patient serum. A positive correlation was found between total IgE and GATA-3 (Pearson Correlation=0.283, P=0.042). We have shown that GATA-3 is increased in the asthmatic patients (0.541±0.140) than in the controls (0.312±0.076). The GATA-3 was found over expressed in patients with severe asthma.

Conclusion: Increased level of GATA-3 and IL-17A might be useful as diagnostic marker for patients with symptomatic asthma there is need for further larger scale studies to establish the role of these biomarkers in asthmatic patients.

Keywords: Asthma, GATA-3, FOXP3, IL-17A, Indian Population

Introduction

Among many persistent inflammatory respiratory diseases, asthma is the most common. It has been characterized by bronchial hyper-responsiveness, short breaths, and frequent events of wheezing, chest tightness, coughing and increase in total immunoglobulin (IgE) levels.¹ Being one of the most prevalent chronic diseases of airways, asthma has been reported to adversely affect >300 million people worldwide for the most part to the children and adults.² In United States, asthma has affected >23 million adults. As compared to men, women are more vulnerable to asthma with greater morbidity.³ In India, currently about 30 million people are reported to be afflicted with this disease. Looking at the data of the last one decade, the prevalence of asthma in children has been observed to be constantly increasing in the Indian subcontinent.

In previous decade, a major investigation has dealt with the role of T-helper cells (Th1, Th2 and Th17) and their mediators/ cytokines that have been associated in the onset of airway inflammatory response in asthma.⁴ It has been reported that the cytokines released by Th2 cells are essential for Immunoglobulin E (IgE) synthesis, chemokine production, and mucous production in the airways.⁵ The chronic respiratory inflammation and hyper-responsiveness have been indicated to be an outcome of a coordinated interaction between T and B-cells, as well as the mast cells and eosinophils.⁶ We have demonstrated that Th17 cells may be responsible for pathogenesis of inflammation due to allergy in asthma. They have further indicated that allergic asthma may enhance the number of Th17 cells and hence the production of Th17 cytokines in the patients.⁷ This conclusion suggests that there may be involvement of Th17 immunity in the systemic immune responses of allergic asthma.⁸ The results of certain clinical experiments have suggested that Th17 mediated inflammation plays significant role in the patients suffering from severe asthma and neutrophilic inflammation, as well as steroid-resistance.⁹ The interleukin 17 (IL17) is the main cytokine of Th17 cells which plays a key role in imparting protection against infection. IL17 has also been implicated to induce and maintain chronic inflammatory disorders.¹⁰ The IL-17A and IL-17F are the two essential members belonging to the IL-17 family of cytokines.¹¹

Recent data have indicated that the expression of IL-17A in sub mucosa of bronchia is increased,¹² which reflects the possible involvement of IL-17A in the pathogenesis of asthma.¹³ Also, Treg has been shown to play a part in prevention of the allergic diseases via suppression of the production and activities of Th2 cytokines.^{14,15} Like Treg, some other factors which include CD4, CD25, and FoxP3 (fork head box transcription factor) have been shown to be involved in the development as well as in the functioning

of Th2.¹⁶⁻¹⁹ The role of FoxP3 has been assigned to regulate differentiation of native T-cells into Treg phenotype.¹⁸⁻²⁰ These cells suppress the functions of T cells which are auto-reactive in nature and may control Th2 cells implicated in pathogenesis and also the Th1 cells which are expected to be involved into initiation of asthma.¹⁹ Th2 cells and GATA-3 gene have important role in IgE production, allergic inflammation and asthma.²¹ The low expression of GATA-3 gene in asthmatics found under basal conditions and even after *in vitro* stimulation which was expected to be higher alike younger asthmatic groups.^{22,23} GATA-3 expression in both groups was analyzed in basal as well as in activated states. The increased FoxP3 transcription factor modulates the immune response.^{20,24} The aim of study was to analyse the concentrations of IL-17A, FoxP3, GATA-3 and IgE in the blood serum of asthmatic and healthy control groups.

Materials and Methods

Period of Study

The study was conducted for 12 month duration in 2016. Prior approval was obtained from institutional ethics committee constituted by King George's Medical University (KGMU), Lucknow comprising of external experts as members.

Study Population

The study population included cases and control with 125 cases and 125 controls were enrolled on the bases of inclusion and exclusion criteria from the OPD of the Department of Pulmonary and Critical Care Medicine, and King George's Medical University (KGMU), Lucknow. Spirometry test for both cases and controls were assessed in the study for lung function by Spirometry method and predicted values of FEV₁ were calculated. Spirometry was defined by a percentage of FEV₁ within 3 hours after included in OPD of the Department of Pulmonary and Critical Care Medicine, King George's Medical University (KGMU), were considered as one of the parameters.

Collection of Demographic and Epidemiological Information

A pre-designed Performa was employed to collect demographic and epidemiological information on age, sex, occupation, family history, clinical symptoms with more than five days based on records available with the patient and history of illness in the last 12 months suggestive of infectious nature viz, chest infections, chest tightness, Breathlessness, Cough Headache, Disturbed sleep, Chest tightness, Wheezing for which treatment was sought from local practitioners.

Clinical Specimens

Blood samples were collected from patient's visiting the OPD. The patients were classified as cases and controls and

blood were collected in the plain vial for the separation of serum.

Inclusion and Exclusion Criteria

All the samples from controls and cases were categorized under following inclusion and exclusion criteria:

The Inclusion Criteria for Cases

- Age: 18 years to 65 years
- Cases were taken irrespective of the stage of asthma
- Patient who has symptoms of persistent cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry (as per GINA criteria)
- Asthma: >12% reversibility of FEV1 with inhaled bronchodilators

Exclusion Criteria for Cases

- Age <18 years
- Other associated diseases (TB, Pneumonia and other)
- Pregnancy
- COPD Patients have <80% predicted and FEV1/FVC <70%

Inclusion Criteria of Control

- Age sex matched
- Not to be primary relative of the patients

Exclusion Criteria for Control

- Age <18 years
- Other associated disease (COPD)
- Pregnancy
- Patients have <80% predicted and FEV1/FVC <70%

The clinical specimens, comprising of blood and serum samples, were received by the Department of Pulmonary and Critical Care Medicine of KGMU Hospital under standard transport conditions. The specimens were processed for identification as per standard protocol techniques and the levels of haemoglobin, eosinophils, Absolute Eosinophil Count (AEC), Total Leukocyte Count (TLC) and serum Immunoglobulin E (IgE) were estimated. Total serum protein levels was determined for IL-17F, GATA-3 and FoxP3 using standard ELISA kits (M/ s Sunred). 17F levels was determined using ELISA Kits (Sunred M/ s, ELISA Kit Catalogue no. 201-12-0047), FOXP3 ELISA Kit Catalogue no. DZE201120693), GATA3 ELISA Kit Catalogue no. DZE201123855). The tests were performed on 125 cases and 125 controls, as per the manufacturer's protocol.

The ELISA was performed as per the standard procedure. The wells of the ELISA plates were coated with 40 µl of test sample to which 10 µl of biotin labelled IL 17F antibody were added. Further, 50 µl of Streptavidin HRP was added and the plates were sealed and gently mixed. The plates were incubated at 37°C for 60 minutes. The membrane

was carefully removed and the liquid was decanted and the wells were briefly washed. 50 µl of chromagen solution A and solution B each were added in the order and were gently mixed followed by incubation in dark at 37°C for 10 minutes. The reaction was then stopped by adding 50 of the stop solution.

The blank wells were coated with buffer solution in place of the samples. Rest of the procedure was same. Similarly, standard solution was added in place of the samples in the wells labelled as standard.

The plates were read at 450nm wave length soon after adding the stop solution. The OD readings were normalized using blank reading taken as zero.

Data Evaluation and Statistical Analysis

Quantitative variables were compared using Unpaired Student's T-test between two groups and ANOVA test was applied among three groups. Chi-Square test /Fisher's exact test was applied to Qualitative variables and p value found <0.05 considered statistically significant. The Statistical Package for Social Sciences (SPSS) version 16.0 was used to analyze the data.

Result

Characteristics of the Study Population

The demographic profile of patients suffering from cases and the controls have been summarised in Table 1. Our study included 125 cases consisting 46 males and 79 females. Four samples with 18 years, seventy seven cases between 18 to 35 years, forty three cases between 36 and 50 years and one case above 60 years of age were considered for the study. The control group included 45 males and 80 females of age 18 years, seventy seven controls between 18 to 35 years, forty two were between 36 and 50 years and above 60 years. In the present study, we observed tobacco smoking habits were similar in the cases and control (Table 2).

Clinical Symptoms in Study Population

The occurrence of breathlessness, cough, headache, disturbed sleep, chest tightness, and wheezing were recorded to be 89.6%, 87.2%, 84.0%, 76.8%, 76.8%, 91.2% and 81.6%, respectively, in the patients. The FEV1 (%) changes (18.3520±5.160) were also observed. The values of the clinical indices for above parameters in the cases were much higher than that in the controls (Table 3 and Figure 1).

Laboratory Parameters in Study Population

The values of parameters of laboratory investigations of the cases and controls are depicted in Table 4. The levels of IgE, Eosinophil, AEC, TLC and Hb (Mean±SD) were observed to be 399.6±11.27 IU/ml, 7.330±0.4110 % , 541.2±15.67 cell/cum and 6861±236.4 cell/cum 10.95±0.1247 (gm/

dl), respectively, in the cases. Except Hb, the values of other clinical parameters were significantly higher than the controls. The level of Hb, however, was lower 0.95 ± 0.1247 (gm/dl) in the cases when compared to the control (13.01 ± 0.1567 gm/dl).

The levels of IL-17A, FOXP3 and GATA-3 in serum by ELISA of cases and controls were estimated and the sensitivity and specificity was determined as described in the materials and methods section. The results thus obtained are been

summarised in Table 5. The IL-17A levels were found to be 0.439 ± 0.110 ng/l in the cases and 0.318 ± 0.073 ng/l in the controls. The GATA-3 and FoxP3 levels in cases and in controls as shown in Table 5 were estimated to be 0.541 ± 0.140 ng/l in cases and 0.312 ± 0.076 ng/l in controls. The levels of FOXP3 were 0.397 ± 0.101 ng/l in the asthmatics and 0.583 ± 0.143 ng/l in the controls. It was observed in cases contained higher levels of IL-17A and GATA-3 but there were decreased level of FOXP3 in cases (Figure 2).

Table 1. Demographic profile of asthmatics and control: descriptive statistics

			Groups		Total
			Cases	Controls	
Age intervals	18 years	Count	4	5	9
		% within Groups	3.2%	4.0%	3.6%
	18 to 35 years	Count	77	77	154
		% within Groups	61.6%	61.6%	61.6%
	36 to 50 years	Count	43	42	85
		% within Groups	34.4%	33.6%	34.0%
	Above 60 years	Count	1	1	2
		% within Groups	.8%	.8%	.8%
Total		Count	125	125	250
		% within Groups	100.0%	100.0%	100.0%

Table 2. Status of smoking

			Groups		Total
			Cases	Controls	
Status of smoking	Absent	Count	64	69	133
		% within Groups	51.2%	55.2%	53.2%
	Present	Count	61	56	117
		% within Groups	48.8%	44.8%	46.8%
Total		Count	125	125	250
		% within Groups	100.0%	100.0%	100.0%

Table 3. Clinical symptoms

Symptoms	Cases (N=125)		Controls (N=125)		P-value
	N	%	N	%	
Breathlessness	112	89.6	56	44.8	<0.001*
Cough	109	87.2	69	55.2	<0.001*
Headache	105	84.0	76	60.8	<0.001*
Disturbed sleep	96	76.8	76	60.8	0.006*
Chest tightness	114	91.2	86	68.8	<0.001*
Wheezing	102	81.6	80	64.0	0.002*

Chi-square test Applied. *Significance.

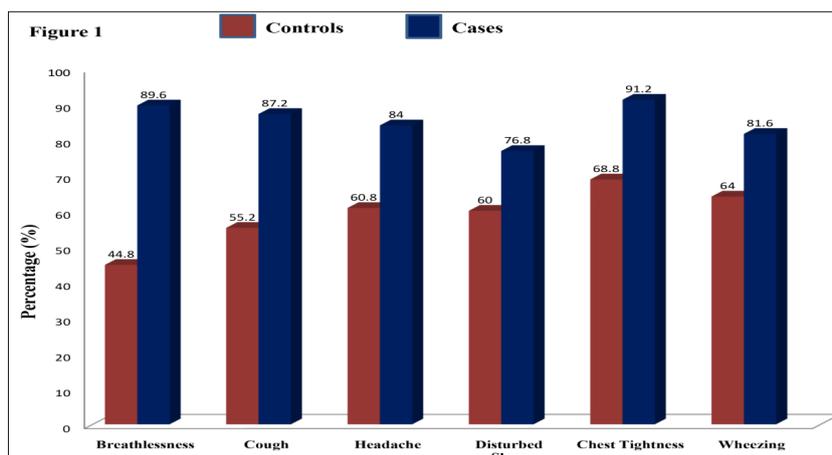


Figure 1. The symptomatic categories of cases in asthmatic patients. The values of these clinical indices as recorded for the above parameters. In the cases the indices were much higher than that in the controls

Table 4. Clinical indices in cases and controls

	Groups	Number	Mean	Std. Deviation	p-value
Hb (gm/dl)	Cases	125	10.8480	1.15742	<0.001*
	Controls	125	12.9712	1.58612	
Eosinophil (%)	Cases	125	7.1280	3.81207	<0.001*
	Controls	125	3.9920	2.14587	
TLC (cell/cum)	Cases	125	6.4667E3	2434.10330	<0.001*
	Controls	125	4.7287E3	1254.31956	
IGE (IU/mL)	Cases	125	4.0147E2	112.58293	<0.001*
	Controls	125	1.9281E2	78.27698	
AEC (cell/cum)	Cases	125	5.3013E2	146.65842	<0.001*
	Controls	125	4.2441E2	84.45824	
FEV1 (%)	Cases	125	18.3520	5.16073	<0.001*
	Controls	125	8.8080	1.67859	

Table 5. The levels of IL-17 A, FOXP3, GATA3 in serum

Protein	Groups	Number	Mean	Std. Deviation	p-value
IL-17 A (ng/l)	Cases	125	0.439	0.110	<0.001*
	Controls	125	0.318	0.073	
FOXP3 (ng/l)	Cases	125	0.429	0.124	<0.001*
	Controls	125	0.583	0.143	
GATA3 (ng/l)	Cases	125	0.541	0.140	<0.001*
	Controls	125	0.312	0.076	

Correlation among Interleukin and Transcription Factors in Different Categories of Cases

The correlations among the proteins IL-17F, GATA-3, FoxP3 and IgE have been shown in Table 6. A positive correlation established between total IgE and GATA-3 levels (Pearson Correlation=0.283, P=0.042) (Figure 3A). But there no

correlation was found for the other transcription factor (FoxP3) and IL-17A, with the IgE values (Figure 3B and C). Statistical differences were observed between these analytes of asthmatics and controls for the IL-17A/ GATA-3 (Figure 2). The balance between Treg/ Th effector cells may also regulate the level of inflammation in asthmatic (Figure 3).

Table 6. Correlations among the Proteins

		IgE (IU/mL)	IL-17 A (ng/l)	GATA3 (ng/l)	FOXP3 (ng/l)
IgE (IU/mL)	Pearson correlation	1.0	0.097	0.182*	-0.103
	Sig. (2-tailed)		0.283	0.042	0.255
	N	125.0	125.0	125.0	125.0
IL-17 A (ng/l)	Pearson correlation	0.097	1.0	0.230**	0.063
	Sig. (2-tailed)	0.283		0.010	0.488
	N	125.0	125.0	125.0	125.0
GATA3 (ng/l)	Pearson correlation	0.182*	0.230**	1.0	0.026
	Sig. (2-tailed)	0.042	0.010		0.775
	N	125.0	125.0	125.0	125.0
FOXP3 (ng/l)	Pearson correlation	-0.103	0.063	0.026	1.0
	Sig. (2-tailed)	0.255	0.488	0.775	
	N	125.0	125.0	125.0	125.0

*. Correlation is significant at the 0.05 level (2-tailed).

** . Correlation is significant at the 0.01 level (2-tailed).

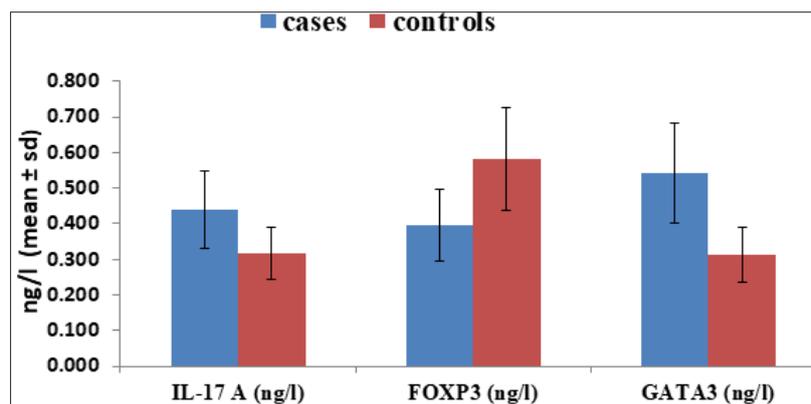


Figure 2. IL-17A, FoxP3 and GATA3 value for asthma patients (n=25) and healthy control (n=25) groups. Results are expressed as ng/l. The results are statistically significant p-value = <0.001*. IL-17A, FoxP3 and GATA3 Mean + Standard Deviation, Asthma vs control. 0.439 ± 0.110 vs 0.318 ± 0.101 , 0.397 ± 0.101 vs 0.583 ± 0.143 and 0.541 ± 0.140 vs 0.312 ± 0.076

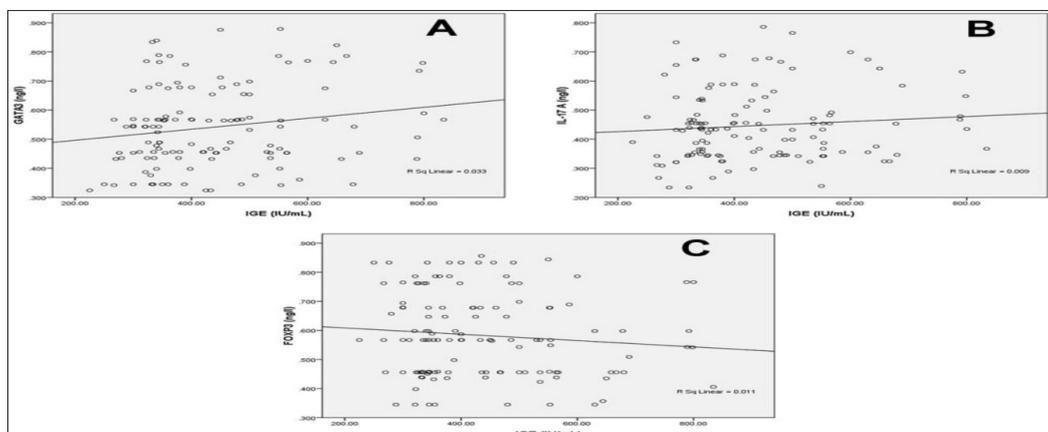


Figure 3. Correlations of IgE with all the three antigenic proteins (IL-17A, GATA-3 and FoxP3) as determined by ELISA. GATA-3 and IgE show a positive correlation

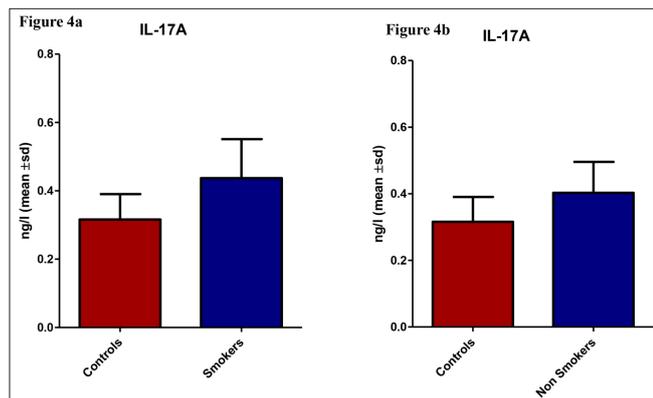


Figure 4. The comparison of antigenic response between smokers (a) and non-smokers (b) using IL-17A. The ELISA was repeated three times and mean ±SD was determined

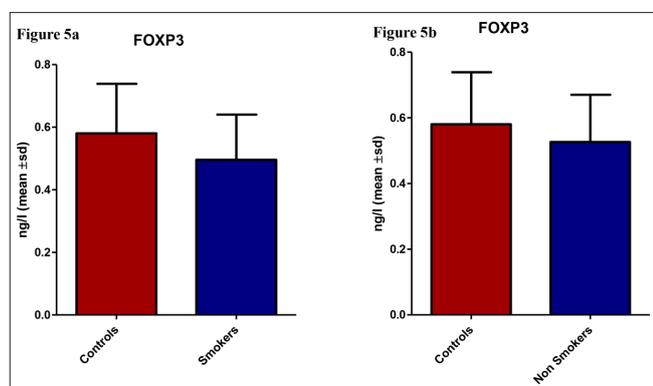


Figure 5. The comparison of antigenic response between smokers (a) and non-smokers (b) using FoxP3. The ELISA was repeated three times and mean ±SD was determined

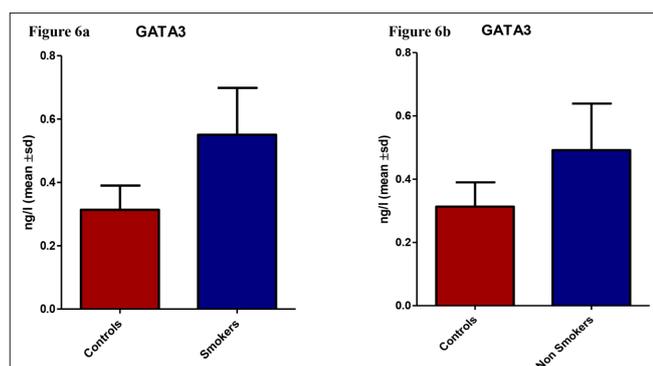


Figure 6. The comparison of antigenic response between smokers (a) and non-smokers (b) using GATA-3. The ELISA was repeated three times and mean ±SD was determined

Comparative of Smoking and Non-smoking Asthmatics

In order to look for the correlation between the expression of different factors and the effect of tobacco inhalation in asthmatic patients, we have categorically determined the

levels of IL-17A, FoxP3 and GATA-3 in smokers and in non-smokers. Surprisingly, the levels of IL-17A (Figure 4a and 4 b), FoxP3 (Figure 5a and 5b) and GATA-3 (Figure 6a and 4b) were not able to discriminate the patients between smokers and non-smoker groups.

Discussion

Asthma, a chronic disease affecting kids, young and adults at greater intensity, is often characterized by different levels of chronic inflammation as well as structural alterations in airway causing morbidity and mortality. Alyasin et al. have demonstrated that both the inflammatory as well as structural changes (airway remodeling) may be cause of inflammation in asthma.^{25,26} The structural changes include sub-epithelial thickening, epithelial detachment, airway smooth muscle hypertrophy, hyperplasia of goblet cell, enlargement of bronchial gland, angiogenesis and changes in the components of extracellular matrix, which are influenced by a complex cytokines network.²⁷ Thus, a thorough knowledge about the cytokine network's modulation during asthma may significantly contribute to understanding of pathogenesis of disease and also towards developing new therapeutic strategies to cure.

The data obtained from this study suggested that though the age and height were almost the same in asthmatics and in the controls; the cases displayed loss of weight in comparison to that of controls. Also among the total people recruited for this study, the smokers in the cases were higher with longer smoking duration than controls. However, the family history of asthma, breathlessness, cough, headache, disturbed sleep, chest tightness and wheezing were significantly higher in the asthmatics in comparison to the controls. Our results corroborate with the findings earlier reported while studying the expression of mRNA IL-17A in atopic asthmatics.²⁸

In the onset of asthma attacks, the cytokine IL-17A plays a crucial role but in varied ways. It has been shown by various groups that IL-17 is involved in influencing the number of respiratory tract neutrophil, generates hyper-reactivity in respiratory tract, induces hyper-secretion of mucus, causes remodelling of airway, and also the steroid resistance.²⁹⁻³² possibly, these cascades of events are the causes of pathogenesis of inflammation of airway due to allergic reactions. The variations in different genes associated with the occurrence and severity of asthma have also been recently demonstrated by Piva SR et al.³³

The results from the present investigation reflected enhanced Immunoglobulin E (IgE) levels, eosinophils, AEC and TLC in the cases. However, the Hb content was lower in the cases in comparison to the controls. The elevated total IgE level is considered as one of the chief characteristics in the atopic asthmatics or allergic asthmatics.²⁸ Mowahed

M et al. have also reported the significantly higher concentration of serum IgE in the asthmatics than the normal individuals.³⁴ The results of present investigation showing increased levels of eosinophils, AEC and TLC in the patients corroborate with the findings earlier presented, who have indicated that there could be some asthmatics with both eosinophilic and neutrophilic inflammations.³⁵

The recent studies have indicated that T helper 17 (Th17) cells may be involved in the onset/ severity of asthma via inducing inflammation in airways through secreting interleukin IL-17A, a cytokine of Th17. Mowahed et al. have indicated that the serum IL-17A concentration got significantly elevated in the asthmatics in comparison to the controls.³⁴ In our study, this pattern was recorded to be equivalent to their finding i.e. the serum IL-17A level was higher in the cases than the controls. The increased level of serum IL17-A seems to be associated to the pathophysiology of allergic asthma.

Mowahed et al. have further expressed that IL-17A, like the IgE, rises in sera of asthmatics as the different indicators i.e. IgE increased in the serum consistently with the disease severity whereas IL-17A increased in serum with increase in severity of the disease.³⁴ Thus they demonstrated almost no correlation between these two clinical indices. The results of our investigation reflected increase in the levels of these two parameters with the onset/ increase in the severity of the disease there by indicating a positive correlation between them.

In another study, it has been demonstrated that asthmatics exhibited a significantly higher level of serum IL-17A in comparison to controls (healthy) subjects thereby suggesting that IL-17A can be exploited as a potential clinical biomarker for prospective diagnosis and therapeutic management of asthma.³⁶ In our study, the FoxP3 concentration was found significantly higher in asthmatic in comparison to healthy controls ($p=0.000$). The FoxP3 levels were also significantly higher in asthmatic group on corticosteroids. According to the Hori S et al. FoxP3 expression was also higher in CD4+CD25+ Treg cells in asthmatics as anti-inflammatory.^{37,38} In contrast; Karengiannidis et al. found no significant difference in FoxP3 level in both healthy and asthmatics.³⁹ There is an increased level of suppressive cytokines and transcription factor FoxP3 expression found on corticosteroid treatment.³⁹⁻⁴² No data were yet found in the previous studies concerning the effect of clinical variables and other asthma medications on Treg FoxP3 expression. Our study have shown that FoxP3 levels were not affected by the age, exposure to environmental tobacco smoke, disease control, asthma severity, lymphocyte percentage, eosinophil percentage or FEV1%. FoxP3 levels are increased in healthy control as compared to asthmatic patients. FoxP3 levels are usually low in smoker

and non-smoker in asthmatic patients group compare to the control group (Figure 5a and b). These findings propose that FoxP3 is important to predict the long-lasting asthma in the elderly, and can be implied for future therapeutic approach and asthma therapy. The zinc finger transcription factor GATA-3 has been found to control the expression and production of Th2 specific interleukins in isolated cell systems and invertebrates, which is found to be crucial transcription factor for immune activation.⁴³⁻⁴⁵ However, there has been demonstrated the expression of GATA-3 in mast cells and also found to be expressed in airway epithelial cells, associated with the allergic reaction.⁴⁶⁻⁴⁸ In our findings (Table 5) we have shown that GATA-3 is increased in the asthmatic patients (0.541 ± 0.140) than in the controls (0.312 ± 0.076) indicating over expression of GATA-3 in patients with severe asthma as reported by other groups.⁴⁹

The biomarkers were found to be responsive to the asthma in humans. The blood samples of the patients with other complications such as, cardiac disease that are symptomatically similar to asthma were excluded in the study. The response of these biomarkers needs to be studied in those complications as well before being proposed as diagnostic biomarkers for confirming asthma. These biomarkers are thus, candidate for further studies.

Conclusion

The increase in the extent of serum IL-17A, GATA-3, and IgE in the asthmatic patients may have a key role in disease pathogenesis. FoxP3 is generally increased in the control and is lower in patient serum. FoxP3 protein secreted by Treg may be a natural anti inflammatory in hyperimmune states like bronchial asthma. The FoxP3 production may be the cause of anti inflammation by anti-inflammatory agent (which is cortisol). Thus, the serum IL-17A, GATA-3 and FoxP3 as well as IgE, may be exploited as a potential clinical biomarker for the suitable diagnosis and timely therapy of the disease.

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Conflict of Interests: None

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Nonimplant, Nonadhesive Overlay Approach to Retain a Partial Auricular Prosthesis

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Keywords

Maxillofacial prosthetic silicone; partial auricular prosthesis; polyvinyl chloride sheet; spectrophotometer.

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Abstract

Partial auricular prosthesis fabrication presents a more complex challenge than complete ear fabrication, with added aspects of merging/camouflaging a larger prosthetic marginal area, pattern try-in, and compromised retention. Better alternatives are excision of the remnant ear to make an implant-retained complete ear prosthesis or surgical reconstruction of the missing ear portion. Both need additional surgery/ies and expenses, neither of which may be acceptable to the patient. This report describes a prosthesis fabrication approach for such patients. This approach does not require implants or adhesives for retention. Issues of marginal camouflage and pattern trial were also addressed satisfactorily.

Every person has a unique physical appearance. Those who lose part of their face due to trauma, illness, accident, or disease, face numerous challenges in everyday life, affecting psychology and social behavior.¹ It is important for patients to return to their lifestyle as early as possible and regain their confidence. Auricular defects, which can range from a grossly normal ear, to microtia, to anotia, can be due to congenital malformations, trauma, or surgical removal due to neoplasms.² Defects are reconstructed either by surgery³ or conservatively by silicone prostheses.⁴ Prosthetic treatment is gaining wide popularity due to low cost, shorter treatment time, and less invasiveness. Surgical reconstruction results in morphology less similar to the opposite side due to the complex morphology of the ear and is considered to be one of the more demanding challenges for the plastic surgeon.⁵

Long-term success of the prosthesis depends on accurate fit and retention.⁶ Conventionally, for partial auricular defects, ear remnants are removed, and an implant-retained complete ear prosthesis is fabricated, or the missing ear is surgically reconstructed; however, if the patient is not ready to undergo surgery, this option is excluded. A partial auricular prosthesis presents a complex challenge, with the task of merging/camouflaging longer prosthetic margins, compromised retention, and pattern try-in. Patterns are normally made in rigid wax, and tissue undercuts therefore must be blocked to ensure uneventful removal and insertion. This leads to poor retention, making a proper trial troublesome.⁷

A technique is described here, wherein a complete auricular prosthesis, with increased retention and better esthetics, covering remnants, is fabricated for a patient with microtia. Further, incorporation of a polyvinyl chloride (PVC) sheet in the pattern leads to better adaptation of the pattern on the model and face, with no risk of distortion/breakage during repeated trials.^{8,9}

Clinical report

A 36-year-old patient reported to the department, with a chief complaint of unesthetic appearance due to a missing ear stemming from a road traffic accident 7 months prior (Fig 1). The patient did not opt for surgical reconstruction and wanted prosthetic replacement. Facial skin and hair around the defect and the contralateral ear were covered by a thin layer of petrolatum gel. The external auditory canal was blocked with gauze to prevent entry of impression material. An impression of the residual ear was made in irreversible hydrocolloid and poured in high-strength dental stone (Kaldent; Kalabhai Karson Pvt Ltd., Mumbai, India). An impression of the normal counterpart was made for replicating details and formation of mirror image (Fig 2).

A 5 × 5 inch (0.040 inch) PVC thermoplastic sheet (Sof-tray sheets; Ultradent Products Inc., South Jordan, UT) was adapted on the model of the residual ear with a vacuum former machine (Model P105-U02; Ultradent Products Inc), taking care that the template was properly extended. A butane gas-powered



Figure 1 Frontal and side views before prosthesis fabrication.

soldering iron instrument was used to cut the template to desired borders without damaging the original model, and its margins were feather edged with a carbide bur (No. 471; DFS-Diamon GmbH, Riedenburg, Germany) for blending. Anatomic reference points were marked on the model to facilitate correct positioning of the wax pattern (modeling wax; DPI, Mumbai, India), which was carved over the PVC template, using a mirror image drawn from the counterpart ear model. The pattern and template covered the remnant entirely (Fig 3).

The pattern was tried on the patient, orientation was checked, and necessary alterations were made. Skin folds, wrinkles, and stippling were created on the pattern, which was then finished to achieve proper texture, and margins were merged and sealed on the model. The pattern was then invested in high-strength dental stone (Orthokal; Kalabai Karson Pvt Ltd.), using the three-pour technique (multisectional mold) because of the convoluted design of the ear. The first pour was done up to the base of the pattern (Fig 4A). After application of separating media, the second pour was done to the level of the helix (Fig 4B). The third pour covered the first and second pour entirely. Such a mold decreased the risk of the prosthesis tearing during recovery, or mold fracturing during deflasking, rendering it reusable.¹⁰ The invested pattern was dewaxed in boiling water for 10 minutes,



Figure 2 Impression of partial ear.

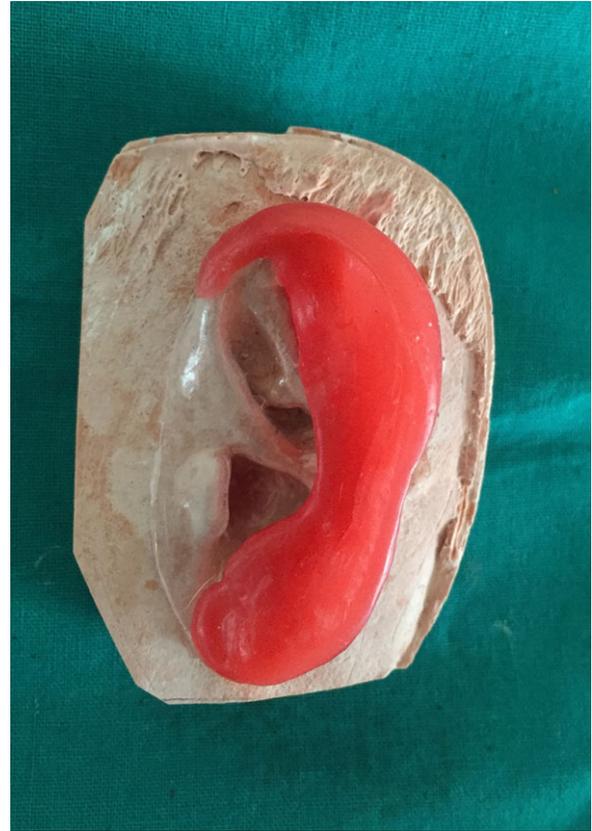


Figure 3 Wax pattern with adapted PVC sheet onto the partial ear model.

and the PVC sheet was removed. The mold was ready for silicone material packing (Fig 4C).

The shade for the auricular prosthesis was taken from the nape of neck for darker areas and from the back of ear for lighter areas, with a digital maxillofacial prosthetic spectrophotometer (Spectromatch Ltd., Bath, UK). The silicone was mixed according to color codes, and packing was done. The prosthesis was polymerized for 60 minutes at 100°C (Fig 5). The polymerized prosthesis was retrieved and tried on the patient for fit, color, and translucency.

Further color matching was done with extrinsic stains. Deeper areas were colored darker (scaphoid fossa and concha). Areas such as the helix and anti-helix were demarcated using redder/pinker shade of stains (Fig 6). Retention of the prosthesis was adequate without adhesives, and the patient was satisfied with the esthetics.

Discussion

An ear can be missing congenitally or due to acquired causes such as trauma or malignancy. Ear defects occur at the rate of three in every 100,000 births.¹¹ An auricular prosthesis can either be retained by implants, adhesives, or mechanical methods such as with a spectacle¹² or magnet.¹³ The challenges encountered during fabrication of a partial auricular prosthesis are distortion of the wax pattern during repeated trials and inadequate retention of the prosthesis. Also, merging of the

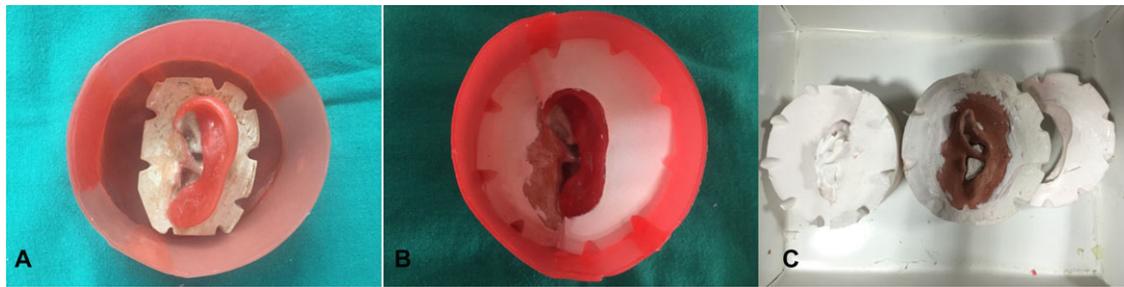


Figure 4 (A) Pouring the first part of the mold. (B) Second part of the mold poured. (C) All three parts of the mold poured.



Figure 5 Silicone prosthesis before extrinsic pigmentation.

prosthetic ear with natural remnants is difficult. The aims of this technique were to fabricate a pattern that did not distort during trial and to produce a more-retentive auricular prosthesis. Adaptation of the PVC sheet^{8,9} leads to ease in repeated trials and better orientation for comparison with the normal ear position and size. In this technique, the prosthesis covered the entire remaining ear, leading to increased surface area, use of tissue undercuts, better retention, and easier camouflage.¹¹

Adaptation of a PVC sheet-based pattern has been reported, but previously this was incorporated in the final prosthesis.⁸ In the present technique, it was removed and replaced with

silicone for better strength, esthetics, and merging of the prosthesis with the remnant ear. Silicone has been the material of choice for many years, for properties like esthetics, flexibility, biocompatibility, ability to accept intrinsic and extrinsic colorants, translucency, chemical and physical inertness, moldability, softness, and ease of cleaning.^{14,15} Any question of PVC and silicone not bonding was also thus removed. As of this writing, the patient has used the prosthesis for 6 months, and it still has adequate esthetics and retention.

Rehabilitation using an adhesive-retained silicone prostheses is a conservative and reversible approach but has disadvantages such as less retention, allergic reactions to adhesive, and difficulty in compliance and maintenance. Unkovskiy *et al* reported that CAD materialized by technologies such as fused deposition modeling, selective laser sintering, and stereolithography, are feasible alternatives to manual pattern carving and prosthesis coloration.¹⁶ Though implant-retained prostheses are superior, they have disadvantages for patients with financial constraints and/or who are apprehensive of surgery. Further, extraoral implants require adequate thickness of bone, which may be deficient in certain cases. The limitation of this technique is an increased thickness of prosthesis over the remnant ear and some diminution in hearing.

Conclusion

The final prosthesis made by this approach showed adequate retention and esthetics, along with being economical and convenient. Hence, it may be successfully applied to partial auricular prosthesis fabrication.

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Figure 6 Frontal and side views after prosthesis fabrication.

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Fabrication of Silicone Prosthesis for an Amputated Pollex with Kapandji Score 8: A Case Report

ANSHULIKA SINGH¹, MAYANK SINGH², SAUMYENDRA V SINGH³, POORAN CHAND⁴, DEEKSHA ARYA⁵

ABSTRACT

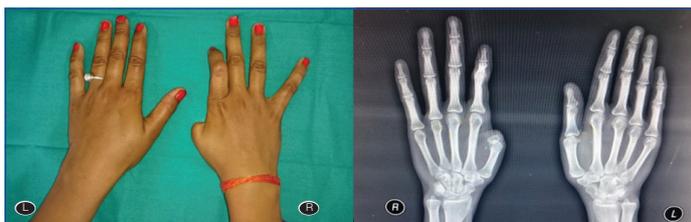
Amputations are most commonly seen due to the accidents, congenital malformations and diseases. Regardless of the cause of the loss of the part of the body, an amputation results in aesthetic, physical and psychosocial damage to an individual. An amputation can be surgically treated but in some cases where patient reports to the prosthetist, when the damage is irreversible, it can be treated with prosthetic replacements of the lost part. A prosthetist acts as an important link in helping such patients in regaining the lost confidence by rehabilitation. Prosthetic management of an amputated thumb aims to deliver a well-fitting silicone prosthesis that can mimic the opposite thumb as closely as possible, with good range of movement without dislodgement. This case report presents rehabilitation of the amputated thumb with minimal residual thumb in a conventional way along with restoring the range of movements with evaluation of the range of movement without the use of an extra retentive aid.

Keywords: Prosthetic rehabilitation, Retentive aid, Trauma

CASE REPORT

A 20-year-old female patient reported to the Department of Prosthodontics, with a chief complaint of missing thumb of right hand [Table/Fig-1]. History revealed the patient had lost her pollex in a traumatic injury when she was 1½-year-old.

Physical and antero-posterior radiographic examination of right hand revealed amputated thumb at proximal phalanx [Table/Fig-1]. The index finger was osseointegrated at the interphalangeal joint of distal and middle phalanx in the flexed position because of an attempt to reattach the distal phalangeal portion at the time of injury. The patient was naturally not able to straighten the index finger [Table/Fig-1]. The skin of the amputated finger was completely healed.



[Table/Fig-1]: Pre Rehabilitation clinical and radiographic view.

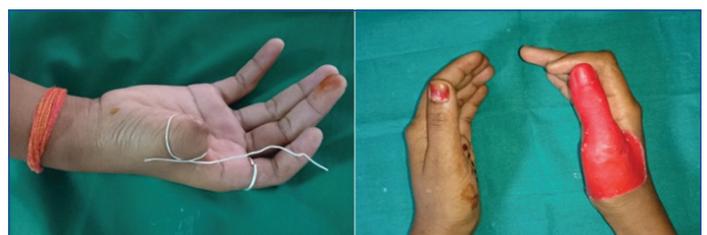
The rehabilitation of her thumb was challenging due to level and site of amputation. The patient was informed about both possible treatment options-surgical reconstruction and prosthetic rehabilitation. But, due to surgical trauma and financial constraints, the patient agreed to prosthetic rehabilitation. So, thumb prosthesis was planned for the patient. As the patient was unwilling for any surgery, implant retained prosthesis was ruled out. Mechanical retention with devices such as Velcro strap would be quite discernible for pollex location. Therefore, glove type thumb prosthesis with retention aided by an incorporated wire in the silicone prosthesis was planned to work in harmony with the flexed osseointegrated index finger of the right hand.

Patient was informed about the procedure and her consent was obtained. An impression of the right amputated thumb stump was made using irreversible hydrocolloid impression material (Zelgan) and poured with Type-III dental stone (Kalstone, Kalabhai Pvt., Ltd., Mumbai, India) to obtain the working model [Table/Fig-2]. Then

1 mm reduction was done all around the thumb stump to enhance fit to the elastic silicone prosthesis. After that, an impression of the patient's left thumb was made with alginate and poured in molten modelling wax (Link dental modelling wax no. 2, MDM Corporation, Delhi, India). This wax pattern of the left thumb was adapted to pollex stump model [Table/Fig-2] and the borders were merged with the area adjacent to the defect site. A 20 gauge silver wire was incorporated into the wax pattern as an aid for mechanical retention of the prosthesis. It was adapted at the root of the stump extending upto the metacarpophalangeal joint of the index finger, attaching to a ring worn on the index finger [Table/Fig-3]. Fabrication of silicone prosthesis with incorporated wire to aid in retention is hardly documented. Anatomic crease lines were carved to give a more natural appearance. Then, the wax pattern was tried on the patient's hand [Table/Fig-3]. Along with the shape and size, the fit, orientation, emergence and borders of the pattern were evaluated.



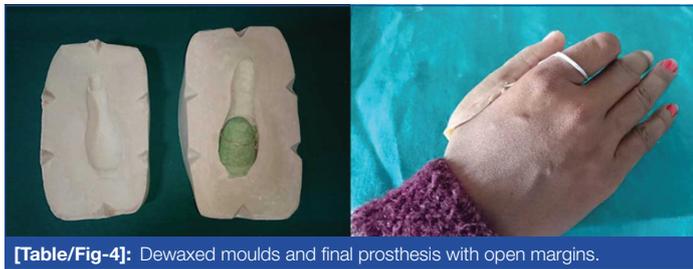
[Table/Fig-2]: Working model and wax pattern adapted to the thumb stump.



[Table/Fig-3]: Silver wire try in for wax pattern and the wax pattern tried on the patient's hand.

The pattern was then invested in a two piece mould made using type I dental stone. The two piece mould was made by pouring the dorsal and palmer halves separately. The first pour

enscoring the palmer half was made with type 1 dental stone, at slight angle. Keys were made into the first piece of mold and separating media was applied on the surface. This was followed by pouring the second half of the mold with type 1 dental stone. After the investment was set, dewaxing was done and moulds were obtained [Table/Fig-4]. The correct position of wire element was ascertained in the mold.



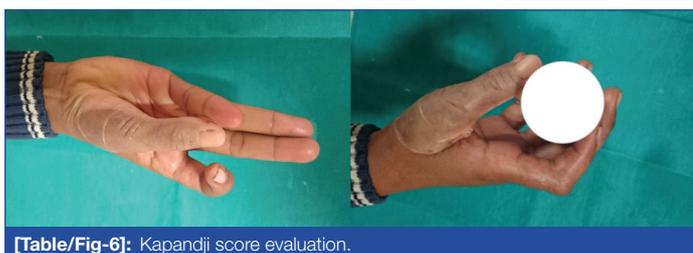
[Table/Fig-4]: Dewaxed moulds and final prosthesis with open margins.

Appropriate shades were matched for both the dorsal and the palmer surfaces with the help of digital spectrometer. The pigments were quantitatively measured, mixed with the heat temperature vulcanising silicone and added to the dewaxed mould. Surface tension releasing agent was applied to the mold surfaces. The molds were compressed and the curing process was performed according to the manufacturer's instructions. After curing, the prostheses was removed gently, trimmed and finished. The shade was evaluated and extrinsic colouring done to match the exact colour of the patient.

The prosthesis was inserted and retention was attempted by attaching the silver wire to a ring worn on the index finger. With this mode, prosthetic retention was good but on movement of the thumb the margins of the prosthesis opened up [Table/Fig-4]. So it was planned to cut the silver wire and medical adhesives were used for retaining the prosthesis [Table/Fig-5]. This also resulted in good retention and range of movement with a score of 8 as assessed with the help of Kapandji's rule of 10 [1], where the patient was asked to touch ten specified areas of 4 fingers with the tip of the thumb. For assessment of the opposition of the thumb Kapandji score was used as a tool, based on where the tip of their thumb touches the patient's hand [Table/Fig-6]. The patient was also asked to hold boxes of varying diameter to check for the grip [Table/Fig-6]. Post delivery the patient was instructed to remove the prosthesis daily and clean it with isopropyl alcohol, also asked to clean the underlying skin. A 6-month follow up for assessing the maintenance was planned for the patient.



[Table/Fig-5]: Post Rehabilitation final prosthesis.



[Table/Fig-6]: Kapandji score evaluation.

DISCUSSION

Pollex is an important part of hand used to perform daily tasks including pinch, grip, grasp, and precision handling [2]. From

functional standpoint it is the most important digit which performs the movements of opposition and apposition [3].

The patient is not able to perform various functional activities with the loss of thumb. The immediate loss of grasp, strength and security and the aesthetic impact may cause a great psychological trauma [4]. The thumb may be lost due to traumatic injuries or may be congenitally absent.

Traumatic amputation of thumb puts the patient through great aesthetic and psychological trauma, besides inability to perform functional movements, various gripping and opposing actions. To overcome these problems efforts are made to restore the lost thumb surgically or prosthetically. The first choice for treating amputated digits generally is surgical reconstruction while prosthetic rehabilitation may be considered in unsalvageable cases or in surgical reconstruction failure [5]. Options such as solitary digit transfer, bone lengthening or ray transposition allow for surgical reconstruction of lost digits achieving function and patient acceptance [6]. Prosthetic options include implant retained prosthesis which aids in higher degree of functional movements and aesthetics. Implant retained silicone finger prosthesis allow some pressure perception and tactile sensation, facilitating surface and texture distinction [7]. Tip pinch grip score can be used to determine the grip strength with marked pinch gauge, where the patient is asked to place the thumb under the gauge with the pulp of the index finger on top and dial facing upwards. This formed an O-shape whilst the other fingers are flexed [8]. However, there might be problems associated with loss of integration of these implants. Many patients do not agree to undergo surgery for implant or reconstruction due to surgical trauma, time consuming procedure and cost factors. Prosthetic replacement with mechanically retentive silicone prosthesis can serve as an acceptable option. This is non-invasive, less expensive and has good patient acceptance.

Similar case reports have been published for prosthetic rehabilitation of amputated finger/s [4,8], but rehabilitation has been without attempt at incorporation of wire. In the cases where stump length is severely reduced, there is associated difficulty in retention of the prosthesis. In such cases, where the patient is unwilling/unsuitable for osseointegrated implants, wire incorporation in silicone prosthesis might aid in retention.

CONCLUSION

This thumb prosthesis was designed to be fabricated with a silver wire incorporated, which would be attached with a ring to be worn on the index finger as an extra retentive tool since the pollex stump was very small. But due to problems like open margin and dislodgement of the prosthesis during movement of the residual stump or finger, the wire was cut and detached from the ring. Also, disadvantages such as show through of wire, susceptibility of silicone to tear from the portion where wire was emerging and difference in flexibility of the two materials, were expected with the prosthesis if the wire was retained. In the present case, since the disadvantages of using a wire to aid in mechanical retention was more, so medical adhesives were used to retain the prosthesis. Kapandji score was used as an assessment tool for evaluation of the functional movement and results with a good range of movement, without dislodgement were seen. This was achieved without any extra retentive element on the residual pollex stump of very small size.

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Somatoprosthetic Rehabilitation of Digitus Minimus Using Mini-Dental Implant: A Report of Negative Outcome

Himanshi Aggarwal, MDS, Mohd Anwar, MDS, Saumyendra Vikram Singh, MDS, Brijesh Mishra, MS

ABSTRACT

Introduction: Although digitus minimus may possess the least range of motion in all fingers, its amputation due to any reason leads to severe emotional trauma along with compromise in aesthetics and function. Inadequate retention associated with conventional vacuum-retained finger prosthesis is one of the major areas of concern.

Case Report: A 23-year-old male patient reported with amputated little finger of left hand. Examination revealed minimal residual digit. A mini-dental implant with O-ring type of attachment was used to retain the customized silicone digit after early loading protocol. Excellent immediate results in terms of aesthetics, retention, and psychological satisfaction to the patient were obtained. However, implant failed at 3-months follow-up.

Conclusions: The use of mini-dental implants to retain finger prostheses in patients with short residual digits seems to be a viable clinical concept; however, this technique should be used cautiously. (*J Prosthet Orthot.* 2020;32:71–75)

KEY INDEXING TERMS: mini-dental implants, digitus minimus, somatoprostheses

Digitus minimus, the humble fifth finger, is the smallest finger of the hand and is often considered as a bit of a decorative accessory. Conversely, this does not indicate it is insignificant. Together with other fingers, it forms a strong and powerful team. The dynamic function of the little finger is represented by its contributions in grasp, grip, gestures, and absorbing and transferring forces. The little finger contributes to 33% of total hand strength.¹ Although the middle and index fingers work with the thumb in grabbing and pinching, the little finger functions with the ring finger to generate hand power.¹ Many conditions ranging from congenital disorders to traumatic injury affect the little finger. Alteration in anatomy of the hand is associated with varied emotional and physical responses as well as social restrictions. The responses are associated with aesthetic changes, discomfort, and loss of function.^{2–6} Microsurgical reconstruction by reimplantation, solitary digit transfer, toe-foot transfer, and use of osteocutaneous flaps have been attempted to reestablish function of some individuals with finger amputation. These procedures may not always be feasible for various reasons.^{3,4,7} As an alternative, prosthodontic rehabilitation with silicone prosthesis is considered.

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Disclosure: The authors declare no conflict of interest.

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A major inherent problem with standard silicone digital prostheses is instability. The residuum of the amputated finger should be at least 1.5 cm to fit the standard prosthetic digit.^{8,9} Inadequate retention may stem from reduced tissue support or weight of prosthesis. A number of methods have been used to augment retention such as medical grade adhesives, adhesive tape, vacuum effect on residual digit, and use of ring at the junction of prosthesis and residual digit.³

For patients with short residual digits, where a conventional prosthesis is not successful, bone-anchored implants may be used as an alternative. Dental implants with a diameter less than or equal to 3 mm (lengths from 10 mm to 18 mm) are called mini-dental implants (MDIs)¹⁰ and are often indicated in cases where available bone width is inadequate for conventional implants, but bone quality is not impaired. The single component (one-piece ball end) nonsubmerged mini-implant is categorized as one-stage implant.^{11,12} Although one-stage surgical procedures using conventional dental implants have been reported,^{13,14} there are no references for prosthetic rehabilitation of an amputated finger with MDI. The present case report describes use of a mini-implant to retain somatic prosthesis in a patient with traumatic amputation of little finger having insufficient available bone volume to receive a conventional implant.

CASE REPORT

A 23-year-old male patient whose little finger of the left hand was lost at 12 years of age as a result of traumatic injury by a roller machine visited the Department of Prosthodontics for early esthetic rehabilitation, as he was getting married in 2 months. Physical examination revealed the amputation at the level of the proximal interphalangeal joint. Joint mobility and Web spaces were preserved. The residual digit appeared normal, was 1 cm in length, with no signs of infection or inflammation (Figure 1).

After informed written consent was obtained from the patient, implant of retained finger prosthesis was planned. Preoperative cone beam computerized tomographic examination showed inadequate width for conventional implant placement. An MDI (Equinox, Myriad plus implant system, the Netherlands), 11 mm in length and 2.5 mm in diameter, was selected. By its aggressive thread design, self-tapping, and bone condensing feature, this MDI is intended to be placed via a one-stage surgical procedure.¹²

Under regional anesthesia (brachial block) and an ischemic tourniquet control, an ellipsoid flap was raised with debulking of skin flap to prevent “wobble” of the implant later.¹⁴

Implant osteotomy was completed with a single 1.5-mm pilot drill. Drill depth was restricted to one half the implant length so as to cause bone condensation during mini-implant insertion.¹² Implant insertion was done into prepared osteotomy with insertion torque above 35 Ncm. Initial implant stability was recorded as 68 ISQ by resonance frequency analysis (RFA). Flaps were sutured with 3-0 silk (Figure 2). Postoperative radiograph was taken to confirm the accuracy of implant placement. Analgesics and antibiotics were prescribed,⁵ and postoperative instructions were given. The wound was inspected after 7 days and sutures removed.

In the fourth week of follow-up, implant stability was 74 ISQ by RFA. Prosthetic rehabilitation was initiated with attachment of transfer coping to the ball attachment. Pickup impression was taken with polyvinyl siloxane elastomeric impression material (Aquasil, Dentsply, United Kingdom). Implant analogue was attached to transfer coping after pickup impression. Impression was poured with type IV dental stone (Kalstone, Kalabhai Pvt. Ltd, Mumbai, India). Once the impression material had



Figure 1. Preoperative view.



Figure 2. Immediate postoperative view.

set, a working model was recovered and transfer coping was removed from implant analogue. Female metal housing was then attached with ball attachment on the residual digit model (Figure 3). To facilitate bonding between silicone and metallic attachment, metal housing was covered in an autopolymerizing acrylic resin cap (Pyrex polymers, Roorkee, India; Figure 4).

Impression of the little finger of the other hand was made with an irreversible hydrocolloid impression material (Zelgan; Dental Products of India, Mumbai, India); molten modeling wax was poured into the negative mold of the finger. At the same time, the residual digit model (lubricated) with resin-covered female housing was placed into the corresponding finger space of alginate impression. Wax pattern along with residual digit was recovered, and necessary modifications were made to simulate the left little finger. After satisfactory try-in of wax pattern (Figure 5), the residual digit model along with wax pattern was invested to



Figure 3. Residual digit model with female metal housing.

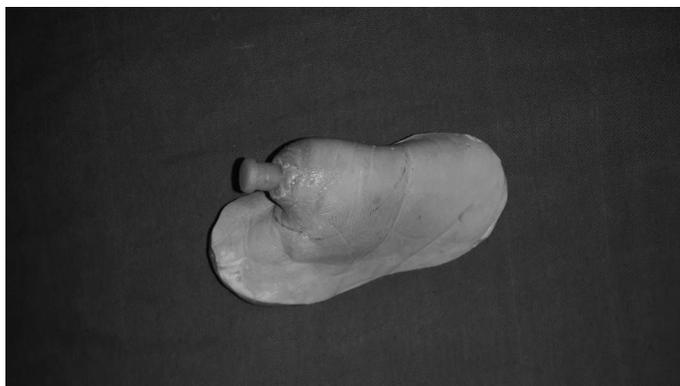


Figure 4. Acrylic resin cap over female housing.

obtain a two-piece mold. After dewaxing, separate shade matching was done for dorsal and ventral aspect of the finger by using digital spectrophotometer (E-spectrophotometer; Factor-II Inc. SPECTRO). Silicone material (M511; Technovent, United Kingdom) was layered into the mold in required locations; primer (Platinum primer-G611; Technovent, United Kingdom) was applied to the acrylic cap of female housing. The packed silicone material was cured at 100°C for 1 hour. After sufficient cooling, the prosthesis was carefully retrieved and finished. Fit and retention of prosthesis was evaluated. Extrinsic stains were applied in natural daylight for final shade matching. Prosthesis was delivered to the patient (Figure 6). Instructions for care were given. The patient was advised against applying heavy pressure on the finger or excessive sun/dust/dirt exposure. The appearance of the prosthesis was scored subjectively using a visual analogue scale (VAS)¹⁵ as excellent (score, 8). Although the patient was not very concerned about function with the prosthetic finger, it was assessed objectively by using the Jebsen Hand Function Test, which evaluates hand function by the time taken to carry out specific daily activities.¹⁶ The test displayed consistently slower functions with prosthesis fitted hand compared with the contralateral normal hand. The patient was also able to perform some activities such as grasping and holding light objects. Patient was recalled initially 1 week after prosthesis insertion and further after 1 month for periodic evaluation.

The follow-up of the patient at 2 months, however, revealed some biological complications related to peri-implantitis, pain, soft tissue swelling, and implant mobility. Efforts were made to prevent implant failure by oral antibiotics, rest, and hygiene procedures, but unfortunately, the implant failed at 3-month follow-up. The implant was removed and space was created and filled with graft material to preserve bone for future implant placement.

DISCUSSION

Total or partial amputations of digit leave individuals with an inevitable abnormality and variable function of the hand. Although vacuum-retained prostheses can provide exceptional aesthetics for some amputations, they require sufficient residual

finger length and are prone to dislodgement. These shortcomings of conventional prostheses might be mitigated by using bone-anchored implants.^{2,5,8,9}

Apart from providing a secure attachment for a prosthesis, a titanium implant offers additional advantages such as less feeling of weight, more control over the prosthesis, and possible restoration of some tactile feedback.^{14,17} The vibration and position sensations acquired by osseointegration of the implant have been described as “osseoperception” by Lundborg et al.⁵ The phenomenon is based on transmission of tactile stimuli from bone to intraosseous nerves through the osseointegrated implant. Aydin et al.² and Doppen et al.⁸ have described the use of bone-integrated conventional oral implants with customized attachments to retain finger prostheses. In the present case, MDI with O-ring system for retention was used. This resilient retention system is composed of a metal housing and a rubber ring. The hexagon-shaped base of the retention unit provides an antirotational feature.

The surgical and prosthetic protocols followed in the present case for placement of MDI in amputated digit were adapted from intraoral mini-implant protocol.^{11,12} The majority of authors have advocated conventional (two-stage) surgical procedure for implant placement mainly for two reasons: to prevent infection and to prevent early implant failure owing to loading with prosthesis.⁷ Number of stages also depends on the initial/



Figure 5. Wax pattern try-in.

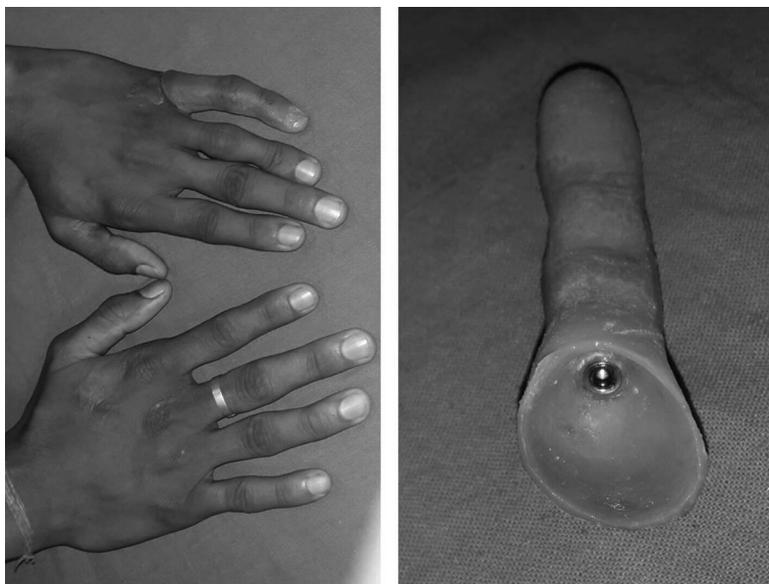


Figure 6. Final prosthesis.

primary stability of the inserted implant and quality of bone at the implant site. The self-tapping design of MDI led to bone compression and condensation during its insertion, which ultimately helps to establish good primary stability. Therefore, early loading was carried out with prosthesis. Amornvit et al.¹³ and Yeshwante et al.¹⁷ have also reported one-stage technique for implant (conventional) placement to retain finger prosthesis.

Less treatment time, less postoperative pain, fewer hospital visits, ability of immediate loading after surgery, and cost-effectiveness are some of the advantages of MDI compared with two-stage surgery using conventional implants.¹⁰ The smaller diameter of MDIs allows them to be successful in cases with limited bone that might not be a candidate for conventional wide-diameter implants. MDI are less invasive and can be placed and loaded on same day, or some days after implant placement as compared with their wider counterparts.

The outcomes of the present case showed that an implant-retained finger prosthesis provides a high level of aesthetic enhancement and limited functional enhancement as well. Successful osseointegration and excellent prognoses have been reported for various titanium implants used in finger rehabilitation^{2,5,9,13}; however, failures do exist in literature.^{8,14} Doppen et al.⁸ reported implant failure owing to infection, and Sierakowski et al.¹⁴ addressed loosening of implant due to trauma. In the present report, an implant was placed in the little finger, which failed at 3-month follow-up. Failure might be attributed to the following: inappropriate selection of case, early loading of implants, excessive functioning with prosthesis, and inability to maintain adequate soft tissue hygiene.

Once an implant has been removed for any reason, it is feasible, after allowing soft and hard tissue to resolve, to repeat the entire process, provided healing is uneventful.

The take-home lessons from this case included need for a shorter follow-up timeline with early implant loading, better case selection, and great emphasis on initial and long-term

follow-up instructions. With MDI, there is guarded prognosis with early loading protocol in case of MDI-retained finger prosthesis; therefore, one may prefer delivering an MDI-retained finger prosthesis at least 4 to 6 months postimplant placement.

CONCLUSIONS

The use of osseointegrated MDIs to retain finger prostheses in patients with short residual fingers seems to be a viable clinical concept as it provides aesthetics, function, and generally excellent retention to the prostheses, although some complications and failure might be experienced. One-stage surgery reduces the treatment time and could provide more comfort and psychological satisfaction to the patient. However, this approach should be used cautiously as it is technique sensitive, requires an expert multidisciplinary team, careful patient selection, and suitable follow-up of surgical and prosthetic protocols as well as proper home care and hygiene. Long-term studies of implant-retained finger prostheses are needed.

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An Innovative Technique to Simplify and Improve Pattern Fabrication for Digital Somatoprosthesis

Himanshi Aggarwal, MDS, Saumyendra Vikram Singh, MDS

ABSTRACT

Introduction: Patterns for somatoprostheses are conventionally made of modeling wax.

The rigidity, brittle nature, reduced edge strength, and susceptibility to distortion of this wax often leads to failure in achieving marginal thinning and desired aesthetics.

Technique: A technique for fabrication of digital somatoprosthetic wax patterns with thin accurate margin by incorporation of a vacuum-formed polyvinyl chloride (PVC) template is described.

Results and Discussion: The technique helps in overcoming limitations of an all-wax pattern and improves accuracy and aesthetics of outcomes.

Conclusions: Incorporation of a PVC template in a somatoprosthetic wax pattern is a valuable technique to achieve good aesthetics and accuracy with the prosthesis. (*J Prosthet Orthot.* 2019;31:67–69)

KEY INDEXING TERMS: vacuum-formed formed polyvinyl chloride, digital somatoprosthesis, wax pattern, marginal fit

The most frequently encountered defects requiring a somatoprosthesis are partial finger amputations.¹ Such defects result in reduced manual dexterity and cause marked psychological burden arising from aesthetic loss. The residual digit at the site of amputation is often thickened with redundant soft tissue, leading to difficulty in obtaining ideal prosthesis shape and thickness in this region. Surgical recontouring is recommended in such cases. However, a patient's reluctance to undergo surgery often precludes this option.² In such cases, a wax pattern fabrication and trial is challenging.

A good prosthesis should have feathered margins merging with adjoining normal tissue. Redundant soft tissue at the distal end of the residual digit necessitates compensatory thinning of the prosthesis. The final prosthesis can only be as good as the pattern it is made from. Wax with its intrinsic disadvantages of distortion, rigidity, poor edge strength, and brittleness^{3,4} lends itself poorly to the cause. Thickened margins to compensate for these intrinsic defects are likely to be replicated in the final prosthesis. Another approach is to arbitrarily thin the pattern after final try-in and before investing. However, the result of this can only be an estimate. Therefore, aesthetics of the most crucial

area of the prosthesis often gets compromised. The given technique describes a method to overcome this issue.

TECHNIQUE

1. Examine the site of amputation for presence of redundant soft tissue (by palpation and radiological examination (Figure 1).



Figure 1. Residual digit.

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Figure 2. Residual digit model with PVC template.



Figure 4. Pattern fabrication over PVC template.

2. Make an impression of the residual digit using irreversible hydrocolloid impression material (Alginate; Aramex Trading Co), and pour with diestone/dental stone (Kalstone; Kalabhai Pvt Ltd) to obtain the working model.
3. Reduce residual digit model by 1 mm all around the designated area of contact to ensure a snug fit.^{1,5}
4. Adapt a thermoplastic 1-mm-thick (0.040 inch) 5 × 5 inches polyvinyl chloride (PVC) thermoplastic sheet (Sof-tray sheets; Ultradent Products Inc) on the residual digit model with a vacuum former machine⁵ (Figures 2 and 3).
5. Check for adaptation and extension of the PVC template till intended margin on reduced residual digit. Trim if needed.

6. The template may be thinned out or feather-edged, if required, with direct heat and burnishing pressure.
7. Use either donor technique or patient's opposing hand for pattern fabrication.¹
8. Orient and attach the finger pattern on to the PVC template.
9. Shape and texture the pattern on the residual digit. In areas at the margin where the pattern seems to be thick, even entire wax may be removed (Figures 4 and 5).
10. Proceed with trial and make necessary modifications for fit, emergence, and orientation of the wax pattern on the patient's natural residual digit (Figure 6).
11. Invest the completed wax pattern (on PVC template), followed by dewaxing.



Figure 3. Residual digit model with PVC template.



Figure 5. Pattern fabrication over PVC template.

- Remove the template from dewaxed mold and process silicone according to manufacturer recommendations (Figure 7).

DISCUSSION

This article describes a technique for fabrication of a digital somatoprosthetic wax pattern where a PVC template is used as a substitute for wax in marginal areas that demand thinness. This technique helps to overcome limitations of the all-wax pattern, allowing shaping of the pattern more anatomically, easing its clinical evaluation and improving the overall aesthetic outcome. Flexibility and tear strength of PVC facilitate better marginal thinning/merging.

Use of PVC sheet as base/liner in relation to orbital and auricular pattern/prosthesis^{2,4} has already been documented. This article presents its use for the first time in a fabrication of a somatoprosthetic pattern.

The disadvantages of this technique include need of additional equipment such as vacuum former machine, increased cost of PVC sheet,⁴ added steps in pattern fabrication, and dewaxing.



Figure 6. Somatoprosthetic wax pattern trial with thin well-adapted margins.



Figure 7. Final prosthesis in situ.

CONCLUSIONS

Incorporation of a PVC template facilitates fabrication and clinical evaluation of a digital somatoprosthetic wax pattern, with overall improvement in the aesthetic outcome.

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So

Custom-Soldered, Double-Ring Retained Silicone Finger Prosthesis

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ABSTRACT

Introduction: Accomplishment of adequate retention in prosthesis is vital to patient comfort. The purpose of this article is to present a technique of fabrication of a nonimplant, nonadhesive retained silicone finger prosthesis for a short, flabby residual digit.

Materials and Methods: To achieve adequate retention in this compromised clinical scenario, two rings were used: one on the residual finger and the other on the adjacent finger, which were soldered at accurate orientation using a custom-made putty index.

Results: Retention of the prosthesis was found to be satisfactory and alleviated the apprehension of the patient regarding surgical placement of implants.

Conclusions: The technique described in this report provides an effective, reversible, and straightforward method of managing the compromised situation. The double-ring technique offers a nonsurgical alternative to rehabilitation of patients with compromised residual digits. (*J Prosthet Orthot.* 2019;31:159–162)

KEY INDEXING TERMS: silicone, finger prosthesis, small, flabby/compromised residual digit, double-ring, prosthesis

Partial or total amputation of fingers can be attributed to various reasons including trauma, burns, congenital absence, and malformations. Loss of a digit results in impairment of function and compromised aesthetics, causing reduced self-confidence and disengaged social behavior.^{1,2} Also, the influence of hand gestures on the body language of an individual cannot be underemphasized.³

The course of treatment depends on the level of amputation, soft tissue condition of the residual digit, and patient preference. In case of a compromised residual digit as presented in this case report, the benefits of microvascular reconstruction of the missing digit or osseointegrated implant retained prosthesis is well recognized. However, these treatment options are irreversible, expensive, and may be associated with postoperative complications.

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This report presents an attempt to fabricate a conventional custom silicone prosthesis for a compromised residual finger with modifications to retain the prosthesis without any invasive technique.

CASE DESCRIPTION AND METHODS

HISTORY

A 35-year-old male farmer reported to this department with the chief complaint of unaesthetic appearance of right hand due to missing fifth digit lost due to trauma 1 year ago. On examination, the fifth digit of the right hand was missing at a level just distal to the proximal joint. The residual digit was covered by healthy skin with no signs of scarring or pigmentation. No sensory disturbances were observed (Figure 1).

The patient was aware that he was the subject of a case study, that information about him including photos related to the case was being published, and that he had been given an opportunity to review the submitted manuscript. A written consent was signed by the patient.

MATERIALS AND METHODS

An impression of the residual digit was made along with the adjacent finger in irreversible hydrocolloid material and poured in high-strength dental stone. The impression of the residual digit alone was not made as it caused distortion of the anatomic form of the residual digit at the area of junction with the adjacent ring finger.

The residual digit was separated from the adjacent finger by cutting with a fret saw (Figure 2). The dorsal and ventral sides of the residual digit were labeled, and uniform 2-mm circumferential reduction of the residual digit was done up to the metacarpophalangeal joint.

An irreversible hydrocolloid impression of the little finger of the normal hand was made, and modeling wax was poured into it.



Figure 1. Residual digit.

The patient was instructed to slightly flex the interphalangeal and the metacarpophalangeal joints during impression making. The residual digit was oriented and inserted into the poured molten wax finger.

Once the wax hardened, the wax finger was removed, inspected, and altered for appropriate fit, orientation, anatomy, details, and contour (Figure 3).

Then, the pattern was invested in high-strength dental stone using a two-pour technique (Orthocal), dewaxed, and made ready for packing of silicone. Shade matching was done using a digital spectrophotometer. Silicone material was mixed according to color code and packing was done. Curing of the prosthesis was done for 90 minutes at 100°C.

The cured prosthesis was retrieved and tried on the patient. It was decided to use silver split rings with adjustable diameter for retention. Adequate retention was not achieved using a primary retentive finger ring on the residual digit. Therefore, it was decided to use another ring (secondary retentive ring) on the adjacent finger, which was welded to the primary ring.

The orientation of the prosthesis and the rings was determined on the patient's hand (Figure 4). The rings were joined in correct spatial position using sticky wax (Figure 5). Their



Figure 2. Residual digit model.



Figure 3. Wax pattern trial.

position was preserved on a putty index. The rings were soldered in this position (Figure 6).

To achieve accurate color matching, extrinsic staining of the prosthesis was done. The prosthesis was inserted along with the soldered double ring (Figure 7).

RESULTS

Retention of the prosthesis was found to be adequate and the patient was satisfied.

DISCUSSION

Retention is one of the most important aspects in designing a finger prosthesis. Silicone stretches and grasps the residual digit



Figure 4. Prosthesis before extrinsic staining.



Figure 5. Oriented double rings.

with positive pressure. This requires the residual digit to have firm, bony content and at least 1.5 cm in length.⁴

With reduction in the length of the residual digit, the contact area of the silicone is reduced. This diminishes the gripping effect of silicone. The reduced length of the residual digit, along with excessive redundant fibrous tissue in this case, compromised the retention, even with the use of adhesives.



Figure 6. Double-ring index.

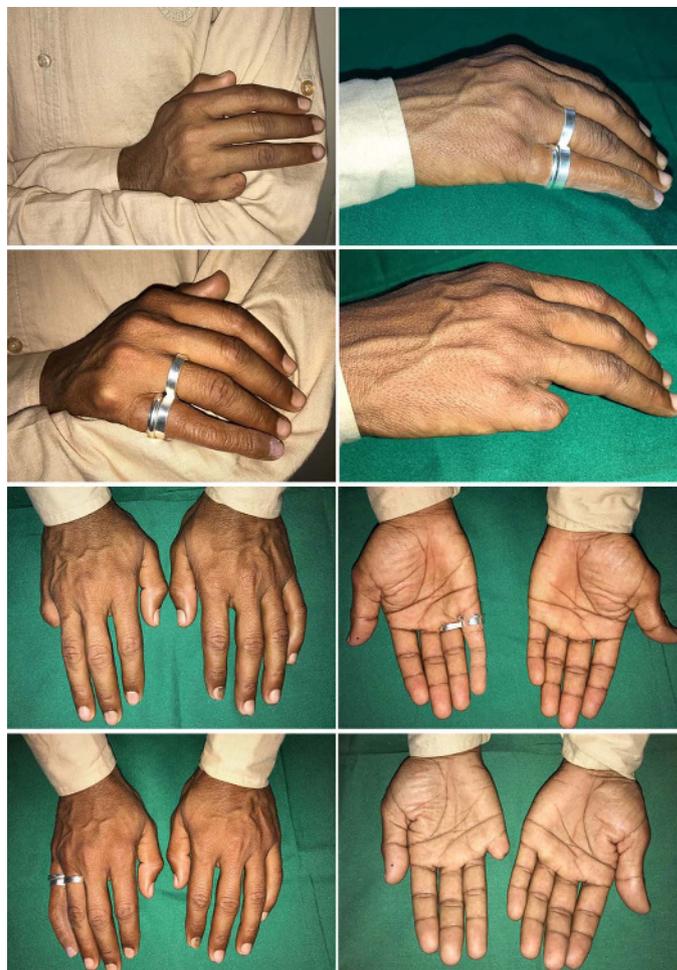


Figure 7. Final prosthesis from different views.

The use of adhesives are associated with prosthetic complications like discoloration and tear at the margins,⁵ reduction in the bond strength of acrylic polymer-based adhesives on contact with water,⁶ difficulty in removal of adhesive from the surface of the skin, and increased likelihood of fungal infection. The adoption of implants for retention, although preferred in such a case,⁷ is not readily accepted by many patients. The adverse consequences⁸ of implant surgery such as infection,⁹ loosening of implant due to trauma,¹⁰ increased expenses, and heightened time of treatment makes it unacceptable for some patients, such as the participant in this report.

Accordingly, modifications in the treatment plan were made during different stages of treatment. Uniform, anatomical reduction of the residual digit diameter was done to achieve a positive grip on the residual digit. Making the impression of the contralateral normal finger provided a provisional wax pattern. The contour of this pattern was improvised such that it resembled that of the opposite finger. This method was more predictable and immediate than carving out a new prosthesis from scratch.

The secondary ring used on the ring finger provided required retention. Soldering the rings using putty index was an important step in maintaining orientation of the rings.

CONCLUSIONS

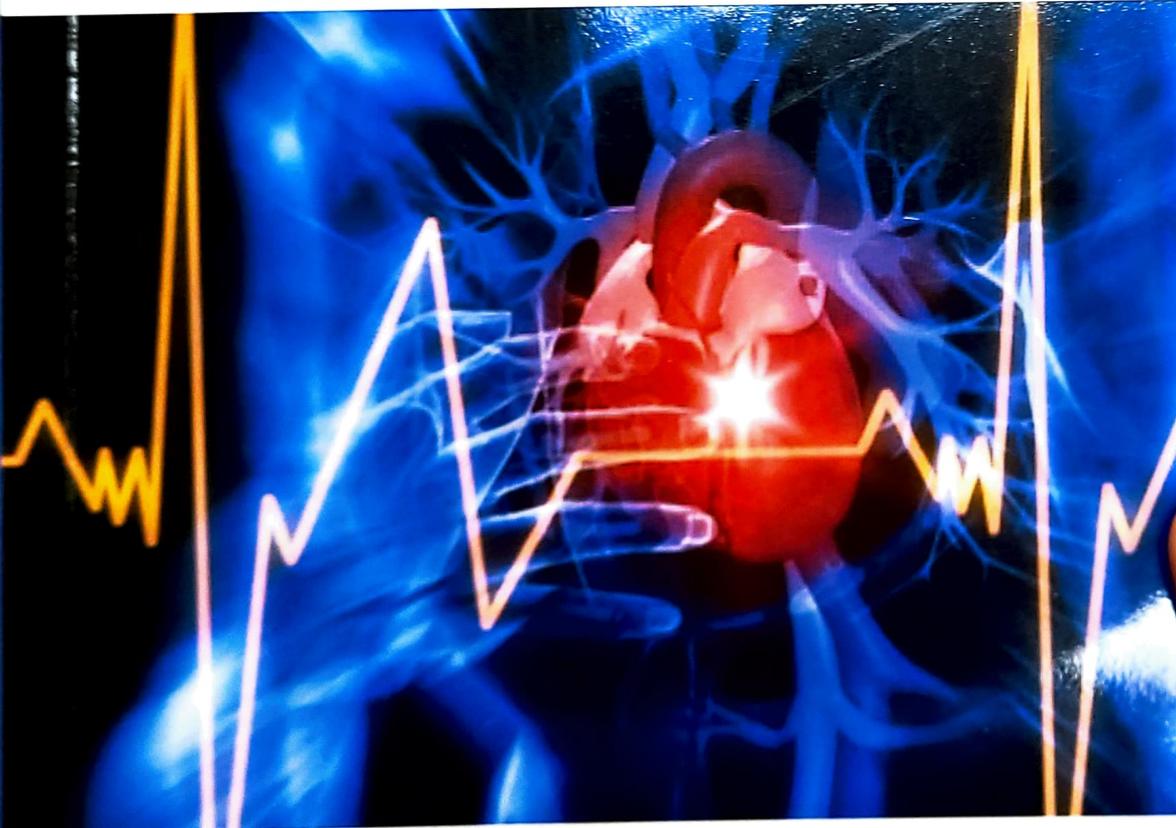
Despite the challenges presented in this case, a satisfactory outcome was observed without the use of adhesives. This signifies that basic prosthetic principles, with some reworking, can be of great caliber in managing such a case.

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Peripartum Cardiomyopathy— Diagnosis and Management

Rishi Sethi, Akshyaya Pradhan, Amit Kumar Singh

DEFINITION

The 2010 European Society of Cardiology (ESC) working group defined peripartum cardiomyopathy (PPCMP) as “an idiopathic cardiomyopathy with the following characteristics: Development of heart failure (HF) toward the end of pregnancy or within 5 months, absence of another identifiable cause for the HF, and left ventricular (LV) systolic dysfunction with an ejection fraction (EF) of usually <45%.¹ The left ventricle may or may not be dilated. Generally, it is a diagnosis of exclusion.

PREDISPOSING FACTORS

Age >30 years, teenage pregnancy, African descent, multiparity, a history of pre-eclampsia, eclampsia, peripartum hypertension, diabetes, and long-term (>4 weeks) oral tocolytic therapy with β -adrenergic agonists such as terbutaline are the predisposing factors for PPCMP.²⁻⁴

CLINICAL PRESENTATION

The presentation of PPCMP is often indistinguishable from other forms of systolic dysfunction of the left ventricle. Additionally, it may mimic other forms of peripartum discomforts in healthy women (fatigue, shortness of breath, and edema). Signs and symptoms of systemic or pulmonary thromboembolism may be present, particularly if left ventricular ejection fraction (LVEF) <35%. The incidence of LV thrombus is as high as 10–17% in this subset of females.^{3,4}

DIAGNOSIS

Timing of presentation is of utmost importance for suspecting the diagnosis. Most of the patients present within 1 month postpartum, preferably in the 1st week. Presentation before 36 weeks of gestation is unlikely.

- *Electrocardiography:* These changes are nonspecific but do help out in ruling out other potential differential diagnoses such as myocardial infarction and pulmonary embolism.
- *Echocardiography:* It is the imaging modality of choice, which generally shows global hypokinesia with LVEF <45%. Echocardiographic marker

which portend poor prognosis include initial LVEF <30%, marked LV dilation (LV end-diastolic diameter >6.0 cm), and right ventricular involvement.⁵

- **Biomarkers:** Because of high morbidity associated with the disease, biomarkers have the potential for early identification of cases and referral to experts for further management. Natriuretic peptides remain the maximally utilized and widely available biomarker [i.e., brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP)] and normal values can essentially exclude acute HF immediately.

Cardiac magnetic resonance imaging (MRI) is not generally required to make the diagnosis of PPCMP, but it can be helpful to assess LV systolic function and LV volumes, particularly if echocardiography is suboptimal.

Right heart catheterization and endomyocardial biopsy are generally not recommended routinely in patients with suspected PPCMP.

MANAGEMENT

Management is largely similar to treatment for HF with reduced EF. In the antepartum period, however, modifications to standard therapy are often necessary to ensure the safety of the mother and the unborn or breastfeeding child (See **Table 1**).^{6,7} Diuretics are used with caution to avoid volume

TABLE 1: Safety of heart failure pharmacotherapy during pregnancy and lactation.

Drug	Use in pregnancy	Use in lactation
ACE inhibitor	Contraindicated; teratogenic	Use with caution as limited data; captopril and enalapril have maximum safety data
ARB	Contraindicated; teratogenic	Avoid; use ACE inhibitor instead; no data
ARNI	Contraindicated, fetotoxic	Avoid; use ACE inhibitor instead; No published data; if needed, use alternative methods of feeding
BB	<ul style="list-style-type: none"> • Use with caution; can cause IUGR • Watch for signs of bradycardia and hypotension in new born 	Use with caution; metoprolol has maximum safety data and bisoprolol has limited data
MRA	Contraindicated; feminization in fetus in animal studies	Use with caution—can suppress lactation; spironolactone has limited data for safety
Loop diuretics	Use with caution; potential for jeopardizing uterine flow	Use with caution—can suppress lactation; no data for safety
Thiazide diuretics	Use with caution; potential for jeopardizing uterine flow	Use with caution—can suppress lactation; hydrochlorothiazide has maximum data for safety
Ivabradine	Contraindicated; teratogenic	Avoid; no published data; if needed, use alternative methods of feeding
Digoxin	Use with caution, especially indicated when AF if present	Use with caution; limited data

(ACE: angiotensin-converting enzyme; AF: atrial fibrillation; ARB: angiotensin-receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor; BB: β -blocker; IUGR: intrauterine growth restriction; MRA: mineralocorticoid receptor antagonists)

depletion in mother which can have adverse effects on the fetus. Thiazides are the best-studied group of diuretics in these patients. Diuretics are used for symptomatic benefit and are the first drug to withdraw, once the patient stabilizes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are contraindicated in the antepartum period, while hydralazine/nitrate is one drug combination that can be used in the antepartum period to reduce preload.

Postpartum management of HF is none different from other individuals, except caution for drugs which can be excreted in breast milk. During lactation, ACE inhibitors—enalapril and captopril can also be used as spironolactone.

Acute HF is managed aggressively with supplemental oxygen and assisted ventilation (if $SpO_2 < 95\%$) as needed, optimization of preload and hemodynamic support with inotropes and vasopressors, if required. Nitroprusside is recommended to be better avoided due to possible cyanide toxicity and with dobutamine, the outcomes may be worst.¹

Anticoagulation

Anticoagulation is advised by American Heart Association (AHA) if LVEF is $< 30\%$ during late pregnancy and up to 8 weeks postpartum. Warfarin, we know is contraindicated during pregnancy, but low molecular weight heparin can be used. Both these agents are safe during lactation.¹

Arrhythmia

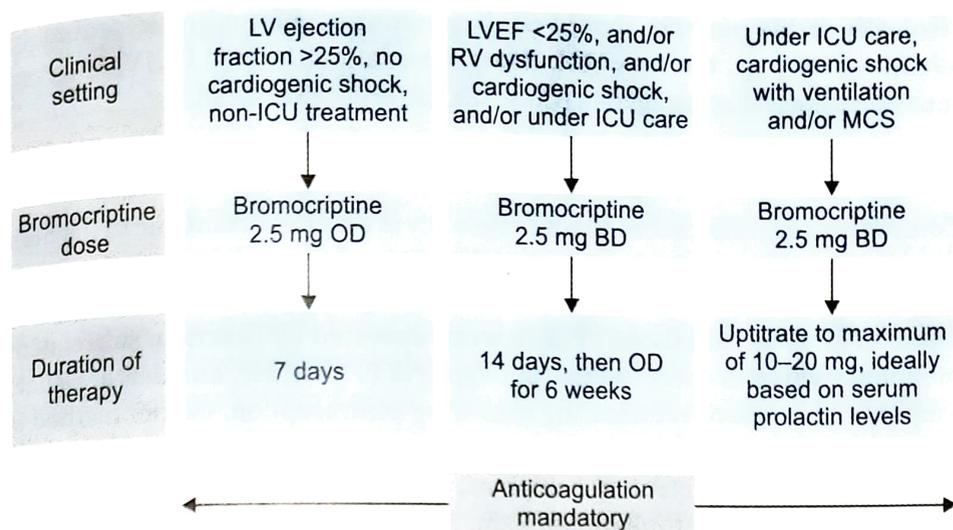
Arrhythmias are common in patients hospitalized for PPCMP. The reported incidence of arrhythmias in hospitalized patients for PPCMP is around 18–20%.² Out of which, ventricular tachycardia constituted 4–5% and atrial fibrillation in around 3.1–11.9%. Generally, ventricular tachycardia in PPCMP is refractory to pharmacologic treatment (e.g., lidocaine, metoprolol, and amiodarone) and may require direct current cardioversion. During pregnancy, a rhythm control strategy is often preferred over rate control for atrial fibrillation.

Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) should generally be deferred at least 3 months and possibly, even 6 months following the presentation, with the patient receiving optimal medical therapy (OMT) to determine whether, criteria for placement are present.

Patients with hemodynamic instability and unresponsiveness to medical therapy with maximal inotropic support are early candidates for mechanical circulatory support.

Bromocriptine

Based on the pathogenetic role of 16-kDa prolactin fragment, a therapeutic role of bromocriptine in PPCMP has been proposed.³ In small randomized studies, it has shown improvement in EF and lower mortality. However, small sample size, open labelling, and lack of placebo arm are few criticisms of these studies precluding generalization of results. No difference in outcomes was found in different dosing regimens. Moreover, the drug is also notorious for thromboembolic complications and hence, use is justified when benefits outweigh the risk. Hannover School of Medicine advises the use of prophylactic



(ICU: intensive care unit; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; RV: right ventricular)

FIG. 1: Bromocriptine regimens in peripartum cardiomyopathy based on different clinical scenarios in the patient. Hannover protocol

anticoagulant, while using bromocriptine because of its prothrombotic effect, especially when pregnancy itself is a procoagulant state.⁶ **Figure 1** depicts the various bromocriptine regimens proposed by the Hannover school of Medicine based on the clinical scenario of the patient. The usual duration of therapy is 8 weeks.

Other investigational therapies being utilized include antisense oligonucleotide against microRNA (mi-RNA) 146a, vascular endothelial growth factor (VEGF) analogs, serelaxin, perhexiline, and pentoxifylline.¹⁰

Delivery

Urgent delivery may be required in women with advanced HF with hemodynamic instability, while planned cesarean delivery is preferred for women with advanced HF requiring inotropic therapy or mechanical circulatory support. As for women with other types of cardiac conditions, cesarean delivery in patients with stable cardiovascular status is generally reserved for obstetrical indications (e.g., failure of progression of labor, placenta previa, and fetal intolerance of labor).

Breastfeeding

Prolactin is implicated in the pathogenesis of PPCMP, so, the 2010 European guidelines on PPCMP advise against breastfeeding.¹ But, some small studies have shown that breastfeeding is safe. Breastfeeding confers a multitude advantages, especially on resource-poor countries, where availability of formula feed and clean water, both can be challenging. Moreover, most of the frontline HF drugs are compatible with breastfeeding except ARBs. Bromocriptine therapy is a concern as bromocriptine suppresses lactation. But, there are many reports of successful breastfeeding on bromocriptine. Hence,

clinically stable patients should not be discouraged from breastfeeding. In advanced HF [e.g., the New York Heart Association (NYHA) III/IV] however, breastfeeding is discouraged in (Class IIb, Level of evidence B).

Contraception

Counseling regarding subsequent pregnancy is very important due to the high chance of recurrence. Patients with LVEF $\leq 25\%$ at diagnosis are at high risk of recurrent PPCMP and should avoid future pregnancy (III B). For those with index LVEF $>25\%$ and those PPCMP with recovered LV function, subsequent pregnancy will still carry the risk of relapse of PPCMP, HF, and death. Hence, they should be offered counseling regarding contraception. Barrier method is a good option. Estrogen-progestin contraceptives should be avoided because it may increase fluid retention, which may worsen HF and has the potential to increase the risk of thromboembolism. Progesterone-only implant is a good option. Copper intrauterine device (IUD) or hormone-releasing IUD may be other alternatives.

MATERNAL MORTALITY AND MORBIDITY

It has been reported as approximately 8–9% at 2 years in recent studies.¹¹ The recently published ESC global registry of PPCMP has shown that the 6 months mortality rate was 6% and nearly 50% of the deaths occurred within the first 30 days of diagnosis.¹² This represents a dramatic improvement from the initial studies of the 1970s, when the mortality was in the range of 30% at 5 years. Data from Indian studies, percutaneous endoscopic gastrostomy (PEG) mortality estimates somewhere between 5 and 55%, indicating the heterogeneous nature of studies.¹³ The markers of adverse prognosis include higher NYHA functional class, LVEF $\leq 25\%$, multiparity, and age >30 –35 years.

RECOVERY OF LEFT VENTRICULAR FUNCTION

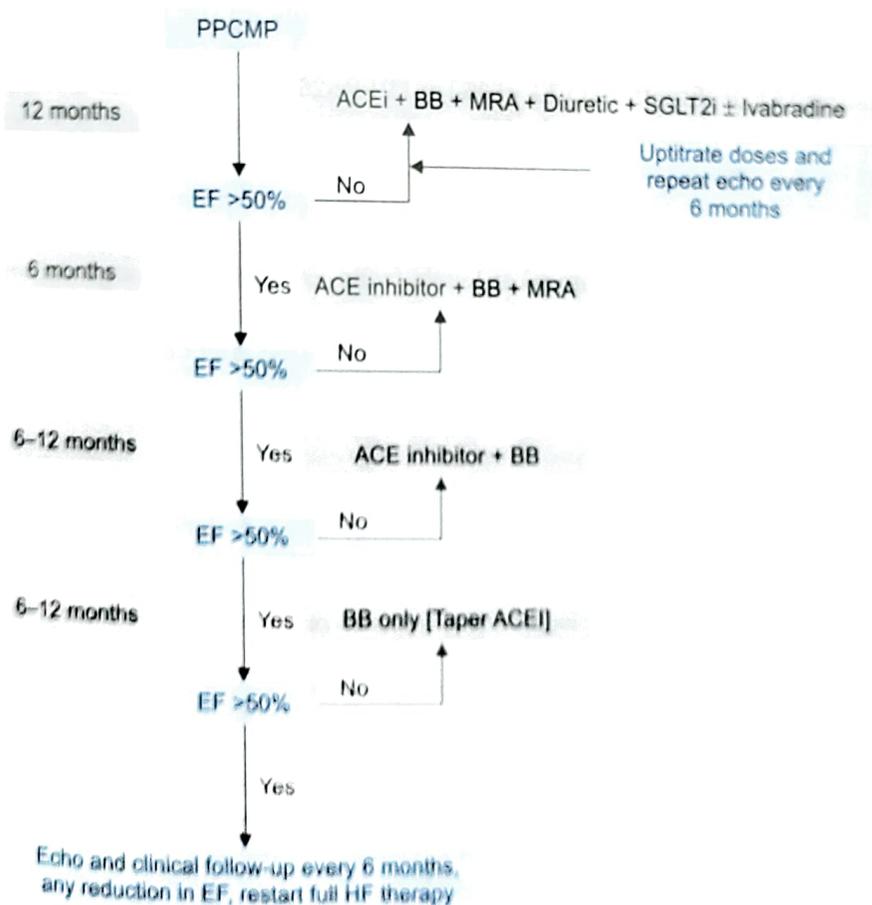
Partial or complete recovery of LV function is common among patients with PPCMP and appears to be more frequent than with other types of dilated cardiomyopathy (DCM). Complete recovery of LV function (defined as recovery to an LVEF $>50\%$) has been reported in 20–60% of patients in various series.^{3,4,14} In the recent ESC-EORP (EURObservational Research Programme) global registry, the recovery of LV function to $>50\%$ was seen in $<50\%$.¹² Although nearly most of the recovery of LV function occurred within 6 months of diagnosis in some series, delayed recovery of LV function has been observed in other studies. Predictors of persistent LV dysfunction at follow-up: LVEF $\leq 30\%$, fractional shortening $<20\%$ and an LV end-diastolic dimension ≥ 6 cm, elevated cardiac troponin T, black race, diagnosis during pregnancy, reduced right ventricular function, and presence of LV thrombus.

While the recovery of LV function in patients with PPCMP is related to the degree of dysfunction at the time of diagnosis, baseline LVEF has limited sensitivity for prediction of improvement in individual patients. The impact of pre-eclampsia or hypertension on the prognosis of PPCMP is unclear.

THERAPY AFTER RECOVERY OF LEFT VENTRICULAR FUNCTION

In those patients, who continue to have LV dysfunction, HF therapy is to be continued.

A subset of patients with PPCMP will achieve full recovery of LV function (LVEF >50%) eventually, but LV dysfunction can reoccur despite initial full recovery and this recurrence risk is not limited to occurring during subsequent pregnancies. There are no major societal guidelines regarding the stoppage of HF drugs on recovery of ventricular function. The TRED HF (A Pilot Feasibility Study in Recovered Heart Failure)² has shown that up to 44% of the patients with DCM had recurrence of LV function on complete withdrawal of HF therapy within 6 months.¹⁵ Though DCM and PPCMP cannot be equated, we have to exercise caution in completely withdrawing HF therapy in those who have recovered. **Flowchart 1** represents a suggested algorithm for duration and weaning of pharmacotherapy for PPCMP.



ACEi = angiotensin-converting enzyme; BB = β -blocker; D = digoxin; Diuretic = furosemide; EF = ejection fraction; PPCMP = peripartum cardiomyopathy; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter 2 inhibitors.

FLOWCHART 1: Duration of heart failure pharmacotherapy (respirancy) following delivery based upon conditional recovery of ventricular function.

In those with recovered LV function, available observational data support continued therapy indefinitely.¹ There is a school of thought that patients who have recovered (LVEF >50%) for a period of at least 6 months, stepwise weaning of the HF regimen can be tried. This should be with close clinical follow-up (e.g., initially monthly, then every 3–4 months) and with echocardiographic monitoring (every 3–6 months) to ensure the stability of LV function during and for at least 1–2 years after weaning of HF medications to ensure stability. A decline in LV systolic function as documented by echocardiographic assessment, or the recurrence of HF symptoms at any point in the process of weaning HF medications, would dictate a reinstitution of standard HF therapy and life-long continuation.

These recommendations are based on expert opinion only; there is a paucity of data in this area to guide clinicians. It is highly imperative that if HF therapies are withdrawn, the patient should be followed very closely clinically and by echocardiography to ensure stability.

EFFECT ON SUBSEQUENT PREGNANCIES

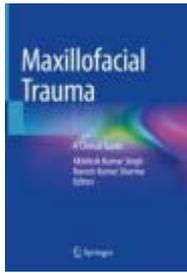
All women with PPCMP should receive counseling on the potential risk of recurrence with future pregnancies. Women with a history of PPCMP who have persistent LV dysfunction (LVEF <50%) or LVEF ≤25% at diagnosis is advised to avoid pregnancy due to the risk of HF progression and death (Grade 2C). Those who have recovered also carries risk of recurrence, but there are some reports of successful uneventful pregnancies. In subsequent pregnancies, women who had PPCMP should be very closely followed with clinical assessments, echocardiograms, and biomarker levels from conception through delivery and up to 6 months. ACE inhibitors/ARB and aldosterone blockers should be discontinued prior to conception and may be restarted after delivery.

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Maxillofacial Trauma

A Clinical Guide

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- Naresh Kumar Sharma
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Chapter 78

Balancing Bleeding Risk with Risk of Embolism in AF: The Eternal Dilemma

RISHI SETHI • AKSHYAYA PRADHAN • MAHIM SARAN

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice affecting 1%–2% of patients and is more prevalent in the elderly. Apart from symptoms and haemodynamic deterioration, the most dreaded complication of AF is embolism due to clot. This clot originates in more than 80% of cases from left atrial appendage. Stroke is the most devastating complication associated with embolic risk. Therefore, long-term oral anticoagulation (OAC) has been the cornerstone of therapy to prevent these embolic episodes. Although anticoagulation is very effective in reducing the risk of stroke, it is associated with a significant risk of bleeding.

Warfarin has been the standard anticoagulant for the prevention of stroke but a narrow therapeutic range and bleeding are the major problems associated with its use. With the advent of newer oral anticoagulants (NOAC), the bleeding risk has declined significantly. Still in all indicated patients and more so, while dealing with special patient groups like elderly, hypothyroid and renal dysfunction patients, and those requiring antiplatelets, balancing anticoagulation and bleeding becomes a matter of clinical dilemma.

ATRIAL FIBRILLATION AND STROKE

AF is the most common sustained arrhythmia encountered in clinical practice. It is an independent risk factor for stroke, thromboembolism and death (fivefold risk). Twenty five per cent of patients with stroke are found to have AF¹. Eighty five per cent of strokes in patients with AF are due to thromboembolism and 90% of identifiable thrombi are from left atrial appendage².

Although all grades of stroke can occur in patients of AF, majority of strokes are large, disabling and often lead to mortality as compared to strokes

of other aetiologies^{3–5}. Hence, the role of oral anti-coagulants becomes of paramount importance.

ASSESSING THE RISK OF STROKE

Risk factors for stroke have been formulated by various systematic reviews. The strongest and most consistent risk factors for stroke as reported by Stroke in AF Working Group were a history of prior stroke or transient ischaemic attack (TIA) (relative risk [RR], 2.5), hypertension (HTN) (RR, 2.0), diabetes mellitus (DM) (RR, 1.7) and increasing age (RR, 1.5 per decade). The various risk factors have been used to formulate stroke prediction tools. The most commonly used are CHADS₂ (see ref 6) and CHA₂DS₂VASc (see ref 7) (Table 78-1).

Female gender independently increases the risk of stroke overall. However, if the criterion of age >65 years (lone AF) is clearly fulfilled, female gender is not associated with an increased stroke risk. Also, it has been reported that stroke rates in these patients (age < 65 years and lone AF) are so low in either of the genders (male and female) that antithrombotic therapy is not recommended. Thus, in a female patient,

TABLE 78-1 CHADS₂ AND CHA₂DS₂-VASc SCORES

Clinical Characteristics	CHADS ₂ Score	CHA ₂ DS ₂ -VASc Score
C: Congestive heart failure	1	1
H: Hypertension	1	1
A: Age ≥ 75 years	1	2
D: Diabetes mellitus	1	1
S: Stroke or TIA	2	2
V: Vascular disease ^a		1
A: Age 66–74 years		1
Sc: Sex category (female)		1

^aPrevious myocardial infarction, peripheral vascular disease or aortic plaque.

gender alone (still a CHA₂DS₂-VASc score of 1) would not necessitate the use of anticoagulants.

ASSESSING THE RISK OF BLEEDING

Risk factors for stroke prediction and bleeding are more or less the same and hence patients who are at high risk of stroke are also at high risk of bleeding. HAS-BLED score is the most common predictor tool used (Table 78-2) (see ref 8). HAS-BLED score more 1 or equal to 3 is associated with significantly high MACE rates as compared to less than 3 (Fig. 78-1). However, major intracranial bleeding rates with warfarin are 0.2%–0.3% per year.

IMPACT OF ANTICOAGULATION

Anticoagulation in patients with AF has been shown to reduce the incidence of stroke significantly with an acceptable risk of bleeding^{9–11}. However, in some group of patients, balancing the risk of stroke (or

TABLE 78-2 THE HAS-BLED SCORE

Clinical Characteristic	Score
H: Hypertension	1
A: Abnormal renal or liver function	1 (each)
S: Stroke	1
B: Bleeding	1
L: Labile INR	1
E: Elderly age	1
D: Drugs or alcohol	1 (each)

Notes: HTN: >160 systolic.

Abnormal renal function: Chronic dialysis, renal transplant, serum creatinine \geq 2.26 mg/dL.

Abnormal liver function: Bilirubin level >2xULN in association with AST/ALT/ALP >3xULN.

Bleeding: History, predisposition.

Labile INR: Unstable/high INRs, in therapeutic range < 60%.

Drugs/Alcohol: Concomitant use of antiplatelets, NSAIDs, etc.

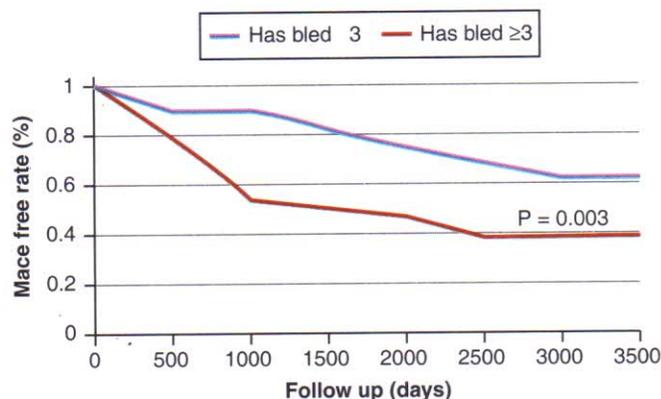


Figure 78-1. Significantly high MACE rates for HAS-BLED score \geq 3. ($P = .003$).

thromboembolism) and bleeding becomes challenging. Hence, assessing the risk of stroke and bleeding for each individual gains importance.

Warfarin has been the mainstay of anticoagulation for past five decades. It reduces the annual risk of stroke by 64% and mortality by 25% compared to control (antiplatelet therapy or placebo)². However, many shortcomings have made a need for an ideal anticoagulant necessary.

NOACs entail two classes of molecules – selective factor Xa inhibitors (the *-xabans*) or direct thrombin inhibitors (the *-gatrans*). They have been studied in various large, multicentre and randomized trials for nonvalvular AF. One of the largest meta-analysis of NOACs versus warfarin demonstrated benefits in favour of NOACs with a significant reduction in stroke and embolism by 19% (RR = 0.81, $P < .0001$), significant reduction in mortality by 10% (RR = 0.49, $P < .0001$) and reduction in Intracerebral hemorrhage (ICH) by 50% (RR = 0.48, $P < .001$)¹².

However, gastrointestinal (GI) bleeding was more frequent with NOACs, especially high-dose dabigatran (RR = 1.25, $P = 0.4$). This evidence led to prescription of NOACs over warfarin in European Society of Cardiology Guidelines for management of AF 2016 (see ref 13). These differences lost most of their significance when tested in patients with renal failure and elderly.

BALANCING THE ACT

Although anticoagulation has been shown to be of great importance in patients of AF with high risk of stroke, its use has been found to be low. Overall, only 55% of warfarin-eligible patients actually use the drug, with the lowest rates seen in the oldest patients – who are at highest risk of stroke^{14,15}. Advancing age is one of the strongest patient-related predictors of withholding use of warfarin in eligible patients. Age more than 80 years is associated with a decreasing use of warfarin, while its use increases with a history of ischaemic stroke. On the other hand, the most common physician-related reasons for not using an anticoagulate is the perception of low benefit versus risk of therapy, lack of patient reliability regarding compliance or monitoring (INR) and fear of catastrophic bleeding.

DILEMMA – THE RISK FACTORS FOR INCREASED BLEEDING ARE MORE OR LESS SAME AS THOSE FOR THROMBOEMBOLISM

The clinical complexity of prevention of thromboembolism in patients of AF is illustrated by the fact that those who are at the highest risk of stroke and

require anticoagulation the most, also have the maximum risk of bleeding. This is reflected in the overlap of stroke predictors and risk factors for bleeding. Anticoagulation in patients with high risk of stroke is therefore a dilemma. Hypertension, prior stroke and elderly age for example, are not only commonly associated with AF but also risk factors for both increased embolic as well as bleeding risk.

Patients with a CHA₂DS₂-VASc score of 0 have been found to have a risk of bleeding on anticoagulation higher than embolic risk without it. However, patients with a high HAS-BLED score (≥ 3) were shown to derive a higher net clinical benefit. The absolute gain in ischaemic stroke reduction in these patients far outweighed the small increase in intracranial bleeding^{16,17}. NOACs may provide an even greater net clinical benefit in these scenarios. In patients with a CHA₂DS₂-VASc score of 1, apixaban and both doses of dabigatran (150 and 110 mg twice daily) were shown to have a positive net clinical benefit. All three NOACs (dabigatran, rivaroxaban and apixaban) appeared to have achieved a superior net clinical benefit when compared to warfarin in patients with a CHA₂DS₂-VASc score ≥ 2 , regardless of their bleeding risk. Thus, in patients where the risks of both stroke and bleeding are elevated, the NOACs appear to have a greater net clinical benefit when compared with warfarin¹⁸.

MITIGATING THE BLEEDING RISK WITH ORAL ANTICOAGULANTS

Multiple pharmacological and nonpharmacological manoeuvres can be utilized to decrease the risk of bleeding in patients on oral anticoagulants (Fig. 78-2).

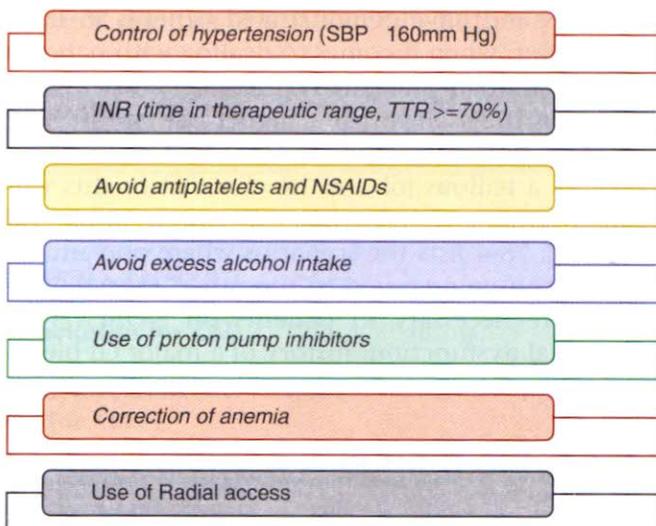


Figure 78-2. Key interventions to reduce bleeding risk with oral anticoagulants.

(a) *Control of hypertension* (SBP < 160 mm Hg): Patient with hypertension should be advised to keep as optimum blood pressure goal as possible. Adherence to antihypertensive medications is of paramount importance to reduce the risk of bleeding (especially intracranial). Aim of reduction of blood pressure should be to at least lower systolic blood pressure below 160 mm Hg.

(b) *Time in therapeutic range* (TTR $\geq 70\%$): Clinically, the adequacy of anticoagulation is measured by the TTR or the time spent in therapeutic range. It influences the likelihood of haemorrhagic complications and has a strong relationship with the incidence of complications such as bleeding, and thromboembolic episodes. TTR < 60% when compared to TTR > 75% is associated with a higher incidence of both major bleeding and mortality rates¹⁹. Patient education and motivation should be done to achieve good TTR by adhering to OAC as well as regular monitoring of INR. Availability of reliable point of care testing for INR is a must. Many studies have shown that patients on warfarin often have very low TTR even in the specialized anticoagulation clinics in the West (see ref 20).

Some groups have devised TTR-based scores and if the probability of keeping TTR > 75% is low in specific patient then the choice of anticoagulation shift towards NOACs.

The **SAMe-TT2R2** score is one such simple score and has been well validated in multiple cohorts with impressive results²¹. Patients with scores > 2 have lower likelihood of attaining TTR > 70% and are predisposed to complications as discussed above. Such patients would not do well on warfarin and hence strong consideration for NOAC use is must. With low scores of 0–2, TTR is expected to be good and trial of vitamin K antagonist (VKA) is reasonable. However, regular follow-up for compliance and TTR monitoring should continue to assess the need to switch to NOAC (Fig. 78-3).

(c) *Avoid antiplatelets and NSAIDs*: Concomitant use of antiplatelets is required in AF patients in post-PCI setting (seen in up to 5%–10% of the cases). Use of both antiplatelets, especially dual antiplatelet, along with OAC leads to increased risk of bleeding^{22,23}. Thus, curtailing of duration of triple therapy is the best strategy. The short duration of triple drug can be achieved by more usage of bare-metal stents. Concomitant use of NSAIDs should also be highly discouraged as much as possible.

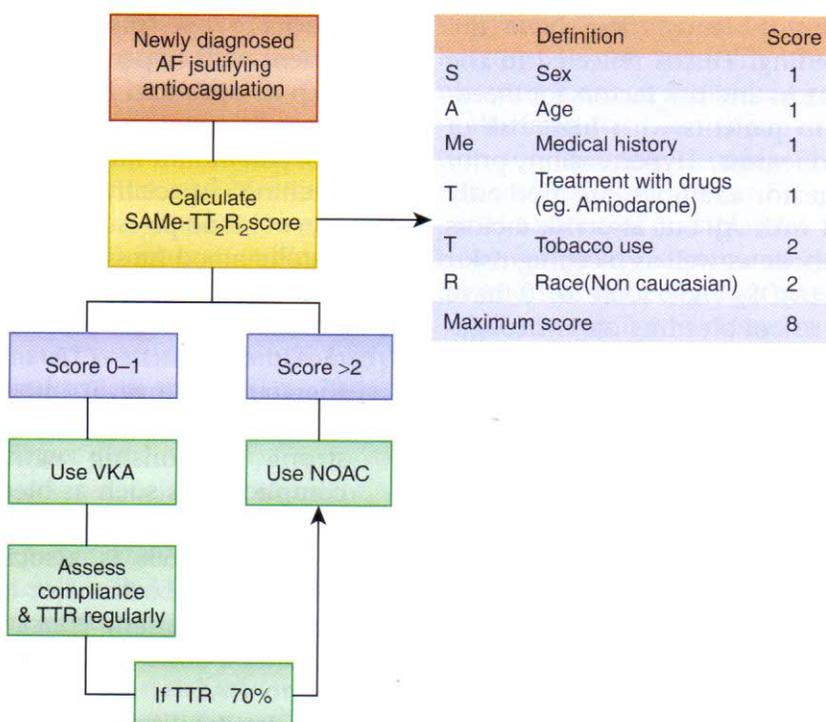


Figure 78-3. Use of SAMeTT₂R₂ score for choosing between NOAC & VKA.

* More than any two of the following- hypertension, diabetes, coronary artery disease, peripheral arterial disease, congestive heart failure, Hepatic disease, renal disease, prior stroke.

(d) *Avoid excess alcohol intake:*

Moderation of alcohol should be advised to candidate of OAC to avoid unpredictable response of OAC therapy. To achieve good TTR, excessive alcohol intake should be discouraged.

(e) *Correction of anaemia:*

It should be priority to correct any underlying anaemia to prevent labile milieu of excessive bleeding and thrombotic events. Comorbidity of anaemia and chronic kidney should be dealt simultaneously.

(f) *Use of proton pump inhibitors*

Elderly people (age greater than 65 years) on oral anticoagulants are vulnerable to GI bleeding. Thus, proton pump inhibitors should be administered to reduce the risk of GI bleeding.

(g) *Reduction of bleeding in PCI setting:*

Radial approach is the most rewarding measure to reduce the local bleeding complications. RIVAL, SAFE-PCI and MATRIX trials have shown benefits of radial route in reducing bleeding events in setting of acute coronary syndrome^{24,25}. Another simple precaution is to take smaller sheath sizes for intervention. Dose of heparin before diagnostic and therapeutic procedure should also be reduced to achieve balanced state of anticoagulation.

VITAMIN K ANTAGONISTS VERSUS NOACs

Warfarin has been the mainstay of anticoagulation in most of the case scenarios. However, many shortcomings have made a need for an ideal anticoagulant necessary. Shortcomings of warfarin include a narrow therapeutic index, variations in individual response and need for regular monitoring. Newer anticoagulants (NOACs) overcome many of these problems and have demonstrated benefits in large studies. But, when it comes to dealing with patients of renal failure or the elderly, these benefits are lost. Balancing the scales with a higher risk of bleeding on one side and a higher stroke risk on the other becomes a tedious job for the clinician in this vulnerable group. Considering the various pros and cons, Fig. 78-4 lists the scenarios where one anticoagulant can be preferred to the other. Dose adjustments are necessary in patients on NOACs who have renal dysfunction, history of a major GI bleeding in the past, age ≥ 75 years or lower body weight.

MANAGING HIGH-RISK GROUPS

1. *Renal dysfunction:*

Patients with CKD are at increased risk of thromboembolism and also bleeding. Hence,

NOAC Preferred	VKA Preferred
<ul style="list-style-type: none"> • Patient can afford • Monitoring INR is difficult • No history of major GI bleed • Non valvular AF (no evidence of moderate to severe mitral stenosis or Prosthetic Heart Valve) • SAMeTTR score >2 • High HAS-BLED Score 	<ul style="list-style-type: none"> • INR within target range and time in therapeutic range >60%, continue warfarin • Valvular AF (Moderate to severe mitral stenosis or Prosthetic Heart Valve)

Figure 78-4. Choice of NOAC versus VKA. NOAC, novel oral anticoagulant; VKA, vitamin K antagonist.

anticoagulation has to be started after carefully assessing the risk versus benefit ratio. One of the major hindrances in starting OACs in these patients was erratic response to warfarin, especially in patients on dialysis. Furthermore, the administration of heparin during dialysis may also add to the anticoagulant effect. The erratic dose response may improve with newer anticoagulants. Dose adjustment for individual NOACs needs to be systematic and hence European Society of Cardiology (ESC) 2016 guidelines for management of AF have given specific criteria (Table 78-3).

In these situations, the economical and psychological burden of the underlying disease and their impact on compliance need to be weighed, as irregular drug administration may only increase the risk of bleeding without any significant benefit.

2. *Elderly:*

Old age is another situation where the risk of thromboembolic stroke as well as bleeding complications is high. Age-related cognitive impairment and risk of frequent falls further add to the

dilemma. Moreover, newer drugs have not shown any additional benefit to warfarin in elderly. When considering anticoagulation in elderly other geriatric problems need to be weighed. In such situations, instead of the widely used scoring systems, proper patient and caretaker counselling and education and individualized approach taking care of the comorbidities become of paramount importance.

3. *Hyperthyroidism:*

Hyperthyroidism being a reversible cause of AF always creates a doubt in both the physician as well as the patients whether to take the risk of thromboembolism or haemorrhage as the AF is likely to resolve once hyperthyroidism is corrected. In a compliant, educated patient with low bleeding risk and risk factors for thromboembolism, anticoagulation should be considered till the AF resolves and LA thrombus is excluded following return to normal sinus rhythm.

ANTIDOTES FOR NOAC

Not only bleeding events with NOAC are consistently reduced, their severity is also diminished^{29,30}. Less frequent and more benign bleeding events equate to fewer anticoagulation interruption. Historically, warfarin scored over NOACs in availability of a specific antidote (vitamin K), should a bleeding event occur. Nevertheless, the onset of reversal with vitamin K is slow and frequently needs fresh frozen plasma or prothrombin complex concentrate. Absence of a specific antidote was also a concern with use of NOACs. Fortunately in past couple of years, several antidotes have come into vogue clearing the dilemma around reversal with NOAC effects (Table 78-4).

TABLE 78-3 DOSE ADJUSTMENTS FOR NOACs AS EVALUATED IN VARIOUS TRIALS

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE-AF-TIMI 48)
Renal Clearance	80%	35%	25%	50%
Dose	150 mg/110 mg OD	20 mg OD	5 mg BD	60 mg/30 mg OD
Exclusion for CKD	CrCL < 30 mL/min	CrCL < 30 mL/min	Serum Cr > 2.5 mg/dL CrCL < 30 mL/min	CrCL < 30 mL/min
Dose adjustment for CKD	None	15 mg OD if CrCL 30–49 mL/min	2.5 mg BD if age ≥ 80 Wt ≤ 60 kg or serum Cr ≥ 1.5 mg/dL	30 mg or 15 mg OD if CrCL < 50 mL/min
Reduction in major haemorrhage as compared to warfarin	Was greater in patients with CrCL > 80 mL/min	Major haemorrhage was similar	Reduction in major haemorrhage	NA

TABLE 78-4 CURRENTLY AVAILABLE ANTIDOTES FOR NOACs WITH COMPLETED CLINICAL TRIALS

Antidotes	Structure	Site of Action	Mechanism of Action	Dose	Clinical Trials
Idarucizumab	Humanized antibody fragment	Dabigatran	Binds dabigatran with high affinity	Two 2.5 g 50 mL bolus IV infusions within 15 min (max 5 g)	REVERSE-AD (phase III) ²⁶
Andexanetalfa	Recombinant human factor Xa	Universal antidote for all FXa inhibitors	Competes with factor Xa inhibitors for binding	400 mg IV bolus 2 h infusion at 4 mg/min	ANNEXA-4 (see ref 27) (phase III)
Ciraparantag/aripazine	Water-soluble cation	Dabigatran, edoxaban, LMWH, UFH	Noncovalent binding	100–300 mg IV single dose	Ansell et al. ²⁸ (phase III)

CONCLUSION

With the available scoring systems and emergence of NOACs, anticoagulation in patients with AF may appear simple mathematics, but when it comes to individual patients with other coexisting problems, weighing the risk and benefits may become a tedious job. Higher cost of NOACs, need for INR monitoring with warfarin, importance of compliance to maintain therapeutic drug levels for significant amount of time and patient understanding of the disease, all need to be weighed before initiation of anticoagulation. It cannot be stressed more that initiation of anticoagulation in a noncompliant patient, uneducated about the disease and unaware about need for follow-up will do more harm than good.

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Chapter 109

Management of Patients Presenting Late after STEMI

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Abstract

Pathophysiology of ST-elevation myocardial infarction (STEMI) involves sudden and total occlusion of an epicardial coronary artery, making immediate restoration of blood flow by primary percutaneous intervention (PCI) as the most logical choice of therapy. Several studies have already established primary PCI as the default strategy for any patient with acute STEMI but its benefits are highly time dependent and wane as time passes. Hence, current guidelines recommend it up to 12 hours from symptom onset to maximize its impact. With certain riders (e.g., hemodynamic and electrical instability), patients can be taken for primary PCI up to 24 hours. Due to various reasons, a significant number of patients seek medical help beyond this limit of 24 hours and a lack of clear-cut recommendations to manage this subset of stable patients complicates the issue. A number of trials and meta-analyses have tried to find out whether revascularization helps these patients but got mixed results. This review article summarizes the available evidence and attempts to find out concordance among discordant results while sketching the best possible strategy to manage these patients. A separate section has been dedicated to different imaging modalities for viability assessment with respect to same subset of patients.

Key words: Latecomer; Delayed revascularization; Myocardial infarction; Myocardial viability.

INTRODUCTION

The prompt restoration of antegrade flow in infarct related artery (IRA) is the core aim of therapy for acute ST-elevation myocardial infarction (STEMI) and is associated with improved survival, reduced reinfarction and hospitalization. Current guidelines advocate primary percutaneous intervention (PCI) as the preferred mode of reperfusion within first 12 hours. The benefit from reperfusion is considered to be minimal beyond 12 hours

from symptom onset. However, due to multiple patient and system related factors, a sizeable number of patients (8.5–40%)¹ present outside the ideal period of 12 hours or even 24 hours after onset of STEMI and are not a candidate for primary PCI. Majority of STEMI patients (35–60%) in India are received at non-PCI capable centers and undergo fibrinolysis.^{2–5} These patients should be referred to a PCI capable centre for routine pharmacoinvasive strategy within 3–24 hours. In developing countries due to

lack of dedicated transfer facilities a significant number of patients miss on this time limit as well and fail to receive any form of reperfusion therapy. The current discussion attempts to delineate the best strategy for managing this subset of latecomers who miss out on the deadline.

OPEN ARTERY HYPOTHESIS

Acute coronary thrombosis leads to irreversible myocardial damage in a time dependent fashion (**Fig. 1**). Experimental studies in dogs have demonstrated that coronary occlusion leads to gradual myocardial necrosis and is complete in 6 hours leaving little or no salvageable myocardium.⁶ However, clinical trials and meta-analyses of fibrinolytic therapy showed that benefits of reperfusion therapy can be seen up to 12 hours from onset of MI.^{7,8} These led to currently proposed time limit of 12 hours even for mechanical reperfusion (primary PCI). However, there are some factors, viz. presence of collaterals,⁹ ischemic preconditioning,¹⁰ subtotal occlusion, and spontaneous reperfusion,¹¹ which help preserve coronary blood flow and maintain viable myocardium for longer duration than expected after coronary occlusions and may predict left ventricular functional recovery following late mechanical

reperfusion. On the other hand, studies have shown that viable and salvageable myocardium exists even after more than 12 hours of symptom onset, even up to weeks after MI.¹²⁻¹⁴ These mechanisms may extend the time window of ischemia and hence reperfusion benefits up to 12–24 hours and possibly beyond 24 hours after onset of AMI. Late open artery (>24 hours after AMI) may improve survival rates not only by myocardial salvage but also by prevention of left ventricle (LV) dilation,¹⁵ improvement in electrical stability,¹⁶ and the provision of a conduit for collateral flow should a contralateral coronary artery become occluded.¹⁷ Previous studies have not only demonstrated that PCI is better than thrombolysis in patients with acute MI, but also that the time window of efficacy for PCI may be wider than that for thrombolysis.¹⁸ The late open artery hypothesis thus forms a solid theoretical basis in favor of late intervention in order to reperfuse occluded IRAs. However, late PCI on IRAs also has the potential for harm from procedure-related complications, distal embolization of atherothrombotic debris resulting in myocardial injury, and loss of recruitable collateral flow to other coronary territories.¹⁹⁻²¹ Hence, the role of PCI after 12 hours of symptom onset in stable patients is confusing and the same beyond 24 hours of onset of AMI is even more challenging.

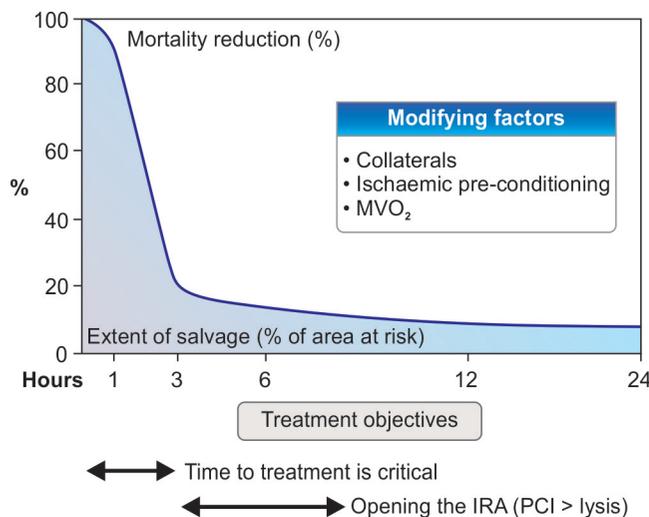


Fig. 1: Hypothetical relationship between time to treatment and the reduction in mortality and extent of salvage. During the first 2–3 hours after symptom onset, time to treatment is a critical determinant of the extent of salvage and reduction in mortality. Subsequently, a benefit persists but the “flattening of the curve” emphasizes that time to treatment is less of a factor and the major priority is opening of the infarct-related artery

TRIALS AND METANALYSES

A few studies have prospectively investigated the benefit of revascularization beyond 12 hours. Most notable of these is BRAVE 2 study, comprising of 365 patients, which showed that routine PCI of MI in late presenters (in the time window of 12–48 hours after symptom onset) led to significant reduction in infarct size as compared to initial medical therapy.¹ Though statistically not powered enough for clinical end points, a trend toward a reduction of the composite of death, MI, or stroke at 30 days was also found (relative risk reduction 33%). Long-term follow-up of patients enrolled in BRAVE 2 trial did show increased survival at 4 years apart from myocardial salvage (adjusted HR, 0.55; 95% CI, 0.31–0.97; $p = 0.04$).²² Another study SWISSI-II (Swiss Interventional Study on Silent Ischemia Type II), performed in the pretesting era, supports the idea that for patients with recent STEMI in whom exercise stress imaging revealed silent ischemia, balloon angioplasty reduces the long-term rates of cardiac death, nonfatal MI, or symptom-driven revascularization, and

improves functional capacity and left ventricular ejection fraction at 4 and 10 years.²³

The Occluded Artery Trial (OAT)—one of the largest randomized trial to test the open artery hypothesis, randomized 2,166 stable patients with an occluded infarct-related artery identified 3–28 days after STEMI.²⁴ At the 4-year follow-up, there were no differences between the groups managed by PCI versus those managed conservatively in either the rate of the primary composite end point of death, reinfarction, or New York Heart Association functional class IV heart failure or mortality. Of note, 90% of the patients in the OAT who had a stress test before randomization had absent or only mild ischemia. Thus, the lack of benefit observed in utilizing PCI beyond 72 hours from the index event in STEMI may be confined to patients without significant residual ischemia. Even in the absence of significant effects on hard end points, the OAT study showed that patients treated with PCI were significantly less likely to have angina at 4, 12, and 24 months. The two studies (OAT and SWISSI-II) have important differences in study design and length of follow-up and, not surprisingly, show conflicting results; SWISSI-II randomized only patients with proven silent ischemia on stress testing, whereas the OAT excluded those patients with postinfarction angina and/or moderate to severe ischemia. Some studies have shown that one-third to two-thirds of patients have residual symptomatic or silent ischemia (silent probably due to necrosis-related sensory denervation) after AMI^{25,26} and OAT study may not be representative of real life treatment scenarios and also less than one-half of the patients in the OAT study had a follow-up that reached 3 years.

Two meta-analyses have tested the strategy of delayed PCI to IRA. The first meta-analysis by Ioannidis and Katritsis²⁷ included data from six studies and one substudy (including OAT trial and TOSCA-2²⁸). It included 2,617 stable patients with an occluded artery 1–45 days after MI. There were no statistically significant differences for any clinical outcome, with trends for an increase in MI (risk ratio 1.26, $p = 0.19$) and decrease in CHF (risk ratio 0.67, $p = 0.19$) in the PCI arm. The PCI arm showed a slight superiority in LVEF.

In the second and more recent meta-analysis by Abbate et al.,²⁹ studies including clinically stable patients more than 12 hours and up to 60 days after acute MI were analyzed. The analysis comprised 3,560 patients and

showed significantly improved survival in the PCI group (OR: 0.49, 95% CI: 0.26–0.94, $p = 0.030$). These benefits were associated with improved left ventricular ejection fraction (LVEF) in the PCI group. Studies included were same as in the meta-analysis of Ioannidis and Katritsis, with the inclusion of four additional studies TOPS,¹⁹ ALKK,³⁰ BRAVE-2,¹ and SWISSI II.²³ These four studies with clinical scenarios more encouraging toward an interventional strategy (e.g., presence of ischemia or patent IRA) apparently tilted the results in favor of PCI, in contrast to the study of Ioannidis and Katritsis, which included only studies closer to the late open artery hypothesis paradigm. This meta-analysis should not be used as an argument against the OAT results. They address two mutually exclusive patient groups. The meta-analysis includes open as well as closed arteries and included some studies that selected patients with ischemia, whereas OAT studied only patients with a totally occluded artery without significant symptoms or severe ischemia.

It is evident from above that those with a totally occluded IRA on initial diagnostic angiogram, whether they have received fibrinolysis, are less likely to see a survival benefit from late revascularization than those with subtotal occlusions, unless high risk features such as inducible ischemia or significant viability are present; while delayed PCI in patent IRA offers survival benefits.

APPROACH TO LATECOMERS

Late presenters at a PCI capable center may be treatment naïve or may be referred from a non-PCI capable center after fibrinolysis. Majority of these latecomers become pain-free by the time they reach while a few may continue to have symptoms of ischemia. About 20% of patients may have patent IRA owing to phenomenon of “spontaneous reperfusion” without any form of reperfusion therapy.¹ On the other hand, the efficacy of fibrinolysis in achieving successful reperfusion is far from perfect (50–60%) leaving a substantial number of patients with occluded IRAs. Thus, these latecomers are in fact a heterogeneous group including totally asymptomatic to hemodynamically unstable patients, treatment naïve group, or post-fibrinolysis, patent IRA versus occluded IRA at the time of presentation; posing a challenge to one size fits all approach. Treatment strategy should differ accordingly and a patient-tailored approach based on the existing limited evidence should be used.

CLINICALLY UNSTABLE PATIENTS

Treatment naïve patients who present with ongoing symptoms of ischemia, electrical instability, cardiogenic shock, or heart failure should undergo primary PCI irrespective of time delay from symptom onset. Presence of chest pain beyond 24 hours from symptom onset may indicate stuttering infarct but must be critically analyzed and differentiated from post-infarct pericardial pain before deciding to intervene. Early revascularization with PCI/CABG has been shown to improve 1-year mortality in these patients when compared to fibrinolysis. Data from SHOCK trial and NRMI-2 registry support hypothesis that high-risk patients gain more mortality advantage with PCI compared to low-risk patients.^{31,32} Patients with failed fibrinolysis (persistent/worsening chest pain or ST segment resolution <50% in lead with maximum ST elevation after 90 minutes of fibrinolytic therapy) or reocclusion after successful fibrinolysis should be considered for “rescue PCI” and be transferred to a PCI capable center immediately. REACT study showed significantly lower primary end points in rescue PCI group primarily driven by reduction in reinfarction rates albeit with elevated risk of minor bleeding.³³

CLINICALLY STABLE PATIENTS

Decision of PCI in clinically stable latecomers is challenging and depends upon a number of factors, for example time from symptom onset, patent or occluded artery on angiogram, demonstrable ischemia or viability in IRA territory.

Current ACC guidelines³⁴ advice against delayed PCI of a totally occluded infarct artery beyond 24 hours after STEMI in asymptomatic patients with one or two vessel disease if they are hemodynamically and electrically stable and do not have evidence of ischemia. Contemporary ESC guidelines³⁵ however have extended this deadline to 48 hours. Reinfarction rates after PCI in such patients tend to be higher. The same applies to the asymptomatic stable patients with occluded IRA who received fibrinolysis but reach PCI capable center beyond 24 hours. However, patients with concomitant significant left main disease or triple vessel disease cannot be treated in the same way owing to large area of myocardium at risk. Other patients must be subjected to noninvasive stress studies

to document ischemic viable myocardium. Lack of viable myocardium should preclude revascularization strategy.

Clinically stable patients after successful fibrinolysis should undergo coronary angiogram within 24 hours as routine invasive strategy. All these patients must be referred to PCI capable center for coronary angiogram with an intent to perform PCI as early as 2 hours to maximize the “muscle gain” while minimizing the bleeding risk. A number of studies (TRANSFER-AMI, CARRESS-in-AMI, and NORDISTEMI trials) including a meta-analysis demonstrated the benefit of this routine pharmacoinvasive strategy (irrespective of presence of high risk features) in reducing death and reinfarction when compared to either standard ischemia-guided approach or rescue PCI.³⁶⁻³⁹ However, this time window was probably used in the trial designs to create the greatest possible difference in outcome when compared with the control group (rather than an a priori expectation that the benefit would be driven entirely within 24 hours). It is highly likely that benefits continue even beyond 24 hours in patent IRA. In stable patients who are not transferred immediately and present well beyond 24 hours after fibrinolysis, catheterization can be considered as part of a routine pharmacoinvasive or ischemia-guided approach. Presence of a severely stenotic but patent IRA with large area of myocardium at jeopardy justifies PCI.

Clinically stable patients who did not receive any reperfusion therapy and present beyond 12 hours but within 24 hours may undergo coronary angiogram as risk stratifying procedure. In this subset of patients with occluded IRA, the benefits of primary PCI may not be as robust. But substantial myocardial salvage can be done even when PCI is performed in patients with occluded IRA 12–72 hours from onset of STEMI.⁴⁰ Those with patent IRA with critical stenosis and large area at risk can be taken for PCI. When in doubt, exercise testing is useful in identifying persistent ischemia and risk stratification for future cardiac events. Submaximal testing may be done in asymptomatic patients after 3–5 days and symptom-limited testing may be done in the same subset of patients after 5 days. Pharmacological stress myocardial perfusion imaging has been shown to have predictive value for postinfarction cardiac events and is useful and safe in patients who are unable to exercise. **Figure 2** simplifies the management algorithm for patients presenting late after STEMI.

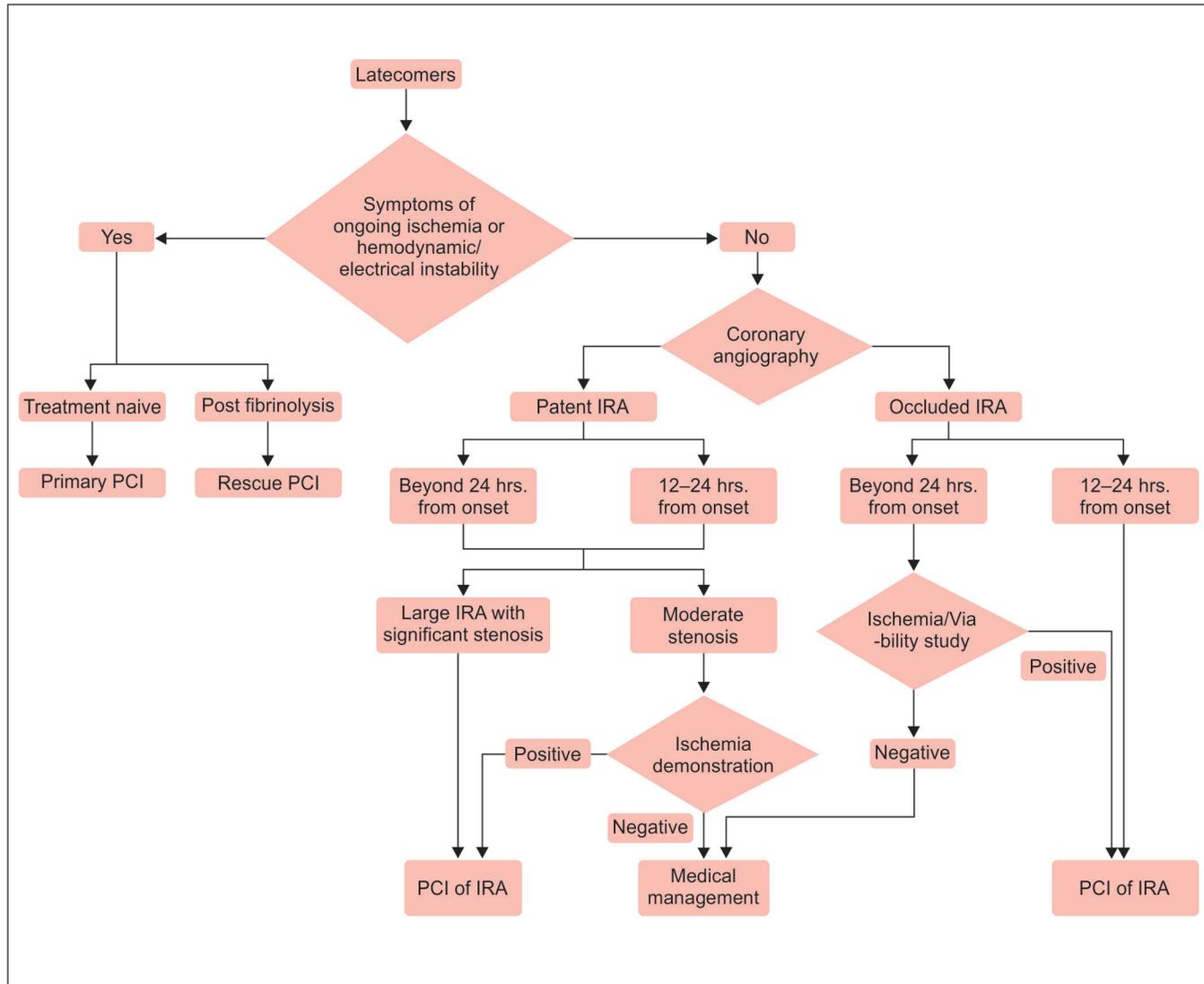


Fig. 2: Simplified algorithm for interventions in acute STEMI with delayed presentation to PCI capable hospitals

ROLE OF IMAGING TECHNIQUES IN THE ASSESSMENT OF VIABILITY IN LATE PRESENTERS

In patients who present after 24 hours post MI with significant amounts of viable myocardium, LV function may improve markedly, and even normalize, following successful revascularization.⁴¹⁻⁴³ A meta-analysis of 3,088 patients from 24 observational studies reported that revascularization, compared with medical therapy, significantly reduced mortality in patients with heart failure and myocardial viability. Among such patients,

average annual mortality with revascularization and medical therapy were 3.2% and 16%, respectively. Patients without significant viability did poorly irrespective of therapy (annual mortality 7.7% and 6.2%, respectively).⁴⁴

The outcome following revascularization is dependent not only on the presence but also the extent of viability, and a critical threshold mass of viable myocardium may be necessary for functional recovery and prognostic benefit to occur from revascularization.⁴⁵⁻⁴⁹ Therefore, while several clinical and laboratory parameters including angina

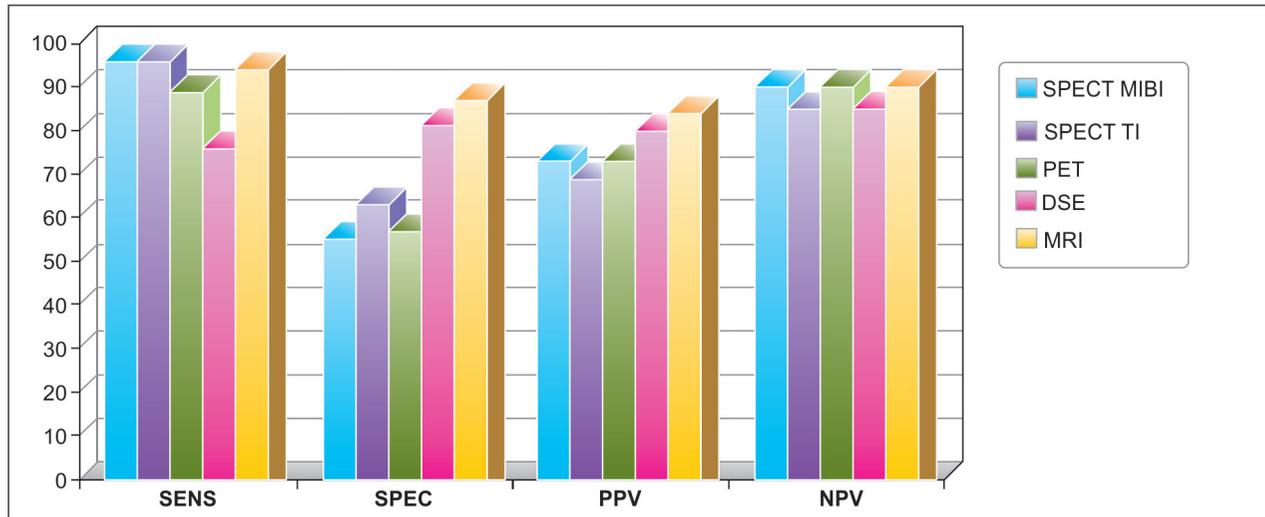


Fig. 3: Sensitivity and specificity of various imaging techniques in the detection of viability

symptoms, absence of Q waves on the electrocardiogram, and regional hypokinesis on echocardiography indicate the presence of viability, a systematic assessment of the degree and extent of viability is thought to be helpful for management planning and prognostication.

For the detection of viability, noninvasive imaging techniques depend on the demonstration of intact mitochondrial function (technetium-99m [Tc-99m] sestamibi and tetrofosmin imaging), preserved myocardial metabolism (positron emission tomography [PET] with fluorine-18 deoxyglucose), and the absence of scar tissue (gadolinium-enhanced magnetic resonance imaging) in areas of dysfunctional myocardium. **Figure 3** shows sensitivity and specificity of various imaging techniques to detect myocardial viability.

In STEMI, the myocardial damage extends from endocardium to epicardium by a wavefront of necrosis. The transmural extent of myocyte loss and replacement with fibrosis decides the recovery of wall motion and its contribution to global LV systolic function.⁴¹

SPECT IMAGING WITH TC-99M LABELED RADIOTRACERS

Technetium-99m (Tc-99m) sestamibi and Tc-99m tetrofosmin are Tc-99m labeled radiotracers. The uptake and retention of this agent requires the presence of intact sarcolemmal and mitochondrial membranes, making it conceptually a good tracer of regional cellular viability.^{50,51}

Nitrate-enhanced SPECT has been shown to have a greater ability to predict improvement of regional function after revascularization,^{52,53} and to provide important prognostic information⁵⁴ (**Figs. 4 and 5**).

When the resting tracer uptake is in the “intermediate range,” as might occur in regions of nontransmural infarction subtended by a non-critically stenosed coronary artery, the demonstration of inducible ischemia in these regions argues for the presence of viable myocardium.

Tc-99m sestamibi imaging and thallium-201 imaging are recommended (Class I indications) for predicting functional recovery in the 2003 guidelines of the American College of Cardiology and the American Heart Association.⁵⁵

POSITRON EMISSION TOMOGRAPHY

PET is an established noninvasive method of evaluating myocardial perfusion and viability.⁵⁶ This technique has the advantage of being able to assess both perfusion and metabolism. PET requires the use of positron-emitting isotopes (such as oxygen-15, carbon-11, nitrogen-13, and fluorine-18), which are cyclotron produced.

Uptake of fluorodeoxyglucose (FDG) by myocytes in an area of dysfunctional myocardium indicates metabolic activity and thus, viability. Regional perfusion can also be assessed with nitrogen N-13 ammonia or rubidium Rb-82. As a result, PET imaging has the potential to differentiate between normal, stunned, hibernating, and necrotic

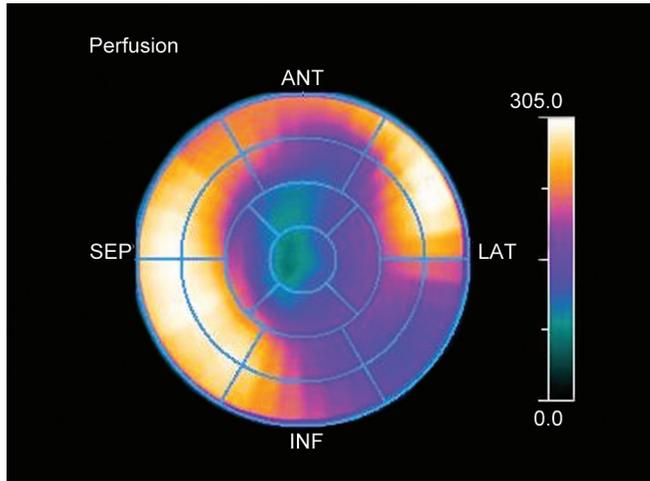


Fig. 4: NTG SPECT depiction of significant viable myocardium in LAD territory

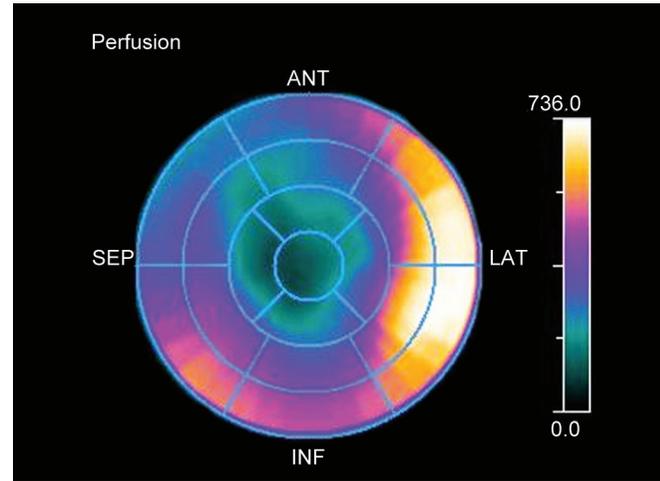


Fig. 5: NTG SPECT depiction of nonviable myocardium in LAD territory

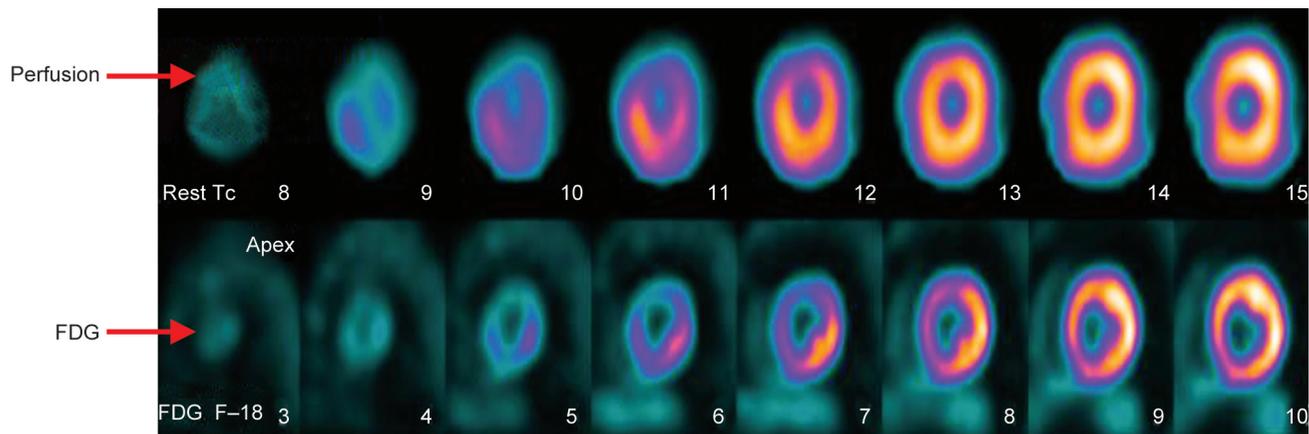


Fig. 6: FDG PET depiction of nonviable myocardium in LAD territory (perfusion-metabolism match)

myocardium. The presence of enhanced FDG uptake in regions of decreased blood flow (known as a “PET mismatch”) defines hibernating myocardium. While a concordant reduction in both metabolism and flow (“PET match”) is thought to represent predominantly necrotic myocardium. Regional dysfunction in presence of normal perfusion is indicative of stunning (**Figs. 6 and 7**).

Myocardial segments with significant reductions in both blood flow and FDG uptake have only a 20% chance of functional improvement following revascularization. In comparison, dysfunctional territories deemed to be hibernating by PET have approximately an 80% chance of functional improvement following revascularization.⁵⁷

Some studies, including one randomized trial, found that the ability to detect myocardial viability with PET or SPECT imaging was the same and that there was no difference in patient outcome when management decisions were based upon the results of either technique.⁵⁸ PET may have an advantage over SPECT in the setting of very severe LV dysfunction.⁵⁹

CARDIAC MRI (CMRI)

CMRI enhanced with gadolinium is being increasingly used for viability assessment. Lack of enhancement is a sensitive marker of the absence of scar tissue, and is taken to imply the presence of viability. Thus, CMRI may be

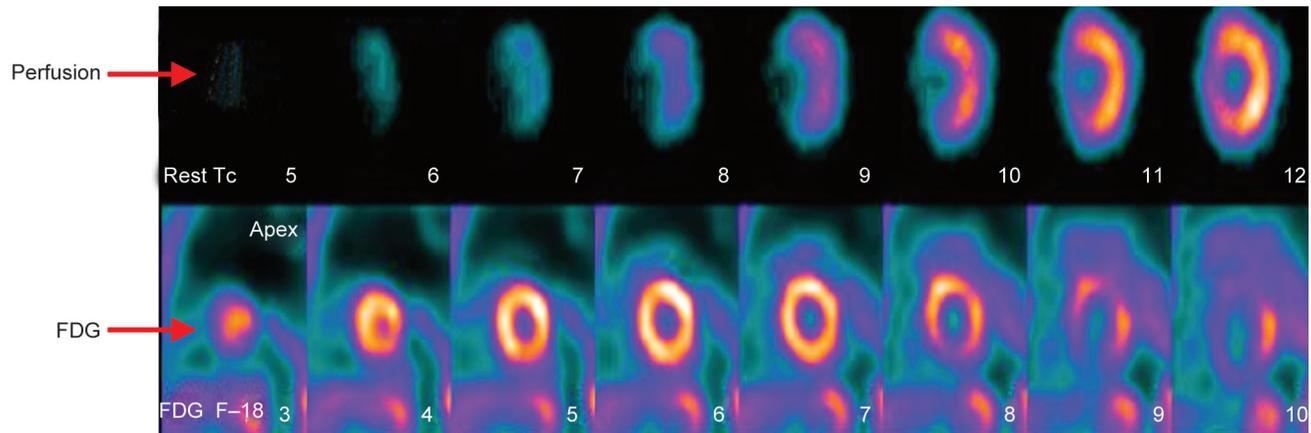


Fig.7: FDG PET depiction of viable myocardium in LAD territory (perfusion metabolism mismatch)

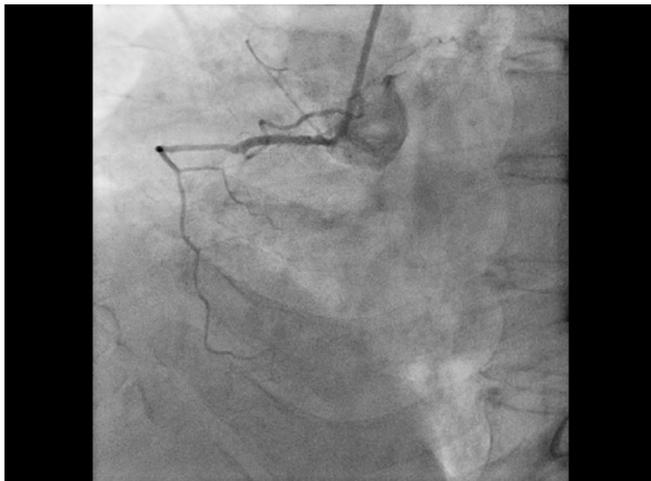


Fig. 8: Total occlusion of RCA after 24 hours

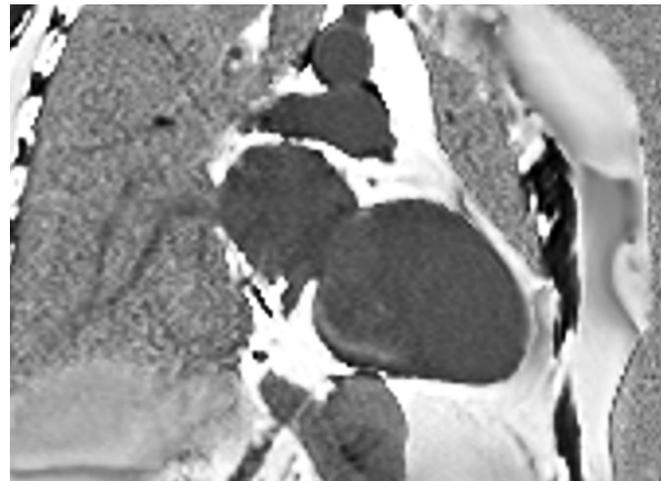


Fig. 9: CMRI depiction of transmural scar in RCA territory

more sensitive for the prediction of function recovery in the most severely dysfunctional myocardial segments.⁶⁰

Various studies have used an LV end-diastolic wall thickness of less than 5.5 mm as a marker of scar tissue. Baer et al.⁶¹ compared LV end-diastolic wall thickness on MRI with glucose use on 18F-FDG PET and demonstrated that regions with an end-diastolic wall thickness of less than 5.5 mm had reduced glucose use, whereas regions with an end-diastolic wall thickness of more than 5.5 mm had preserved glucose use.

Contrast hyperenhancement on delayed rest MRI is defined as regions with increased intensity on T1-weighted images acquired after gadolinium administration. The major advantage of contrast-enhanced MRI is superior

spatial resolution, which allows differentiation between transmural necrosis and subendocardial necrosis.

Thinning suggests scar tissue, with a high accuracy for predicting no recovery after revascularization (**Figs. 8 and 9**). It should be noted, however, that even in the presence of severe wall thinning, recovery of function may occur if there is no enhancement.

Selvanayagam et al.⁶² demonstrated that late-enhancement MRI is a powerful predictor of myocardial viability after surgery, suggesting an important role for this technique in clinical viability assessment.

Assessment of viability requires a carefully thought out strategy in order to be cost effective. The initial evaluation involves the measurement of the end wall thickness of the

SPECT	PET	CMRI
<ul style="list-style-type: none"> • Presence of moderate to severe inducible ischemia in infarcted territory 	<ul style="list-style-type: none"> • Mismatched defects 	<ul style="list-style-type: none"> • Endiastolic wall thickness > 6mm • Delayed contrast hyperenhancement

Fig. 10: Summary of predictors of viable myocardium on various imaging techniques

akinetic segment on the echocardiogram. A segment more than 6 mm on the akinetic segment indicates a more than 50% chance of recovery. In this situation a dobutamine stress echo (DSE) or nitroglycerine augmented SPECT study is sufficient to establish viability. A segment less than 6 mm on the akinetic segment indicates a less than 5% chance of recovery. In this situation a combination of CMRI or FDG PET would be a more precise tool to establish viability. Overall SPECT and PET demonstrate excellent sensitivity while DSE and CMRI demonstrate superior specificity.

A list of parameters on imaging techniques which indicate viability is summarized in **Figure 10**.

CONCLUSION

Patients presenting late after STEMI comprise a diverse group falling in a gray zone of management. Various studies point toward clinically relevant benefit if right patient is chosen. Clinical instability warrants immediate intervention whereas stable latecomers should be thoroughly but swiftly analyzed for indicators of benefit from revascularization, i.e., ischemic and viable myocardium. A large viable myocardium in an occluded artery territory should warrant revascularization whereas IRA with a small viable territory or nonviable myocardium should be dealt with conservative approach. A judicious and individualized approach is the key to manage these patients who have missed their buses.

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CHAPTER

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Should Direct Oral Anticoagulant Use be the Default Strategy Post Percutaneous Coronary Intervention with Atrial Fibrillation?

Rishi Sethi, Akshyaya Pradhan, Pravesh Vishwakarma

ABSTRACT

Atrial fibrillation (AF) and coronary artery disease (CAD) often coexist in clinical practice. The need for percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) mandates a dual antiplatelet therapy (DAPT) regimen while the underlying AF necessitates oral anticoagulation. To circumvent both thromboembolic and ischemic events the combination therapy [triple therapy: oral anticoagulant (OAC) + DAPT] becomes essential. However, the combination comes at price of increased bleeding and we have now realized that post-PCI bleeding is not benign. Attempts to minimize bleeding by combining vitamin K antagonist (VKA) with single antiplatelet therapy (SAPT) and shortening the duration of triple therapy with VKA did not yield expected results in the *WOEST* and *ISAR-TRIPLE* studies, respectively. The advent of direct oral anticoagulant (DOAC) has heralded a paradigm shift in vascular anticoagulation with almost 50% reduction in intracerebral bleeds albeit with preserve efficacy compared to VKA. The DOAC plus single antiplatelet combination (dual therapy) have now been tested in four randomized studies over 10,000 patients in the setting of PCI with AF. Across the board, the novel regimen has demonstrated superiority in bleeding and no difference in efficacy. All guidelines now endorse this dual therapy with DOAC at full doses whenever feasible and a short triple therapy with DOAC at initiation in high-risk cases.

Keywords: vitamin K antagonists, dual therapy, stent thrombosis, WOEST trial, major bleeding

Introduction: Crossroad of Atrial Fibrillation and Coronary Artery Disease

Atrial fibrillation (AF) is the most common sustained arrhythmia in cardiology practice and becomes even more common with increasing age. Comorbid conditions, such as obesity, hypertension, diabetes mellitus (DM), heart failure (HF), coronary artery disease (CAD), valvular heart disease (VHD), and chronic kidney disease (CKD), further increase the risk of AF. The presence of AF significantly increases the risk of thromboembolic complications including stroke and peripheral embolism mandating the use of antithrombotic treatment with control of risk factors to substantially reduce the risk of stroke.

About 20–40% of patients with AF have concomitant CAD, a significant proportion of whom require revascularization using percutaneous coronary intervention (PCI) and stent implantation. In addition, about 5–10% of patients undergoing coronary angiography with or without PCI have AF or other indications for chronic oral anticoagulation (OAC) therapy.¹ Guidelines recommend dual antiplatelet therapy (DAPT) for patients undergoing PCI to prevent the risk of stent thrombosis and additional thrombotic ischemic events. So, in theory, these patients with AF undergoing PCI with a stent need both the therapies viz. OAC and DAPT (called triple therapy). The rationale for prescribing triple therapy is based upon earlier findings that DAPT is superior to an OAC for reducing the risk of stent thrombosis, while

DAPT is insufficient (as compared to OAC) to preventing thrombotic events in patients with AF.² Thus, triple therapy seems to be necessary in these patients to mitigate the thromboembolic risk due to AF-induced stasis in left atrium and platelet-mediated risk of stent thrombosis; and is empirically indicated in AF patients undergoing PCI. However, no randomized controlled trials (RCTs) have tested the efficacy of triple therapy, but it is well known to increase the risk of both fatal and nonfatal bleeding.

Alternative to Triple Therapy: WOEST and ISAR-TRIPLE Trials?

Bleeding with various combinations of antiplatelets and OAC is a real risk and is depicted in **Figure 1**.³ Major bleeding in patients who undergo PCI is not at all benign and results in 3-fold increase in mortality.⁴ Hence, it is prudent to reduce the bleeding risk of these patients by either avoiding it altogether or at least reducing the duration of triple therapy. What is the Optimal antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (**WOEST**) trial tested the first of strategies, i.e. avoiding triple therapy completely. Patients with severe CAD requiring long-term anticoagulation (n = 573) were randomized into dual therapy arm (clopidogrel-only with warfarin) and triple

therapy arm (clopidogrel and aspirin with warfarin).⁴ Dual therapy arm showed 64% relative risk reduction in bleeding episodes, primarily driven by reduction in thrombolysis in myocardial infarction (TIMI) minor/minimal bleeding without any significant difference in TIMI major bleeding event [hazard ratio (HR): 0.36; 95% confidence interval (CI): 0.26–0.50; p < 0.0001]. Though it was not powered for secondary ischemic endpoints, the study showed reduction in major adverse cardiovascular events (MACE) including stent thrombosis and target vessel revascularization in the dual therapy arm (HR: 0.39; 95% CI: 0.16–0.93; p = 0.025). Despite its small sample size and open design, the study provided first randomized evidence that early discontinuation of aspirin may be attempted to reduced bleeding event without any significant rise in ischemic complications.

On the other hand, the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (**ISAR-TRIPLE**) trial tested other strategy of shortening DAPT duration and randomized 614 patients receiving OAC to either 6 weeks or 6 months of DAPT.⁵ At 9 months, the primary endpoint with a combination of ischemic and bleeding events did not differ between groups, but the secondary analysis showed reduced bleeding risk in shorter DAPT duration. Like the WOEST trial, this study was also plagued by small sample size and lack of power

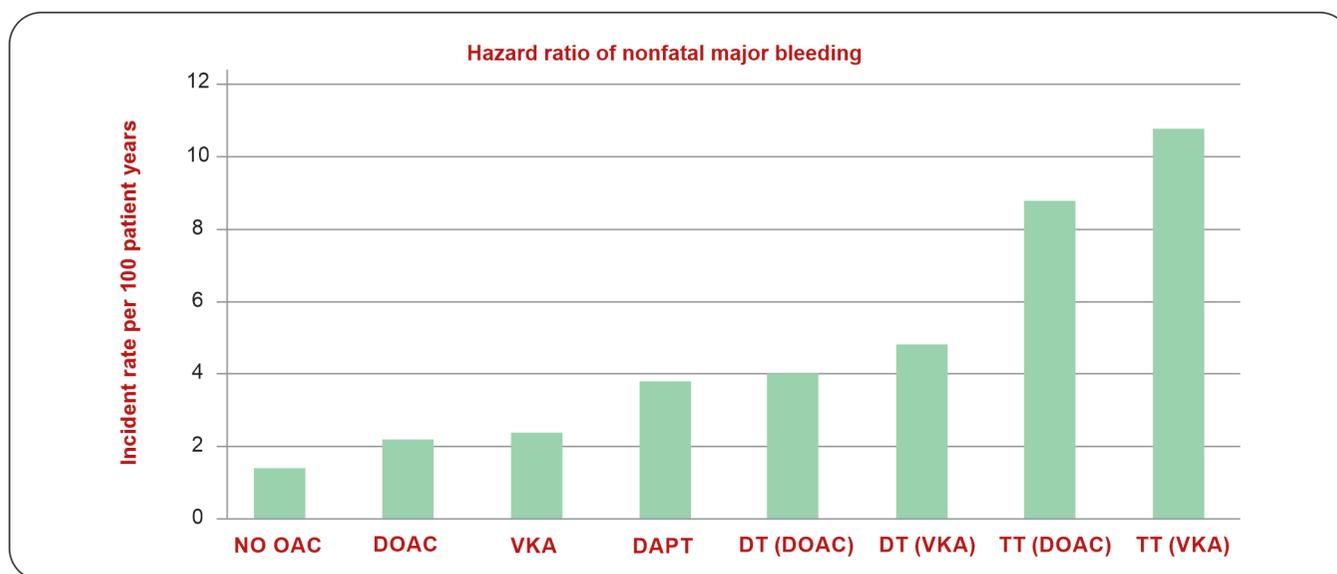


Fig. 1: Hierarchical incidence of bleeding with contemporary antiplatelet and anticoagulant from Danish AF Registry.³

Abbreviations: DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; DT, dual therapy: combination of OAC and single antiplatelet; OAC, anticoagulant therapy; TT, triple therapy: combination of OAC and dual antiplatelet; VKA, vitamin K antagonist

to detect impact on ischemic events. Both these studies unequivocally showed that triple therapy for one year is unnecessary and dual therapy for shortened duration is significantly safe in terms of bleeding.

Dual Therapy: The Game Changer!

While the **WOEST** and **ISAR-TRIPLE** trials had signaled towards the superiority of a VKA-based dual therapy, both studies had their inherent limitations. Despite being the gold standard of vascular anticoagulation for past 6 decades, VKA use had multiple challenges. Periodic international normalized ratio (INR) monitoring, multiple drug/food interactions, and slow onset-offset being the major hurdles. However, rates of major bleed (especially intracerebral bleed) were the primal fear in the mind of physicians while initiating them. To this end, the emergence of direct oral anticoagulant (DOAC) has been a huge relief for the clinician managing anticoagulation. Minimal food/drug interaction, faster onset, preclusion of regular testing, and stable therapeutic action are major advantages. All these benefits are achieved with similar efficacy and reduction of major bleed vis-à-vis VKAs. A meta-analysis of 4 major DOAC RCTs with 71,683 patients showed 19% reduction in stroke or systemic embolism (SSE) compared to VKA.⁶ Not only that, but all-cause mortality was also reduced by 10% and intracranial hemorrhage by 52%. Hence, the use of DOACs in place of warfarin was a feasible and attractive strategy. Four RCTs have tested this strategy now. Because bleeding was one of the major banes of triple therapy and DOACs had already shown superiority for bleeding, most of the trials had bleeding as the primary endpoint.

A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (**PIONEER AF-PCI**) was the first of the series and tested DOAC (rivaroxaban)-based dual and triple therapy.⁷ The study included 2,124 patients of AF undergoing PCI and warfarin-based triple therapy was the comparator. At 12 months, the primary endpoint of bleeding (composite of major or minor defined by TIMI criteria) was significantly lower in the DOAC-based therapy compared to standard therapy (16.8% -DOAC-based dual therapy, 18.0% - DOAC-based triple therapy and 26.7% - warfarin-based triple therapy, respectively; $p < 0.001$). Compared to standard triple therapy, DOAC-based dual and triple therapy reduced bleeding by 41%

and 37%, respectively. The results remained similar when other definitions of major bleeding were utilized such as Global Usage of Strategies to Open Occluded Arteries (GUSTO) or International Society on Thrombosis and Hemostasis (ISTH). Also, rivaroxaban arms had less bleeding requiring medical attention. The overall study result was consistent with subgroup analysis and various strata of DAPT (1 month, 6 months, or 12 months). The efficacy endpoint (MACE) was not significantly different among study groups (6.5%, 5.6%, and 6.1%; $p > 0.05$ for the three arms, respectively). The study was indeed a pioneer in establishing the safety and efficacy of DOAC plus antiplatelet combo. The doses of rivaroxaban use in the study were 15 mg OD and 2.5 mg BD with SAPT and DAPT, respectively and are lower than what is prescribed in AF. Some differences with the WOEST trial are noteworthy - the higher percentage of participant received 12-month duration of DAPT in the WOEST and the **POINEER-AF** was an exclusive AF population (only 69% had AF in the WOEST trial).

The Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting (**REDUAL-PCI**) trial sought to extend the mandate of DOAC-based therapy with dabigatran.⁸ The study enrolled 2,725 patients with AF undergoing PCI (within 5 days) and tested both the doses of dabigatran (110 mg/150 mg) against a warfarin-based triple therapy. DOACs were used only with single antiplatelet agent (clopidogrel or ticagrelor); and, hence, there was no DOAC-based triple therapy arm unlike the **PIONEER AF-PCI** trial. Similar to previous study, the main goal was to evaluate safety - major or clinically relevant bleeding defined by the ISTH criteria and the median duration of follow-up was 14 months. With respect to safety, the study hypothesized that DOAC-based dual therapy will be noninferior to VKA-based triple therapy. Interestingly, elderly patients (>70 years) outside the USA were given 110 mg dabigatran dose only. At study end, bleeding was reduced by 48% with dabigatran 110 mg dual therapy compared to standard triple therapy (15.4% vs 26.9%; HR: 0.52; $p < 0.001$). Similarly, a significant 28% reduction of bleeding was achieved with 150 mg dose of dabigatran ((20.2% vs 25.7%; HR: 0.72; $p < 0.001$). With respect to safety, dabigatran (both doses combined) was noninferior to warfarin for the composite endpoint of stroke, MI, systemic embolism, or death (HR: 1.04; $p < 0.001$). The study successfully demonstrated two

improvisations in contemporary standard of care (triple therapy) namely - use of a DOAC and omission of aspirin. The study differs from the **PIONEER AF** trial in two important aspects - exclusive use of dual therapy based on DOAC and use of standard doses of DOAC as tested in AF (unlike the PIONEER trial where lower doses were utilized).

The Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention (**AUGUSTUS PCI**) and the Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (**ENTRUST-AF-PCI**) subsequently tested apixaban and edoxaban respectively in the setting of PCI with AF.^{9,10} The AUGUSTUS PCI trial was a larger trial of 4,614 patients across >30 countries. It included patients of AF who had either acute coronary syndrome (ACS) or were undergoing PCI. On a background P2Y12 therapy, the trial compared DOAC (apixaban 5 mg BD) versus VKA (INR: 2.0–3.0) as well aspirin or no aspirin in a 2X2 factorial design. At six months, the primary outcome of bleeding (definition similar to REDUAL-PCI) was 31% lower with apixaban compared to VKA (10.5% vs 14.7%; HR: 0.69; p <0.001). Similarly, aspirin use was associated with a higher incidence of bleeding compared to its omission (16% vs 9%; HR: 1.89; p <0.001). Additionally, apixaban arm had lower rates of death or hospitalization compared to VKA, while ischemic events were similar. Aspirin omission had no effect on the secondary outcomes. In the last trial of the series, **ENTRUST-AF-PCI** trial, edoxaban 60 mg (30 mg with renal dysfunction)-based dual therapy was tested against warfarin-based triple therapy in 1,506 patients of AF undergoing PCI. The rate of major or minor but clinically relevant bleeding at 12 months was lower with edoxaban therapy compared to standard triple therapy (17% vs 20.7%; HR: 0.83; p <0.01 for noninferiority). The ischemic efficacy outcome [combination of cardiovascular (CV) death, stroke, systemic embolism, MI, or definite stent thrombosis] was not significantly different among two groups (HR: 1.06; CI: 0.71-1.69). The trial failed to show superiority of DOAC (edoxaban)-based dual therapy for bleeding unlike its predecessors.

Additional credence for dual therapy comes from meta-analyses of these trials.^{11,12} Lopes et al. performed

a large meta-analyses of four DOAC RCT and the WOEST trial including 11,542 patients. Compared to standard triple therapy, the odds ratio for major bleeding with dual therapy with DOAC was 0.57 and 0.69 for DOAC-based triple therapy. The risk of MACE was 0.95 and 0.97, respectively for dual and triple therapy based on DOAC using standard triple regimen as reference. Another meta-analysis based on the 4 RCTs found that DOAC-based therapies had significant lower risk for any bleeding [relative risk (RR): 0.65; p <0.001] and major bleeding (RR: 0.63; p <0.001). For ischemic CV events and death, there was no difference between DOAC-based therapies and VKA-based triple therapy (RR: 1.05; CI: 0.93–1.18 and RR: 1.14; CI: 0.94–1.37; p = NS).

So, now there is convincing data that DOAC-based regimens (especially novel dual therapy- DOAC + SAPT) significantly reduce major bleeding irrespective of definition used, type of DOAC use, and geographical barriers (**Fig. 2**). However, the relative contributions of aspirin omission and DOAC introduction to bleeding attenuation remains to be determined.

Vitamin K Antagonist in Percutaneous Coronary Intervention with Atrial Fibrillation: Is the Door Still Open?

Despite superior reduction of bleeding with DOAC-based therapies, many questions remain unanswered. **First**, most of the RCTs discussed above were clearly underpowered for evaluation of ischemic events and is acknowledged by trialists too. Hence, the ischemic safety of DOAC-based dual therapy will need to be tested in a proper sized RCT. In fact, in the REDUAL-PCI trial, the 110 mg dual therapy with dabigatran had nonsignificantly increased thromboembolic events by 1.8% which was counterbalanced by 4.2 % decrease in bleeding events. Stent thrombosis and MI were also numerically higher (statistically insignificant) with lower dabigatran dose. Two meta-analyses have flagged the ~~insignificant~~ higher risk of MI and significant higher risk of stent thrombosis with DOAC-based dual therapy.^{13,14} Because of predominance of bleeding events, the individual RCTs did not show these signals probably. The relative risk for stent thrombosis almost overlapped in both the meta-analyses (RR: 1.59; p = 0.04 and RR: 1.67; p = 0.04, respectively) and cannot be ignored. The effect on all-cause death and CV death was neutral with DOAC-based dual therapy. The signal of

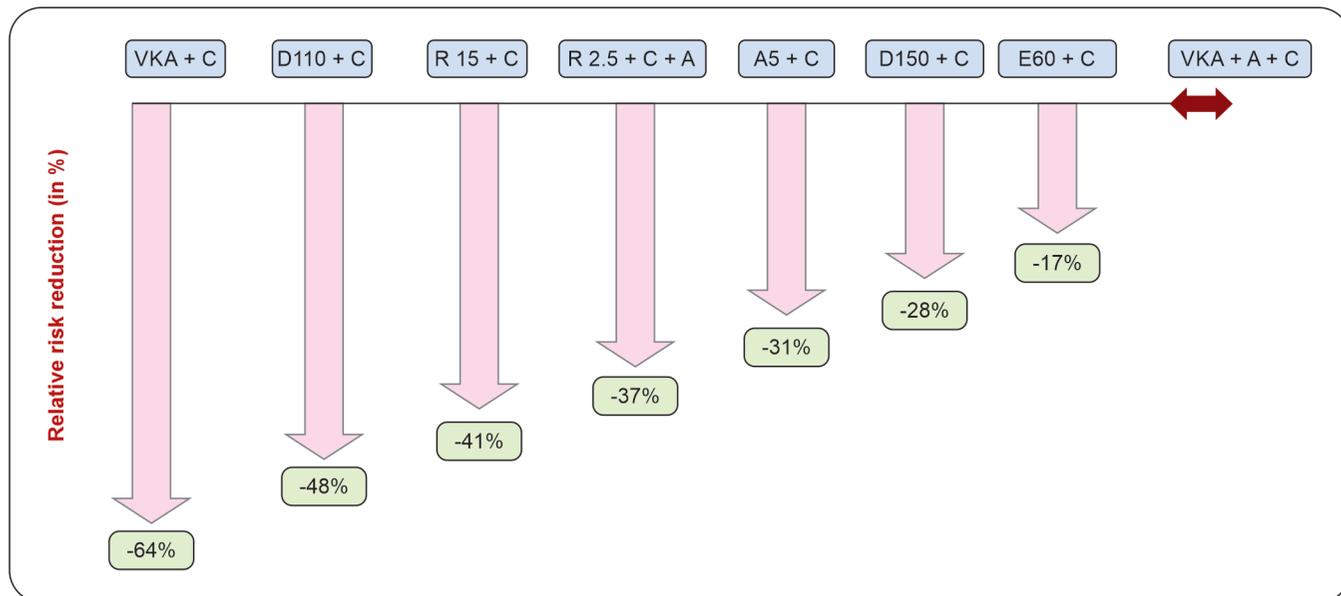


Fig. 2: Relative risk reduction in major bleeding or clinically relevant nonmajor bleeding with standard DOAC doses in various RCTs. Standard VKA-based triple therapy was the comparator

Abbreviations: A, aspirin; A5, apixaban; C, clopidogrel; D110 & D150, dabigatran; DOAC, direct oral anticoagulant; E60, edoxaban; R15 & R2.5, rivaroxaban; RCT, randomized controlled trial; VKA, vitamin K antagonist

ischemic events were primarily seen with 110 mg doses of dabigatran and should be used with caution. Hence, for patients with high-ischemic risk, a short initial triple (at least 1 week) therapy is recommended by the authors. A criticism of all these RCTs is that they used clopidogrel as the seminal P2Y12 inhibitor, while novel P2Y12 inhibitors (prasugrel or ticagrelor) have clearly shown efficacy over it.¹⁵ It is unclear whether the use of these agents could have offset the ischemic side effects discussed above. The MI and stent thrombosis are most probably related to the antiplatelet component of combination therapy and could be potentially correctable. In a nutshell, DOAC-based dual therapy can be a routine in patients with high-bleeding risk; but with high-ischemic risk, a consideration for initial triple therapy (DOAC or VKA) is warranted.

Secondly, the duration of triple therapy has gradually truncated from 12 months in the WOEST trial to 1–6 months in the DOAC RCTs reflecting contemporary practice. Hence, whether DOAC or VKA is used, triple therapy duration should definitely be <12 months and preferably be restricted to initial few weeks or months for high-ischemic risk patients. Of course, direct comparison of DOAC or VKA-based triple therapy is not available in the REDUAL-PCI and ENTRUST-AF-PCI trials. The small cohorts DOAC-based triple regimen from the AUGUSTUS

trial (n = 1,153) and the POINEER-AF-PCI (n = 709) are available.

Thirdly, most studies compared a DOAC-based dual therapy against a VKA-based triple therapy. It has been previously demonstrated that bleeding risk increases with combination of anticoagulant and antiplatelet therapy.^{3,16} So, with respect to bleeding, the triple therapy groups were already at disadvantage compared to dual therapy even before initiation of studies. It is akin to comparison of apples and oranges! With DOACs already reducing bleeding compared to VKA by (almost 52% in ICH), the scales were tilted in favor of DOAC-based therapies. However, even with such advantages, the ENTRUST-AF-PCI study failed to demonstrate superiority with respect to bleeding with edoxaban! Here, it should be noted that VKA-based dual therapy also had reduced bleeding by 65% in the WOEST trial. Comparison of VKA-based dual therapy with a DOAC-based dual therapy in an RCT with adequate power is the need of the hour.

Fourthly, in certain situations with AF, novel oral anticoagulants (NOACs) are not indicated - pregnancy, prosthetic valve, and moderate to severe mitral stenosis. Hence, VKA will still be preferred for combination with antiplatelets should the need arise. Based on the results

of the WOEST trial, a dual therapy will be preferable, especially in high-bleeding risk subjects.

Improving the Safety of Combination Therapy

As noted above, whenever antiplatelet and anticoagulant are combined, bleeding risk is elevated.^{3,16} Multiple pharmacological and nonpharmacological maneuvers can be applied to mitigate bleeding risk.^{15,17}

- **Lower aspirin doses** (<100 mg) continue to retain antiplatelet efficacy while simultaneously reducing bleeding complication. Moreover, the advent of ticagrelor in clinical practice has made lower dose of aspirin a common practice.
- **Radial access** has drastically reduced access site bleeding in multiple RCTs such as MATRIX, RIVAL, RIFLE-STEACS, and many more. Hence, the use of radial route is preferable with oral anticoagulation.
- Concomitant use of **proton pump inhibitor** decreases gastrointestinal bleeding with DAPT and dabigatran. There is no interference with antiplatelet action of P2Y12 inhibitor as shown in large RCT.
- *Avoiding the use of novel P2Y12 inhibitor*: Most RCTs of DOAC have utilized clopidogrel as the default drug as noted above. Using ticagrelor and prasugrel in combination with DOAC will increase bleeding as seen in the Treatment With Adenosine Diphosphate (ADP) Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) study.¹⁸
- **“DE-ESCALATION”**: In patients with high-risk angiographic features, such as bifurcation, left main disease, chronic occlusion, and multiple stents, guidelines indicate the use of potent P2Y12 therapy. De-escalation strategy entails switching from potent P2Y12 inhibitor therapy to clopidogrel after initial few weeks of PCI. This strategy aims to tide over initial periprocedural period with potent P2Y12 inhibitors when risk of ischemic events is high. The second switch phase (to clopidogrel) aims to reduce bleeding risk when ischemic risk has waned. Both guided and unguided de-escalation strategies have already been tested in randomized trials.¹⁹
- **Risk stratification tools**: The Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage (**HAS-BLED**) score has been conventionally

utilized to calculate bleeding risk with oral anticoagulation. Patients with score >3 are at high-bleeding risk and need careful monitoring. The **DAPT** score and **PRECISE-DAPT** scores have been validated to calculate ischemic risk and bleeding risk with DAPT.

Guidelines: The Changing Face

In view of recent evidence available, various guidelines also favor the shortest duration of triple therapy in patients of AF undergoing PCI. The recent 2020 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS)/European Heart Rhythm Association (EHRA) guidelines for management of AF recommend usage of DOACs in preference to VKA if the patient is eligible for DOAC.²⁰ To minimize bleeding risk in patients with high-bleeding risk (HAS-BLED ≥ 3), lower dose of DOAC is preferred (e.g. rivaroxaban 15 mg OD or dabigatran 110 mg BD) for the duration of concomitant antiplatelet therapy (SAPT or DAPT). For patients who are on VKA, and simultaneous antiplatelet therapy is desirable, VKA dosing should be closely monitored with target INR 2.0–2.5 and tolerated therapeutic range (TTR) >70%. Aspirin should be taken off the prescription as early as possible (≤ 1 week) to keep the duration of triple therapy to minimum if ischemic risk is low or bleeding risk is high. If risk of stent thrombosis outweighs bleeding risk, duration of triple therapy may be extended to <1 month. P2Y12 inhibitor (preferably clopidogrel) is the recommended drug as part of dual therapy. Duration of clopidogrel is dependent on clinical profile, bleeding, and ischemic risk. For ACS patients, duration of dual therapy up to 12 months is recommended; while for patients with stable CAD, clopidogrel therapy may be discontinued after 6 months of PCI.

However, the current 2020 American College of Cardiology Expert Consensus Decision Pathway (ACC ECDP) document differs in their default recommendation being dual therapy (consisting of OAC and P2Y12 inhibitor) for such patients.²¹ They recommend against triple therapy in most patients. If ever needed, aspirin may be used with dual therapy for the shortest possible duration (up to 30 days) following PCI. Clopidogrel over other P2Y12 inhibitors and DOAC over VKA are preferred. When aspirin is used with OAC, daily dose should not exceed 100 mg. The duration of clopidogrel recommended is in agreement with current DAPT guidelines and is dependent on clinical scenario (ACS vs stable angina), ischemic and

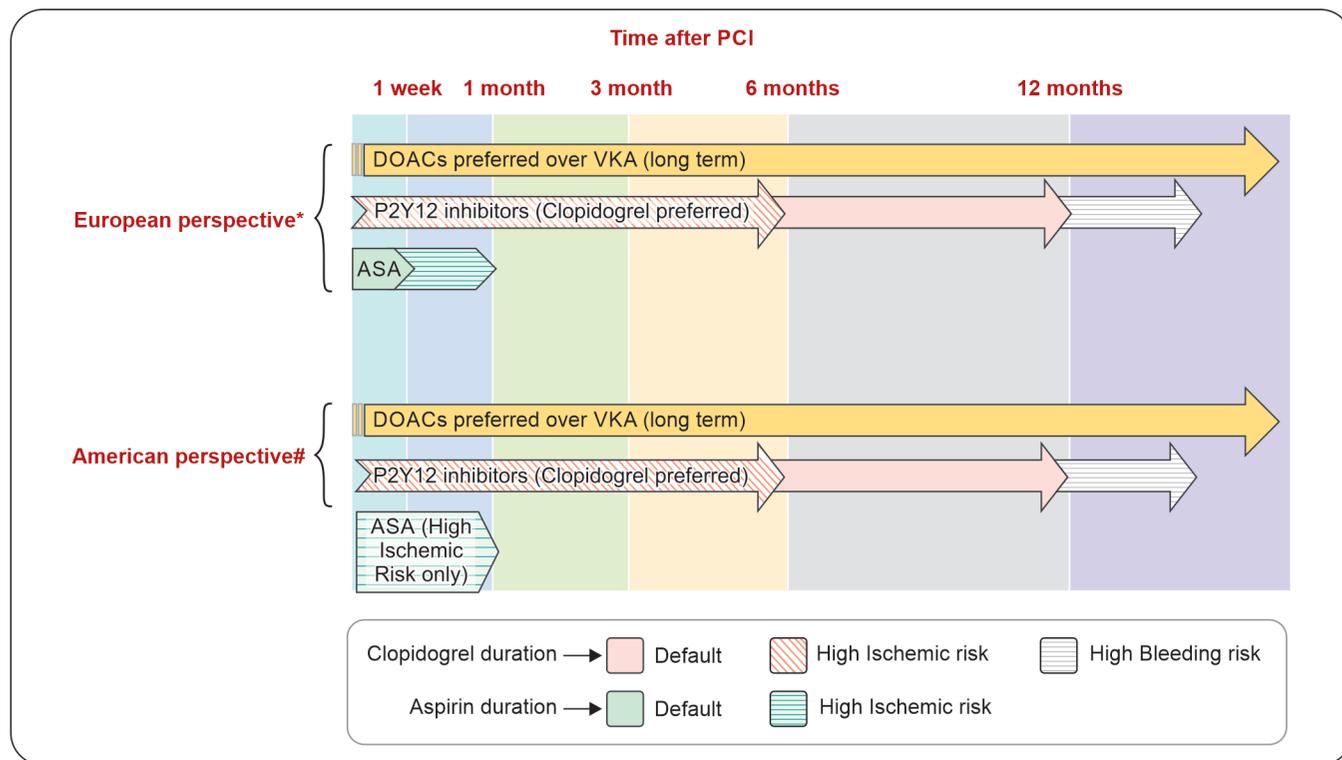


Fig. 3: Comparison of the American and European guidelines on combination of antiplatelet and DOAC therapy in AF patients undergoing PCI. The major difference lies in routine omission of aspirin following PCI as a default strategy in the American iteration, while an initial triple therapy of 7 days is advocated in the European version. Based on ischemic and bleeding risk, the duration of antiplatelets can be tailored. *ESC 2020 Guidelines on NSTEMI & ESC/EACTS/EHRA 2020 guidelines on AF #ACC Expert Consensus Decision Pathway 2020 Abbreviations: AF, atrial fibrillation; ASA, aspirin; DOAC, direct oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist

bleeding risk, and vessel/lesion complexities. For patients with dual and triple therapy, proton pump inhibitors or H2 receptor antagonist along with avoidance of nonsteroidal anti-inflammatory drugs NSAIDs is recommended to reduce the risk of gastrointestinal bleeding.

The 2020 NSTEMI guidelines by ESC and EHRA 2021 practical guide also support the use of dual therapy with DOAC after a short triple therapy of 7 days as a default strategy.^{22,23} **Figure 3** summarizes the recent guideline/consensus statements on DOAC use in AF undergoing PCI.

Future Directions

A large number of studies are ongoing or in pipeline for AF patients undergoing PCI. The Dabigatran Versus Warfarin With NVAf Who Undergo PCI (**COACH-AF-PCI**) trial (**NCT03536611**) is comparing DOAC-based triple therapy with VKA-based triple therapy in the setting of PCI with

AF. What is the Optimal antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation Undergoing revascularization 2 (**WOEST-2**) (**NCT02635230**) study is evaluating the 1-year safety and efficacy of OAC (VKA or DOAC) and P2Y12 combination after PCI/CABG based on the presence or the absence of aspirin. The Optimal Antithrombotic Therapy for ACS Patients Concomitant With AF and Implanted With New-generation DES (**OPTIMA-3, 4**) (**NCT03234114**) studies are enrolling ACS patients with AF undergoing PCI with a new-generation DES. The OPTIMA 3 is looking at VKA-based therapies, while the OPTIMA 4 is looking at dabigatran-based therapies. The Safety and Efficacy Of Rivaroxaban and Ticagrelor for Patients With Atrial Fibrillation After Percutaneous Coronary Intervention (**CAPITAL PCI AF**) (**NCT03331484**) is studying the combination of ticagrelor plus rivaroxaban for 12 months following PCI in patients with AF.

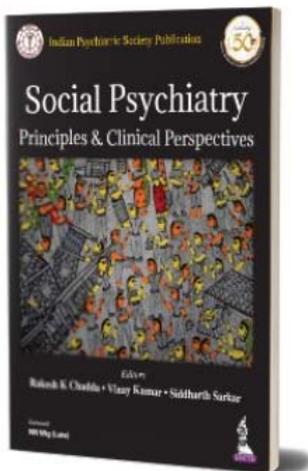
CONCLUSION

The need for long-term oral anticoagulation (AF or venous thromboembolism) in patients undergoing PCI warrants combination of oral anticoagulation and antiplatelets. The ischemic benefits need to be balanced with bleeding risk in such a scenario. The advent of DOAC has been a significant advance in the field of anticoagulation with reduction of intracerebral bleeds by almost 50% which is addition to ease of administration and quick onset of action. Moreover, the use of DOAC-based combination therapies has now been shown to be feasible and has reduced major bleeding by 20–50% compared to standard triple therapy. Although there have been signals of ischemic events with DOAC-based dual therapy, it is primarily restricted to lower dabigatran doses and can be offset by a brief course of triple therapy at onset. All major guidelines now endorse the DOAC-based dual therapies in setting of PCI with AF. The duration of initial triple therapy differs a bit among guidelines. Based on the ischemic and bleeding risk of the patient, DOAC-based therapies need to be individualized. Ongoing studies will clarify the role of potent P2Y₁₂ inhibitors in this scenario and further define the role of VKA-based regimens if any.

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- in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498.
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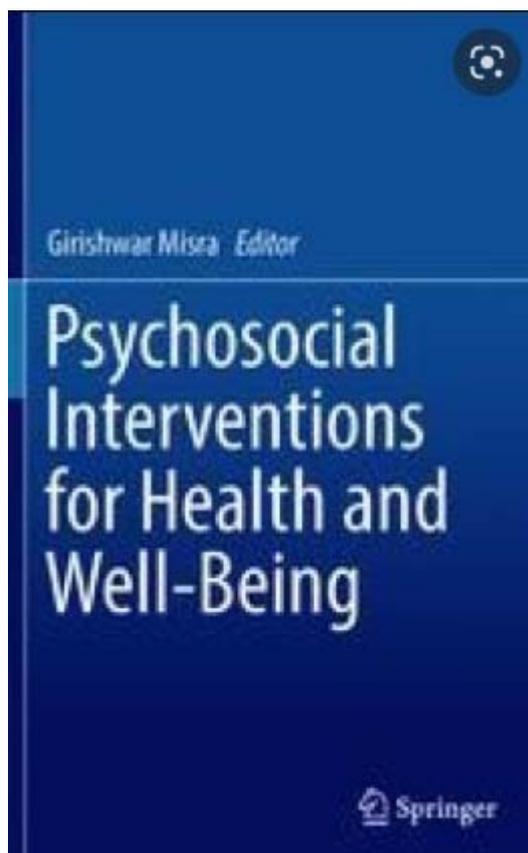
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Chapter-11 Psychology of Subpopulations in the Indian Society

BOOK TITLE: Social Psychiatry: Principles and Clinical Perspectives

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Chapter 11 Interventions for Enhancing Health and Well-Being Among Indian Elderly

Nisha Mani Pandey, Indihar Misra and S. C. Tiwari

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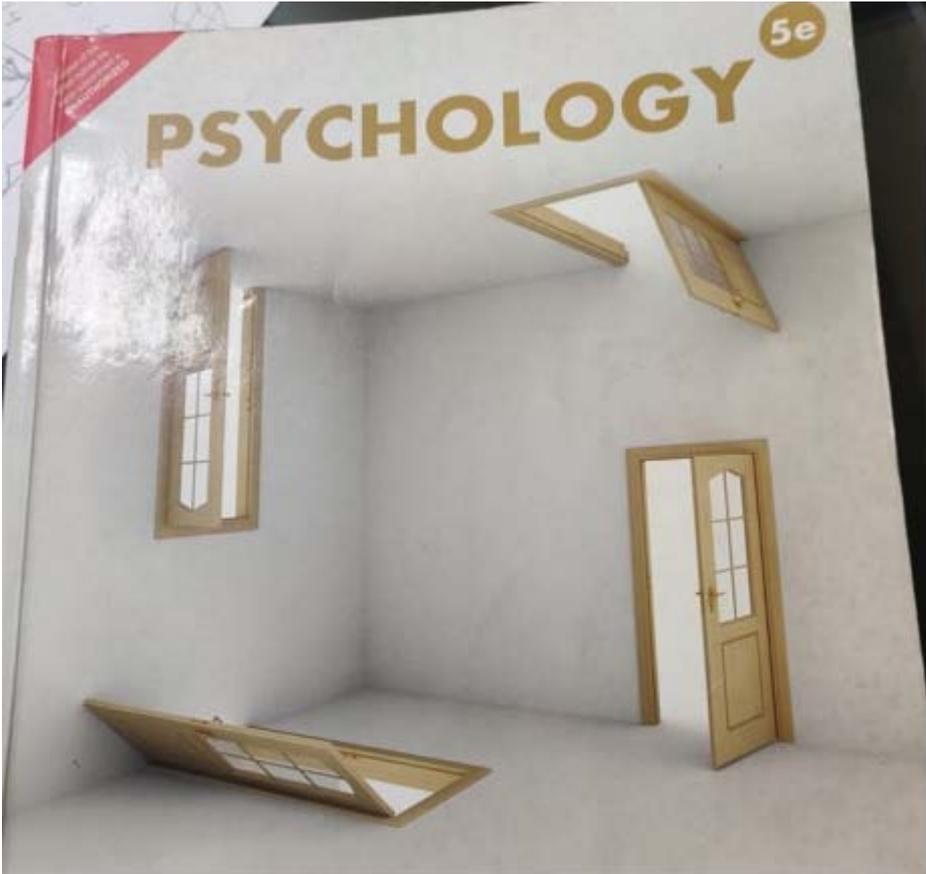
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Chapter 15 Behavioural Intervention Programme for Promoting Healthcare Practices in the Community: An Initiative

Nisha Mani Pandey and S. C. Tiwari

Health is the prime concern for every nation. Behaviour is the key to health. Inter relatedness between health and behaviour is well documented; it is an established fact that many of the illnesses are the result of faulty/unhealthy behavioural patterns (Vaillant and Mukamal 2001; Gary and David 2001; Tiwari et al. 2007; Shukla



PSYCHOLOGY ^{5e}

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- R.C. Mishra, Banaras Hindu University (Varanasi), 'Culture and Psychological Processes' (Chapter 1, page 9)
- Sangeetha Menon, National Institute of Advanced Studies, 'The Puzzle of Consciousness' (Chapter 4, page 133)
- Indiwari Misra, University of Delhi, 'Some Recent Advances in Memory Research' (Chapter 6, page 261)
- Ashok K. Srivastava, National Council of Educational Research and Training, 'The Notion of Intelligence in the Indian Cultural Context' (Chapter 7, page 282)
- Nisha Mani Pandey, King George's Medical University UP (Lucknow), 'Late Adulthood and Ageing' (Chapter 8, page 350); 'AIDS in India' (Chapter 10, page 421); 'Indigenous Therapeutic Practices' (Chapter 15, page 610, and Practice Quiz sections)
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- Rachana Bhangaokar, M. S. University (Baroda), 'Prosocial Behavior in India' (Chapter 12, page 497)
- Akanksha Sonal, King George's Medical University UP (Lucknow), 'Psychological Disorders' (Chapter 14, pp 586-587, cases related to Dissociative Amnesia, Social Anxiety, OCD and Dyslexia and Panic disorder along with Practice Quiz)
- Manu Chauhan, University of Delhi, 'Concept of Science: Positivism and Beyond' (Chapter 1, page 23)
- Narayanan, University of Allahabad, 'Scope of Attention' (Chapter 3, page 96)

Should Direct Oral Anticoagulant Use be the Default Strategy Post Percutaneous Coronary Intervention with Atrial Fibrillation?

Rishi Sethi, Akshyaya Pradhan, Pravesh Vishwakarma

ABSTRACT

Atrial fibrillation (AF) and coronary artery disease (CAD) often coexist in clinical practice. The need for percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) mandates a dual antiplatelet therapy (DAPT) regimen while the underlying AF necessitates oral anticoagulation. To circumvent both thromboembolic and ischemic events the combination therapy [triple therapy: oral anticoagulant (OAC) + DAPT] becomes essential. However, the combination comes at price of increased bleeding and we have now realized that post-PCI bleeding is not benign. Attempts to minimize bleeding by combining vitamin K antagonist (VKA) with single antiplatelet therapy (SAPT) and shortening the duration of triple therapy with VKA did not yield expected results in the *WOEST* and *ISAR-TRIPLE* studies, respectively. The advent of direct oral anticoagulant (DOAC) has heralded a paradigm shift in vascular anticoagulation with almost 50% reduction in intracerebral bleeds albeit with preserve efficacy compared to VKA. The DOAC plus single antiplatelet combination (dual therapy) have now been tested in four randomized studies over 10,000 patients in the setting of PCI with AF. Across the board, the novel regimen has demonstrated superiority in bleeding and no difference in efficacy. All guidelines now endorse this dual therapy with DOAC at full doses whenever feasible and a short triple therapy with DOAC at initiation in high-risk (ischemic) cases.

Keywords: vitamin K antagonists, dual therapy, stent thrombosis, WOEST trial, major bleeding

Introduction: Crossroad of Atrial Fibrillation and Coronary Artery Disease

Atrial fibrillation (AF) is the most common sustained arrhythmia in cardiology practice and becomes even more common with increasing age. Comorbid conditions, such as obesity, hypertension, diabetes mellitus (DM), heart failure (HF), coronary artery disease (CAD), valvular heart disease (VHD), and chronic kidney disease (CKD), further increase the risk of AF. The presence of AF significantly increases the risk of thromboembolic complications including stroke and peripheral embolism mandating the use of antithrombotic treatment with control of risk factors to substantially reduce the risk of stroke.

About 20–40% of patients with AF have concomitant CAD, a significant proportion of whom require revascularization using percutaneous coronary intervention (PCI) and stent implantation. In addition, about 5–10% of patients undergoing coronary angiography with or without PCI have AF or other indications for chronic oral anticoagulation (OAC) therapy.¹ Guidelines recommend dual antiplatelet therapy (DAPT) for patients undergoing PCI to prevent the risk of stent thrombosis and additional thrombotic ischemic events. So, in theory, these patients with AF undergoing PCI with a stent need both the therapies viz. OAC and DAPT (called triple therapy). The rationale for prescribing triple therapy is based upon earlier findings that DAPT is superior to an OAC for reducing the risk of stent thrombosis, while

DAPT is insufficient (as compared to OAC) to preventing thrombotic events in patients with AF.² Thus, triple therapy seems to be necessary in these patients to mitigate the thromboembolic risk due to AF-induced stasis in left atrium and platelet-mediated risk of stent thrombosis; and is empirically indicated in AF patients undergoing PCI. However, no randomized controlled trials (RCTs) have tested the efficacy of triple therapy, but it is well known to increase the risk of both fatal and nonfatal bleeding.

Alternative to Triple Therapy: WOEST and ISAR-TRIPLE Trials?

Bleeding with various combinations of antiplatelets and OAC is a real risk and is depicted in **Figure 1**.³ Major bleeding in patients who undergo PCI is not at all benign and results in 3-fold increase in mortality.⁴ Hence, it is prudent to reduce the bleeding risk of these patients by either avoiding it altogether or at least reducing the duration of triple therapy. What is the Optimal antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (**WOEST**) trial tested the first of strategies, i.e. avoiding triple therapy completely. Patients with severe CAD requiring long-term anticoagulation (n = 573) were randomized into dual therapy arm (clopidogrel-only with warfarin) and triple

therapy arm (clopidogrel and aspirin with warfarin).⁴ Dual therapy arm showed 64% relative risk reduction in bleeding episodes, primarily driven by reduction in thrombolysis in myocardial infarction (TIMI) minor/minimal bleeding without any significant difference in TIMI major bleeding event [hazard ratio (HR): 0.36; 95% confidence interval (CI): 0.26–0.50; p <0.0001]. Though it was not powered for secondary ischemic endpoints, the study showed reduction in major adverse cardiovascular events (MACE) including stent thrombosis and target vessel revascularization in the dual therapy arm (HR: 0.39; 95% CI: 0.16–0.93; p = 0.025). Despite its small sample size and open design, the study provided first randomized evidence that early discontinuation of aspirin may be attempted to reduced bleeding event without any significant rise in ischemic complications.

On the other hand, the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (**ISAR-TRIPLE**) trial tested other strategy of shortening DAPT duration and randomized 614 patients receiving OAC to either 6 weeks or 6 months of DAPT.⁵ At 9 months, the primary endpoint with a combination of ischemic and bleeding events did not differ between groups, but the secondary analysis showed reduced bleeding risk in shorter DAPT duration. Like the WOEST trial, this study was also plagued by small sample size and lack of power

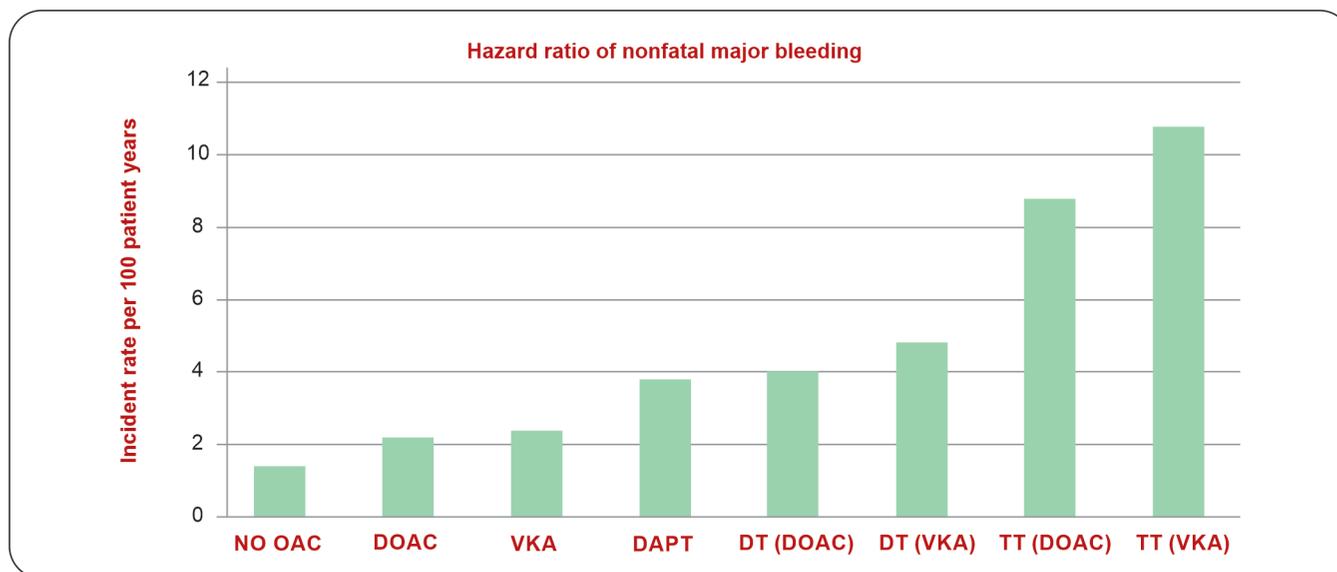


Fig. 1: Hierarchical incidence of bleeding with contemporary antiplatelet and anticoagulant from Danish AF Registry.³
 Abbreviations: DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; DT, dual therapy: combination of OAC and single antiplatelet; OAC, anticoagulant therapy; TT, triple therapy: combination of OAC and dual antiplatelet; VKA, vitamin K antagonist

to detect impact on ischemic events. Both these studies unequivocally showed that triple therapy for one year is unnecessary and dual therapy for shortened duration is significantly safe in terms of bleeding.

Dual Therapy: The Game Changer!

While the **WOEST** and **ISAR-TRIPLE** trials had signaled towards the superiority of a VKA-based dual therapy, both studies had their inherent limitations. Despite being the gold standard of vascular anticoagulation for past 6 decades, VKA use had multiple challenges. Periodic international normalized ratio (INR) monitoring, multiple drug/food interactions, and slow onset-offset being the major hurdles. However, rates of major bleed (especially intracerebral bleed) were the primal fear in the mind of physicians while initiating them. To this end, the emergence of direct oral anticoagulant (DOAC) has been a huge relief for the clinician managing anticoagulation. Minimal food/drug interaction, faster onset, preclusion of regular testing, and stable therapeutic action are major advantages. All these benefits are achieved with similar efficacy and reduction of major bleed vis-à-vis VKAs. A meta-analysis of 4 major DOAC RCTs with 71,683 patients showed 19% reduction in stroke or systemic embolism (SSE) compared to VKA.⁶ Not only that, but all-cause mortality was also reduced by 10% and intracranial hemorrhage by 52%. Hence, the use of DOACs in place of warfarin was a feasible and attractive strategy. Four RCTs have tested this strategy now. Because bleeding was one of the major banes of triple therapy and DOACs had already shown superiority for bleeding, most of the trials had bleeding as the primary endpoint.

A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (**PIONEER AF-PCI**) was the first of the series and tested DOAC (rivaroxaban)-based dual and triple therapy.⁷ The study included 2,124 patients of AF undergoing PCI and warfarin-based triple therapy was the comparator. At 12 months, the primary endpoint of bleeding (composite of major or minor bleeding defined by TIMI criteria) was significantly lower in the DOAC-based therapy compared to standard therapy (16.8% -DOAC-based dual therapy, 18.0% - DOAC-based triple therapy and 26.7% - warfarin-based triple therapy, respectively; $p < 0.001$). Compared to standard triple therapy, DOAC-based dual and triple therapy reduced bleeding by 41%

and 37%, respectively. The results remained similar when other definitions of major bleeding were utilized such as Global Usage of Strategies to Open Occluded Arteries (GUSTO) or International Society on Thrombosis and Hemostasis (ISTH). Also, rivaroxaban arms had less bleeding requiring medical attention. The overall study result was consistent with subgroup analysis and various strata of DAPT (1 month, 6 months, or 12 months). The efficacy endpoint (MACE) was not significantly different among study groups (6.5%, 5.6%, and 6.1%; $p > 0.05$ for the three arms, respectively). The study was indeed a pioneer in establishing the safety and efficacy of DOAC plus antiplatelet combo. The doses of rivaroxaban use in the study were 15 mg OD and 2.5 mg BD with SAPT and DAPT, respectively and are lower than what is prescribed in AF. Some differences with the WOEST trial are noteworthy - the higher percentage of participant received 12-month duration of DAPT in the WOEST and the **POINEER-AF** was an exclusive AF population (only 69% had AF in the WOEST trial).

The Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting (**REDUAL-PCI**) trial sought to extend the mandate of DOAC-based therapy with dabigatran.⁸ The study enrolled 2,725 patients with AF undergoing PCI (within 5 days) and tested both the doses of dabigatran (110 mg/150 mg) against a warfarin-based triple therapy. DOACs were used only with single antiplatelet agent (clopidogrel or ticagrelor); and, hence, there was no DOAC-based triple therapy arm unlike the **PIONEER AF-PCI** trial. Similar to previous study, the main goal was to evaluate safety - major or clinically relevant bleeding defined by the ISTH criteria and the median duration of follow-up was 14 months. With respect to safety, the study hypothesized that DOAC-based dual therapy will be noninferior to VKA-based triple therapy. Interestingly, elderly patients (>70 years) outside the USA were given 110 mg dabigatran dose only. At study end, bleeding was reduced by 48% with dabigatran 110 mg dual therapy compared to standard triple therapy (15.4% vs 26.9%; HR: 0.52; $p < 0.001$). Similarly, a significant 28% reduction of bleeding was achieved with 150 mg dose of dabigatran ((20.2% vs 25.7%; HR: 0.72; $p < 0.001$). With respect to safety, dabigatran (both doses combined) was noninferior to warfarin for the composite endpoint of stroke, MI, systemic embolism, or death (HR: 1.04; $p < 0.001$). The study successfully demonstrated two

improvisations in contemporary standard of care (triple therapy) namely - use of a DOAC and omission of aspirin. The study differs from the **PIONEER AF** trial in two important aspects - exclusive use of dual therapy based on DOAC and use of standard doses of DOAC as tested in AF (unlike the PIONEER trial where lower doses were utilized).

The Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention (**AUGUSTUS PCI**) and the Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (**ENTRUST-AF-PCI**) subsequently tested apixaban and edoxaban respectively in the setting of PCI with AF.^{9,10} The AUGUSTUS PCI trial was a larger trial of 4,614 patients across >30 countries. It included patients of AF who had either acute coronary syndrome (ACS) or were undergoing PCI. On a background P2Y12 therapy, the trial compared DOAC (apixaban 5 mg BD) versus VKA (INR: 2.0–3.0) as well aspirin or no aspirin in a 2X2 factorial design. At six months, the primary outcome of bleeding (definition similar to REDUAL-PCI) was 31% lower with apixaban compared to VKA (10.5% vs 14.7%; HR: 0.69; p <0.001). Similarly, aspirin use was associated with a higher incidence of bleeding compared to its omission (16% vs 9%; HR: 1.89; p <0.001). Additionally, apixaban arm had lower rates of death or hospitalization compared to VKA, while ischemic events were similar. Aspirin omission had no effect on the secondary outcomes. In the last trial of the series, **ENTRUST-AF-PCI** trial, edoxaban 60 mg (30 mg with renal dysfunction)-based dual therapy was tested against warfarin-based triple therapy in 1,506 patients of AF undergoing PCI. The rate of major or minor but clinically relevant bleeding at 12 months was lower with edoxaban therapy compared to standard triple therapy (17% vs 20.7%; HR: 0.83; p <0.01 for noninferiority). The ischemic efficacy outcome [combination of cardiovascular (CV) death, stroke, systemic embolism, MI, or definite stent thrombosis] was not significantly different among two groups (HR: 1.06; CI: 0.71-1.69). The trial failed to show superiority of DOAC (edoxaban)-based dual therapy for bleeding unlike its predecessors.

Additional credence for dual therapy comes from meta-analyses of these trials.^{11,12} Lopes et al. performed

a large meta-analyses of four DOAC RCT and the WOEST trial including 11,542 patients. Compared to standard triple therapy, the odds ratio for major bleeding with dual therapy with DOAC was 0.57 and 0.69 for DOAC-based triple therapy. The risk of MACE was 0.95 and 0.97, respectively for dual and triple therapy based on DOAC using standard triple regimen as reference. Another meta-analysis based on the 4 RCTs found that DOAC-based therapies had significant lower risk for any bleeding [relative risk (RR): 0.65; p <0.001] and major bleeding (RR: 0.63; p <0.001). For ischemic CV events and death, there was no difference between DOAC-based therapies and VKA-based triple therapy (RR: 1.05; CI: 0.93–1.18 and RR: 1.14; CI: 0.94–1.37; p = NS).

So, now there is convincing data that DOAC-based regimens (especially novel dual therapy- DOAC + SAPT) significantly reduce major bleeding irrespective of definition used, type of DOAC use, and geographical barriers (**Fig. 2**). However, the relative contributions of aspirin omission and DOAC introduction to bleeding attenuation remains to be determined.

Vitamin K Antagonist in Percutaneous Coronary Intervention with Atrial Fibrillation: Is the Door Still Open?

Despite superior reduction of bleeding with DOAC-based therapies, many questions remain unanswered. **First**, most of the RCTs discussed above were clearly underpowered for evaluation of ischemic events and is acknowledged by trialists too. Hence, the ischemic safety of DOAC-based dual therapy will need to be tested in a proper sized RCT. In fact, in the REDUAL-PCI trial, the 110 mg dual therapy with dabigatran had nonsignificantly increased thromboembolic events by 1.8% which was counterbalanced by 4.2 % decrease in bleeding events. Stent thrombosis and MI were also numerically higher (statistically insignificant) with lower dabigatran dose. Two meta-analyses have flagged the insignificantly higher risk of MI and significant higher risk of stent thrombosis with DOAC-based dual therapy.^{13,14} Because of predominance of bleeding events, the individual RCTs did not show these signals probably. The relative risk for stent thrombosis almost overlapped in both the meta-analyses (RR: 1.59; p = 0.04 and RR: 1.67; p = 0.04, respectively) and cannot be ignored. The effect on all-cause death and CV death was neutral with DOAC-based dual therapy. The signal of

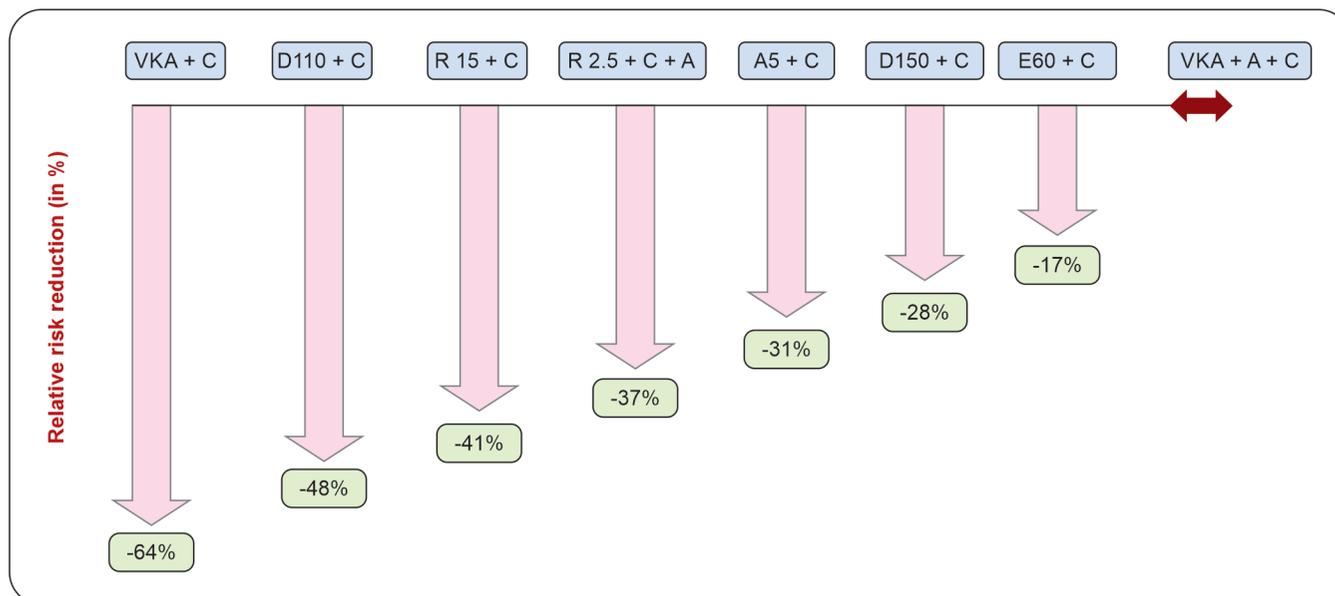


Fig. 2: Relative risk reduction in major bleeding or clinically relevant nonmajor bleeding with standard DOAC doses in various RCTs.

Standard VKA-based triple therapy was the comparator

Abbreviations: A, aspirin; A5, apixaban; C, clopidogrel; D110 & D150, dabigatran; DOAC, direct oral anticoagulant; E60, edoxaban; R15 & R2.5, rivaroxaban; RCT, randomized controlled trial; VKA, vitamin K antagonist

ischemic events were primarily seen with 110 mg doses of dabigatran and should be used with caution. Hence, for patients with high-ischemic risk, a short initial triple (at least 1 week) therapy is recommended by the authors. A criticism of all these RCTs is that they used clopidogrel as the seminal P2Y12 inhibitor, while novel P2Y12 inhibitors (prasugrel or ticagrelor) have clearly shown efficacy over it.¹⁵ It is unclear whether the use of these agents could have offset the ischemic side effects discussed above. The MI and stent thrombosis are most probably related to the antiplatelet component of combination therapy and could be potentially correctable. In a nutshell, DOAC-based dual therapy can be a routine in patients with high-bleeding risk; but with high-ischemic risk, a consideration for initial triple therapy (DOAC or VKA) is warranted.

Secondly, the duration of triple therapy has gradually truncated from 12 months in the WOEST trial to 1–6 months in the DOAC RCTs reflecting contemporary practice. Hence, whether DOAC or VKA is used, triple therapy duration should definitely be <12 months and preferably be restricted to initial few weeks or months for high-ischemic risk patients. Of course, direct comparison of DOAC or VKA-based triple therapy is not available in the REDUAL-PCI and ENTRUST-AF-PCI trials. The small cohorts DOAC-based triple regimen from the AUGUSTUS

trial (n = 1,153) and the POINEER-AF-PCI (n = 709) are available.

Thirdly, most studies compared a DOAC-based dual therapy against a VKA-based triple therapy. It has been previously demonstrated that bleeding risk increases with combination of anticoagulant and antiplatelet therapy.^{3,16} So, with respect to bleeding, the triple therapy groups were already at disadvantage compared to dual therapy even before initiation of studies. It is akin to comparison of apples and oranges! With DOACs already reducing bleeding compared to VKA by (almost 52% in ICH), the scales were tilted in favor of DOAC-based therapies. However, even with such advantages, the ENTRUST-AF-PCI study failed to demonstrate superiority with respect to bleeding with edoxaban! Here, it should be noted that VKA-based dual therapy also had reduced bleeding by 65% in the WOEST trial. Comparison of VKA-based dual therapy with a DOAC-based dual therapy in an RCT with adequate power is the need of the hour.

Fourthly, in certain situations with AF, novel oral anticoagulants (NOACs) are not indicated - pregnancy, prosthetic valve, and moderate to severe mitral stenosis. Hence, VKA will still be preferred for combination with antiplatelets should the need arise. Based on the results

of the WOEST trial, a dual therapy will be preferable, especially in high-bleeding risk subjects.

Improving the Safety of Combination Therapy

As noted above, whenever antiplatelet and anticoagulant are combined, bleeding risk is elevated.^{3,16} Multiple pharmacological and nonpharmacological maneuvers can be applied to mitigate bleeding risk.^{15,17}

- *Lower aspirin doses* (<100 mg) continue to retain antiplatelet efficacy while simultaneously reducing bleeding complication. Moreover, the advent of ticagrelor in clinical practice has made lower dose of aspirin a common practice.
- *Radial access* has drastically reduced access site bleeding in multiple RCTs such as MATRIX, RIVAL, RIFLE-STEACS, and many more. Hence, the use of radial route is preferable with oral anticoagulation.
- Concomitant use of *proton pump inhibitor* decreases gastrointestinal bleeding with DAPT and dabigatran. There is no interference with antiplatelet action of P2Y12 inhibitor as shown in large RCT.
- *Avoiding the use of novel P2Y12 inhibitor*: Most RCTs of DOAC have utilized clopidogrel as the default drug as noted above. Using ticagrelor and prasugrel in combination with DOAC will increase bleeding as seen in the Treatment With Adenosine Diphosphate (ADP) Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) study.¹⁸
- *“De-Escalation”*: In patients with high-risk angiographic features, such as bifurcation, left main disease, chronic occlusion, and multiple stents, guidelines indicate the use of potent P2Y12 therapy. De-escalation strategy entails switching from potent P2Y12 inhibitor therapy to clopidogrel after initial few weeks of PCI. This strategy aims to tide over initial periprocedural period with potent P2Y12 inhibitors when risk of ischemic events is high. The second switch phase (to clopidogrel) aims to reduce bleeding risk when ischemic risk has waned. Both guided and unguided de-escalation strategies have already been tested in randomized trials.¹⁹
- *Risk stratification tools*: The Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage (**HAS-BLED**) score has been conventionally

utilized to calculate bleeding risk with oral anticoagulation. Patients with score >3 are at high-bleeding risk and need careful monitoring. The **DAPT** score and **PRECISE-DAPT** scores have been validated to calculate ischemic risk and bleeding risk with DAPT.

Guidelines: The Changing Face

In view of recent evidence available, various guidelines also favor the shortest duration of triple therapy in patients of AF undergoing PCI. The recent 2020 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS)/European Heart Rhythm Association (EHRA) guidelines for management of AF recommend usage of DOACs in preference to VKA if the patient is eligible for DOAC.²⁰ To minimize bleeding risk in patients with high-bleeding risk (HAS-BLED ≥ 3), lower dose of DOAC is preferred (e.g. rivaroxaban 15 mg OD or dabigatran 110 mg BD) for the duration of concomitant antiplatelet therapy (SAPT or DAPT). For patients who are on VKA, and simultaneous antiplatelet therapy is desirable, VKA dosing should be closely monitored with target INR 2.0–2.5 and tolerated therapeutic range (TTR) >70%. Aspirin should be taken off the prescription as early as possible (≤ 1 week) to keep the duration of triple therapy to minimum if ischemic risk is low or bleeding risk is high. If risk of stent thrombosis outweighs bleeding risk, duration of triple therapy may be extended to <1 month. P2Y12 inhibitor (preferably clopidogrel) is the recommended drug as part of dual therapy. Duration of clopidogrel is dependent on clinical profile, bleeding, and ischemic risk. For ACS patients, duration of dual therapy up to 12 months is recommended; while for patients with stable CAD, clopidogrel therapy may be discontinued after 6 months of PCI.

However, the current 2020 American College of Cardiology Expert Consensus Decision Pathway (ACC ECDP) document differs in their default recommendation being dual therapy (consisting of OAC and P2Y12 inhibitor) for such patients.²¹ They recommend against triple therapy in most patients. If ever needed, aspirin may be used with dual therapy for the shortest possible duration (up to 30 days) following PCI. Clopidogrel over other P2Y12 inhibitors and DOAC over VKA are preferred. When aspirin is used with OAC, daily dose should not exceed 100 mg. The duration of clopidogrel recommended is in agreement with current DAPT guidelines and is dependent on clinical scenario (ACS vs stable angina), ischemic and

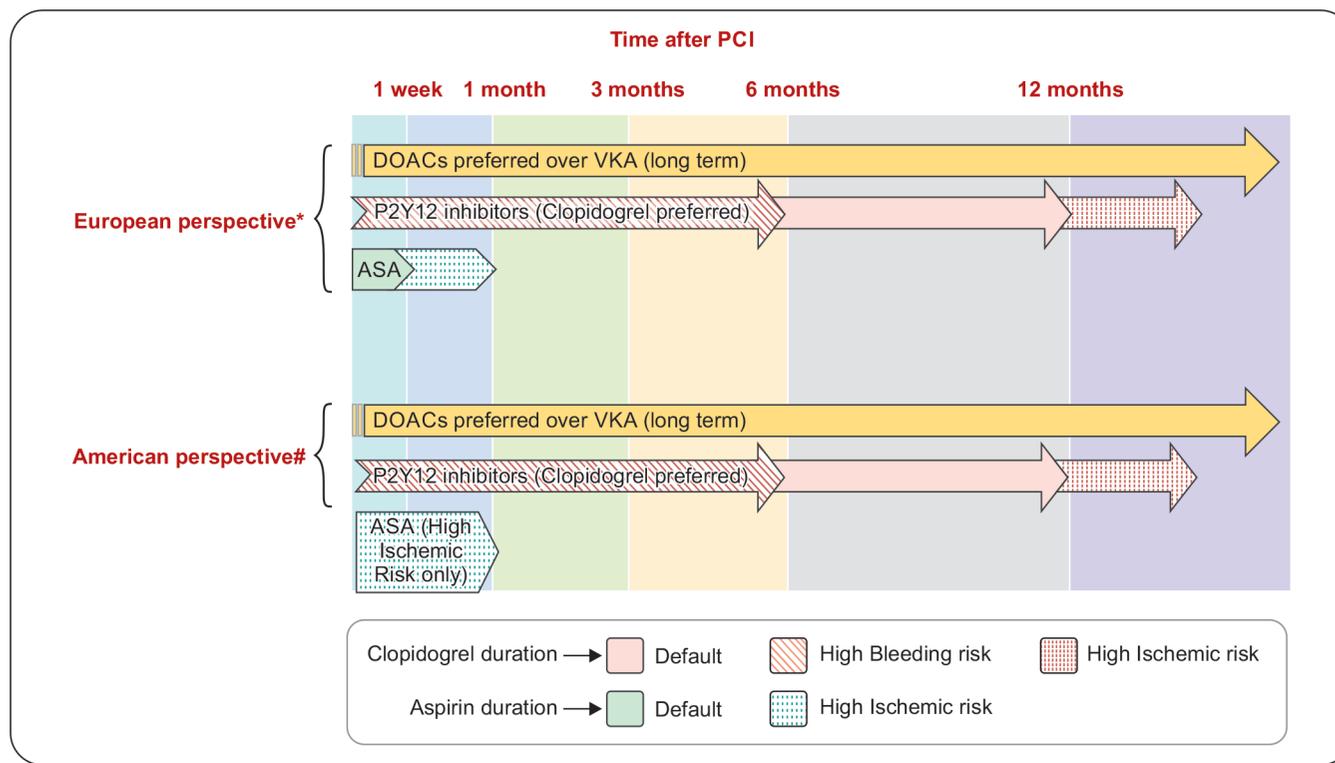


Fig. 3: Comparison of the American and European guidelines on combination of antiplatelet and DOAC therapy in AF patients undergoing PCI. The major difference lies in routine omission of aspirin following PCI as a default strategy in the American iteration, while an initial triple therapy of 7 days is advocated in the European version. Based on ischemic and bleeding risk, the duration of antiplatelets can be tailored. *ESC 2020 Guidelines on NSTEMI & ESC/EACTS/EHRA 2020 guidelines on AF #ACC Expert Consensus Decision Pathway 2020 Abbreviations: AF, atrial fibrillation; ASA, aspirin; DOAC, direct oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist

bleeding risk, and vessel/lesion complexities. For patients with dual and triple therapy, proton pump inhibitors or H2 receptor antagonist along with avoidance of nonsteroidal anti-inflammatory drugs NSAIDs is recommended to reduce the risk of gastrointestinal bleeding.

The 2020 NSTEMI guidelines by ESC and EHRA 2021 practical guide also support the use of dual therapy with DOAC after a short triple therapy of 7 days as a default strategy.^{22,23} **Figure 3** summarizes the recent guideline/consensus statements on DOAC use in AF undergoing PCI.

Future Directions

A large number of studies are ongoing or in pipeline for AF patients undergoing PCI. The Dabigatran Versus Warfarin With NVAf Who Undergo PCI (**COACH-AF-PCI**) trial (**NCT03536611**) is comparing DOAC-based triple therapy with VKA-based triple therapy in the setting of PCI with

AF. What is the Optimal antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation Undergoing revascularization 2 (**WOEST-2**) (**NCT02635230**) study is evaluating the 1-year safety and efficacy of OAC (VKA or DOAC) and P2Y12 combination after PCI/CABG based on the presence or the absence of aspirin. The Optimal Antithrombotic Therapy for ACS Patients Concomitant With AF and Implanted With New-generation DES (**OPTIMA-3, 4**) (**NCT03234114**) studies are enrolling ACS patients with AF undergoing PCI with a new-generation DES. The OPTIMA 3 is looking at VKA-based therapies, while the OPTIMA 4 is looking at dabigatran-based therapies. The Safety and Efficacy Of Rivaroxaban and Ticagrelor for Patients With Atrial Fibrillation After Percutaneous Coronary Intervention (**CAPITAL PCI AF**) (**NCT03331484**) is studying the combination of ticagrelor plus rivaroxaban for 12 months following PCI in patients with AF.

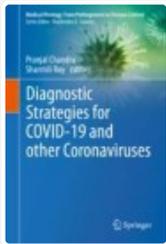
CONCLUSION

The need for long-term oral anticoagulation (AF or venous thromboembolism) in patients undergoing PCI warrants combination of oral anticoagulation and antiplatelets. The ischemic benefits need to be balanced with bleeding risk in such a scenario. The advent of DOAC has been a significant advance in the field of anticoagulation with reduction of intracerebral bleeds by almost 50% which is addition to ease of administration and quick onset of action. Moreover, the use of DOAC-based combination therapies has now been shown to be feasible and has reduced major bleeding by 20–50% compared to standard triple therapy. Although there have been signals of ischemic events with DOAC-based dual therapy, it is primarily restricted to lower dabigatran doses and can be offset by a brief course of triple therapy at onset. All major guidelines now endorse the DOAC-based dual therapies in setting of PCI with AF. The duration of initial triple therapy differs a bit among guidelines. Based on the ischemic and bleeding risk of the patient, DOAC-based therapies need to be individualized. Ongoing studies will clarify the role of potent P2Y₁₂ inhibitors in this scenario and further define the role of VKA-based regimens if any.

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This book provides fundamental information on various techniques for the detection of SARS-CoV-2 including reverse transcriptase (RT) PCR, loop-mediated isothermal amplification, immunodiagnostic tests, and CRISPR-Cas. It reviews various testing kits and detection methodologies that are currently being used for the detection of SARS-CoV-2 and examines strategies for the post-treatment detection and monitoring of SARS-CoV-2. Further, it assesses the diagnostic potential of several SARS-CoV-2 proteins; and analyzes their structural determinants and immunogenicity.

In turn, the book evaluates the potential of CRISPR-Cas 12-based assays for the detection of SARS-CoV-2 using RNA extracted from patients. Lastly, it discusses the use of miniaturized biosensors for the detection of other types of coronavirus.

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Ramanujan Fellowship (Government of India); ECRA (DST, Government of India); BK-21 and NRF Fellowship, South Korea; Technion Post-doctoral Fellowship, Israel; NMS Young Scientist Award; BRSI Young Scientist Award; RSC Highly Cited Corresponding Author Award (general chemistry); and ACS / Elsevier Outstanding Reviewer Awards. He is a reviewer for over 50 international journals and expert project reviewer for various national / international funding agencies. Further, he is an Associate Editor of the journal Sensors International and an editorial board member of Materials Science for Energy Technologies; World Journal of Methodology, USA; Frontiers of Biosciences, USA; and Reports in Physical Sciences, Singapore

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Technology (DST), Government of India, and Post-doctoral fellowship from Stanford University, USA.

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Cognition and Anxiety: An Emerging Role of Complementary and Alternative Medicines

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ABSTRACT

The objective of this Study is to determine the role of various herbs in cognition and anxiety, and Use of Medhya rasayana especially for memory & intelligence as an alternative and relatively safe medicine.

Dementia in the elderly is an epidemic of unprecedented proportion in modern medicine. An "epidemic" of diseases such as Alzheimer's has yet to be met with effective symptomatic treatments or preventative measures. Cholinesterase inhibitors (Donepezil) and N-methyl D-Aspartate receptor antagonists are two examples of current prescription drugs (Memantine). Furthermore, a plethora of pharmaceutical agents are available to treat mood disorders, anxiety, and insomnia, but many patients struggle to tolerate the adverse effects, do not effectively respond, or eventually lose their response. In recent years, there has been a surge in interest in ethnobotanicals for memory, cognition, and anxiety. Medhya herbs are those that promote intelligence in particular. Therapeutic herbs and nutrients have far fewer side effects, and many can be used as an alternative treatment or to boost the effectiveness of prescription medications.

Keywords: Complementary and alternative medicine; cognition; anxiety; medhya rasayana; nootropics.

1. INTRODUCTION

Cognition is a multifaceted process that includes everything from learning and memory to attention. Dementia is defined as a cognitive impairment caused by a loss of intellectual ability that interferes with occupational functioning, social activities, and relationships in the absence of loss of consciousness or motor involvement [1]. The number of people living with dementia is expected to nearly double every 20 years, reaching 42.3 million in 2020 and 81.1 million in 2040 [2]. Anxiety is defined as "a psychological, physiological, and behavioral state induced in animals and humans by an actual or potential danger to well-being or survival" [3]. Globally as of 2010 approximately 273 million (4.5% of the population) had an anxiety disorder. It is more common in females (5.2%) than males (2.8%) [4].

Number of nootropics drugs has been developed for the treatment of cognitive deficits, from the FDA approved acetylcholinesterase inhibitors (e.g., Donepezil) and NMDA receptor antagonist e.g. Memantine, to those still under development ampakines, nicotinic receptor agonists, glycine inhibitors, and PDE inhibitors [5]. Benzodiazepine, selective serotonin reuptake inhibitor (SSRI), monoamine oxygenase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tranquilizers such as buspirone, beta-blockers are the drugs that are indicated for anxiety disorder.

Now a day's herbal medicine and Complementary and Alternative Medicine (CAM) use is widespread in neurological disorders due to their natural origin and less side-effects [6,7]. The World Health Organization (WHO) estimates that 80% of the population uses herbs; in the developing world rates could be as high as 95% [8]. *Medhya Rasayanas* are group of medicinal plants in

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A STUDY ON FUNCTIONING OF THE NUTRITIONAL SERVICES IN ANGANWADIS FOR 0 – 3 YEARS CHILDREN UNDER ICDS PROGRAMME IN DELHI FROM USER'S PERSPECTIVE.

Community Medicine

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ABSTRACT

Introduction: Nutritional services under the ICDS programme aims to improve nutritional status of children in India. Perception of the user regarding the nutritional services provided by the anganwadi, reasons for non-utilization of services is important to understand to achieve its aim.

Objective: To assess perceptions of users regarding nutritional services provided in anganwadi of urban area and reasons for non-utilization of the nutritional services by anganwadi among non-users.

Methodology: Cross sectional and descriptive study conducted at Mehrauli Project of South District and Hastal Project of West District. Mothers were interviewed based on the pre-tested interview schedule.

RESULTS: Significant differences were observed in profile of user and non-user, population with years of stay less than 2 years are utilizing the services less as compared to those who have comparatively more years of stay in the area. Utilization of anganwadi services is less among families with children in age group up to 12 months, lower birth order and families with relatively higher monthly income of household. Awareness about anganwadi services for pregnant women was low (83.3% for supplementary nutrition and 68% for NHE). Utilization of supplementary nutrition and NHE services for pregnant women was also low 57.5% and 9.6% respectively. Among the non-users 34% were not aware of the location of AWC and awareness level for the growth monitoring services was 57.5% and 62.7% for supplementary nutrition / Take Home Rations. Among users 23 (13%) were not aware of importance of growth monitoring and 17 (9%) were not aware about importance of SNP/THR. Awareness among the user about feeding the child during illness and after illness was 72.8% as compared to 33% in the non-user.

Conclusion And Recommendation: Active efforts to include the migrant young population, families with relatively higher household monthly income in the nutrition and health services for growth monitoring to enable detection of under or over-nutrition in these children and appropriate advice for corrective measures.

KEYWORDS

ICDS, User Perspective, Supplementary Nutrition

INTRODUCTION

Poor growth and development can have a lifelong effect on health and nutritional status of the individual. Adverse nutrition-infection interaction results in a vicious cycle with serious consequences to the life of the infant/young child. Stunted and underweight children grow up into short adults and women who are short and under-weight and are more likely to give birth to Low Birth Weight babies. The result is an intergenerational cycle of under-nutrition since low birth weight infants tend to attain smaller stature as adults⁽¹⁾. The need for appropriate growth in childhood is necessary to protect against both under and over-nutrition and consequent health hazards. Right from the Bore Committee the inter-relationship between health and nutrition was understood; this has been emphasised in India's Five-year Plans. Realising the need for a programme to promote adequate nutritional status and prevent under-nutrition especially in the vulnerable groups like pregnant and lactating women and pre-school children the Government of India started the Integrated Child Development Services (ICDS) as a Project in 1975 focussing on "Nutrition, Assisting Health Services. Pre-school Education".

Even after three decades of implementation of nutritional services under the ICDS programme, poor nutritional status of children in India is seen. The percentage of children who are too short for their age (stunted) decreased by less than one percentage point per year over the seven years between the two surveys, from 51 percent in NFHS-2 to 45 percent in NFHS-3. The percentage of children who are underweight also decreased, but only by three percentage points⁽²⁾.

In Delhi 42% of children under age five are stunted, or too short for their age, which indicates that they have been undernourished for some time. 15% are wasted, or too thin for their height, which may result from inadequate recent food intake or a recent illness. 25% are underweight, which takes into account both chronic and acute under-nutrition. Even in the wealthiest households, one-third of children are stunted, 17% are wasted, and 20% are underweight. The nutritional status of children in Delhi has improved slightly since NFHS-2 by one

indicator (the prevalence of underweight), but not by other two indicators. In Delhi children under age three years (the age group for which nutritional status data are available in NFHS-2) are less likely to be too thin for their age, which means that acute under-nutrition among children is less widespread today than it was seven years ago. However, the likelihood of children being too short for their age is same as they were at the time of NFHS-2, and they are slightly more likely to be too thin for their age⁽³⁾.

Children in slum areas are much more likely to be stunted and underweight than children in non-slum areas. The focus has also been on distributing food rather than changing family-based feeding and caring behaviour. Variety of reasons resulting in low community participation and poor coordination between Health and Social Welfare Department has resulted in limited impact and slow pace of improvement.

In view of few studies addressing these issues this study will try to find out: perception of the user regarding the nutritional services provided by the anganwadi, reasons for non-utilization of services. The study will also suggest locally feasible remedial measures for gaps identified.

The National Family Health Survey (NFHS-3), India, 2005-06 showed that only 8-10% of children aged 0-71 months received any service from an AWC in the 12 months preceding the date of the survey in Delhi, Bihar, and Arunachal Pradesh. It also showed equally clearly that children living in urban slums in metros and big cities had very high proportion of under-nourished children. Hence the study was planned in Delhi in a slum/unauthorised colony/underserved area of Delhi.

OBJECTIVE

To assess the perceptions of users regarding the nutritional services provided in anganwadi of urban area and the reasons for non-utilization of the nutritional services by anganwadi among non-users.

METHODOLOGY

Operational Definitions:

User: Mother of (0 to 3 years) child using Anganwadi services (growth monitoring or supplementary nutrition)

Non – User: Mother of (0 to 3 years) child not using Anganwadi services (growth monitoring & supplementary nutrition) matched for user for same geographical area.

The study was conducted at Mehrauli Project of South District and Hastal Project of West District. In South District CDPO of Mehrauli Project granted permission for 12 centres and in West District CDPO of Hastal Project granted permission for areas 10 centres. It was a cross sectional and descriptive type of study. The study population includes User (as per operational definitions of this study) and Non–User (as per operational definitions of this study) for each anganwadi. Variables such as awareness about location and services provided by AWC, services utilized at AWC for the child, reasons for satisfaction or dissatisfaction with the AWC services of users, reasons for non-utilization of anganwadi services by nonusers, awareness about Infant and Young Child Feeding Practices, awareness of services provided by anganwadi for pregnant women, utilization of services provided by anganwadi for pregnant women during pregnancy were taken for study.

For assessing the perception of user and non-user the researcher went to the residence of each of the identified user as well as non-user from the same locality and the mother of the child was interviewed. Mothers were interviewed based on the pre-tested interview schedule

Sample size calculation:

According to National Family Health Survey (NFHS-3), India, 2005-06 among the 46 percent of children under six years in Delhi who are in areas covered by an *anganwadi* centre, only 12 percent receive services of any kind from a centre. The most common services that children age 0-71 months in areas covered by an *anganwadi* centre receive are supplementary food (12%), followed by immunizations (5%) and health check-ups (3%).

The sample size was calculated taking the NFHS -3 data of 12.4% of under five children who received any service from an AWC in the previous 12 months and confidence level of 95% (probability), margin of error accepted (d) 10% i.e. 0.05 and by the following formula.

$$\text{Sample size (N)} = \frac{(Z_2)^2 * P(1-P)}{d^2}$$

p=0.12

q=(1-p)=0.88

z=1.96 as per table of area under normal curve for confidence level of 95 %

d = allowable error, since estimate should be within 5% of true value=0.05

$$\text{Sample size (N)} = \frac{(1.96)^2 * 0.124(1 - 0.124)}{(0.05)^2} = 166.9 \sim 167$$

For users 228 children were selected randomly from the list of users available with the Anganwadi Workers of selected Anganwadis, thus 4 children from each anganwadi were randomly selected from the enrolment register of AWC. Corresponding 228 children (matched for the same geographical area) not using Anganwadi services (growth monitoring & supplementary nutrition) were selected as non-user.

Data collection was done in duration of two months, April – May 2011. Data was analyzed by using Statistical Package for the Social Sciences 19 (SPSS 19) and Microsoft Office Excel 2010 and 97-2003 for windows software as follows: Descriptive statistics and Test of significance

RESULTS

This study was conducted in Delhi, in the anganwadi centres of Neb Sarai (12), Lado Sarai (8), and Andheriya Mod (10) (Mehrauli Project, South District) and Shiv Vihar (10) and Vikas Nagar (17) (Hastal Project, West District) were covered.

Socio – demographic profile of user and non-users

Years of stay in area:

Table 1. Distribution of users and non-users according to year of stay in area

Years of stay in area	User	%	Non-User	%	Total	X ² (4)	P-value
up to 2 years	37	38.5	59	61.5	96	9.804	0.044*
2 years one day to 5 years	57	46.3	66	53.7	123		
5 years one day to 8 years	40	55.6	32	44.4	72		
8 years one day to 12 years	43	56.6	33	43.4	76		
more than 12 years	51	57.3	38	42.7	89		
Total	228	50.0	228	50.0	456		

Details of distribution of users and non-users according to year of stay in area are given in **Table 1**. The proportion of users increases with increasing duration of stay in the area as compare to non-user within each group. This can be because those with shorter duration of stay are recently migrant population who may not be familiar with all services available in the area. Families staying for less than two years are largely composed of unskilled or poorly skilled migrant population who are more vulnerable as they are new to cities and are unaware of location of AWC and services provided by the AWCs, no regular source of income and social security, and nuclear families with no elders accompanying them who are able to guide the young parents.

Table 2. Distribution of users and non-users according to age of the child

Age of child	User	%	Non-User	%	Total	X ² (2)	P-value
Less than 12 months	77	42.5	104	57.5	181	8.037	0.018*
13 - 24 months	77	51.7	72	48.3	149		
25 - 36 months	74	58.7	52	41.3	126		
Total	228	50.0	228	50.0	456		

Age of child: Details of distribution of users and non-users according to age of the child is given in **Table 2**. The proportion of users was more with increasing age of the child. Less than 12 months age group is the most crucial segment as there is a steep increase in under-nutrition as assessed by weight-for-age in this age group; the children will benefit by regular weighing and growth monitoring and advice to mothers if required on necessary IYCF practices

Table 3. Distribution of users and non-users according to birth order of the child

Birth order of child	User	%	Non-User	%	Total	X ² (2)	P-value
1	55	37.2	93	62.8	148	21.79	0.000*
2	94	50.0	94	50.0	188		
3 & >3	79	65.8	41	34.2	120		
Total	228	50.0	228	50.0	456		

Birth order of child: Details of distribution of users and non-users according to age of the child is given in **Table 3**. As the birth order increases there is statistically significant increase in proportion of family using anganwadi services for the child from 37.2% with birth order one to 65.8% with birth order of three or more. Mothers with children of lower birth order requires more support for feeding the infant and young child, child care and for management of childhood illness as they are young and due to increase in nuclear families no one to guide them in child care.

Table 4. Distribution of users and non-users according to monthly income of the household

Monthly income of household	User	%	Non-User	%	Total	X ² (2)	P-value
Low up to Rs 4000	103	55.4	83	44.6	186	6.656	0.036*
Medium Rs 4001 - 6000	77	51.0	74	49.0	151		
High > 6000	48	40.3	71	59.7	119		
Total	228	50.0	228	50.0	456		

Monthly income of household: Details of distribution of users and non-users according to age of the child is given in **Table 4**. There was decrease in proportion of family utilizing anganwadi services (both growth monitoring and supplementary nutrition) for their child in

respect of monthly household income from 55.4% with household income less than Rs 4000 per month to 40.3% with household income of more than Rs. 6000 per month as compare to families of non-user.

Families with relatively higher income are self-excluding themselves which is dangerous as growth monitoring of these children are not done resulting in delay in detection of growth flattening.

Table 5. Distribution of users and non-users

Sex of child	Users	%	Non-Users	%	Total	X ² ₍₁₎	P-value
Male	118	52.7	106	47.3	224	1.264	0.261
Female	110	47.4	122	52.6	232		
Total	228	50.0	228	50.0	456		
Place of delivery of child	Users	%	Non-Users	%	Total	X ² ₍₁₎	P-value
Hospital	136	49.5	139	50.5	275	0.082	0.774
Home	92	50.8	89	49.2	181		
Total	228	50.0	228	50.0	456		
Age of Mother	Users	%	Non-Users	%	Total	X ² ₍₃₎	P-value
17 – 22 years	55	47.0	62	53.0	117	0.951	0.813
23 – 28 years	135	51.7	126	48.3	261		
29 – 34 Years	30	50.0	30	50.0	60		
35 – 40 Years	8	44.4	10	55.6	18		
Total	228	50.0	228	50.0	456		
Education of mother	Users	%	Non-Users	%	Total	X ² ₍₃₎	P-value
Illiterate	103	53.6	89	46.4	192	4.293	0.231
literate but less than tenth	75	51.4	71	48.6	146		
Tenth and less than twelfth	38	44.2	48	55.8	86		
graduate and above	12	37.5	20	62.5	32		
Total	228	50.0	228	50.0	456		
Working status of mother	Users	%	Non-Users	%	Total	X ² ₍₁₎	P-value
Working	19	43.2	25	56.8	44	0.906	0.341
Housewife	209	50.7	203	49.3	412		
Total	228	50.0	228	50.0	456		
Type of family	Users	%	Non-Users	%	Total	X ² ₍₁₎	P-value
Nuclear	128	48.3	137	51.7	265	0.73	0.393
Joint	100	52.4	91	47.6	191		
Total	228	50.0	228	50.0	456		
Religion	Users	%	Non-Users	%	Total	X ² ₍₀₎	P-value
Hindu	196	49.5	200	50.5	396	X ² ₍₀₎	P-value
Muslim	27	54.0	23	46.0	50		
Sikh	2	40.0	3	60.0	5		
Christian	3	60.0	2	40.0	5		
Total	228	50.0	228	50.0	456		
Occupation of head of family	Users	%	Non-Users	%	Total	X ² ₍₀₎	P-value
Legislators, senior officials and managers	2	28.6	5	71.4	7	X ² ₍₀₎	P-value
Professionals	2	18.2	9	81.8	11		
Technicians and associate professionals	9	33.3	18	66.7	27		
Clerks	21	43.8	27	56.3	48		
Service workers and shop & market sales workers	22	59.5	15	40.5	37		
Skilled agricultural and fishery workers	0	0.0	1	100.0	1		
Craft and related trades workers	62	59.0	43	41.0	105		
Plant and machine operators and assemblers	49	55.7	39	44.3	88		
Elementary occupations	60	45.8	71	54.2	131		
Workers not classified by occupations	1	100.0	0	0.0	1		
Total	228	50.0	228	50.0	456		

Details of distribution of users and non-users according to sex of child, place of delivery of child, age of mother, education of mother, working status of mother, type of family, religion and occupation of head of family are given in Table 5. There was no significant difference in proportion of user as compared to non-user in relation to sex of child, place of delivery, age of mother, education level of mother, working status of mother and type of family. However, the study by NIPPCD 2006⁽⁴⁾ observed more registration of male children (59.1%) than those of female children (55.2%). percentage of female children availing supplementary nutrition was (82.5%), as against male children (74.4%).

Awareness, utilization and satisfaction for AWC services among the users

Table 6. Utilization and Satisfaction For Growth Monitoring Supplementary Nutrition / Take Home Ration And Referral Services Provided By Anganwadi Among The Users.

Service	Utilize	% (N=228)	Satisfied	%
Growth monitoring service	228	100.0	174	76.3

Supplementary nutrition/ THR	228	100.0	190	83.3
Referral	188	82.5	184	97.9

* All 228 users were aware of growth monitoring service supplementary nutrition/THR and Referral services.

Table 6 shows that satisfaction for the growth monitoring services was 76.3% followed by 83.3% satisfaction for supplementary nutrition and 97.9% satisfaction for referral services provided by anganwadi among their users. The users understand very clearly the importance of growth monitoring as the most crucial services of AWC required for early detection of growth flattening and corrective actions and appropriate growth of the children, in view of service being not complete, comprehensive and regular satisfaction level for the growth monitoring services was low among all services.

Table 7. Reasons for satisfaction/dissatisfaction for growth monitoring services provided By Anganwadi Among the Users.

Reasons for satisfaction		
Group I	F	% N=174
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Know about weight gain	64	36.78
Know about growth of the child	29	16.66
Get feedback on growth of child	20	11.50
Know monthly growth	10	5.75
If child is weak then get advice what to do and where to go	9	5.17
Know the status of child nutrition	9	5.17
If child is ill weight decreases	6	3.45
Know early if child is weak take action accordingly	3	1.72
Told that the child was weak so referred him/her now child is normal	3	1.72
If weight of the child is less increasing the food quantity	2	1.15
Know the status after illness	2	1.15
Came to know that child was weak after diarrhoea	1	0.57
Group II	F	% N=174
Come to know about weight of the child but weight does not increase and is same as last month	25	14.37
Group III	F	% N=174
Not aware of importance or reason of growth monitoring of child	23	13.22
Group IV	F	% N=174
AWH take child from home	3	1.72
Easy to get weight done	5	2.87
Reasons for dissatisfaction		
Reasons	F	% N=54
Not Regular	48	88.89
No Machine available	43	79.63
No feedback so no importance	12	22.22

Table 8. Reasons for satisfaction/dissatisfaction for Supplementary Nutrition and take-home ration services provided By Anganwadi Among the Users.

Reasons for satisfaction		
Group I	F	% N=190
Added food to child	127	66.84
Added good food we cannot afford	1	0.53
Group II	F	% N=190
Food provided helps in growth of child	31	16.32
Child can play and eat	18	9.47
Child likes the food	14	7.37
The food provided helps to increase the weight gain	12	6.31
At least child eats in competition / company of another child	8	4.21
If do not feed the child then there is less growth	4	2.10
Group III	F	% N=190
Not aware of importance or reason of providing supplementary nutrition or THR	17	8.95
Group IV	F	% N=190
Food is good for child growth but sometimes child do not like food	9	4.74
Reasons for dissatisfaction		
Group I	F	% N=38
Child does not like food	9	23.68
Group II		% N=38
There is no variety, only panjiri, sometimes child do not like	4	10.53
There is no variety, fixed menu children are bored	3	7.89
Nothing like dal and rice or puri and sabji	2	5.26
There should be fresh vegetables	1	2.63
Group III	F	% N=38
Dry ration to be given	7	18.42
Should be dry ready to eat food which child can eat any time in day	12	31.58
Group IV	F	% N=38
Poor quality of grains	15	39.47

Table 9. Reasons for not utilizing Growth Monitoring services provided By Anganwadi Among the Users.

Group I	F	% N=228
No use of weighing for the child	34	14.91
No need of weighting the child	33	14.47
If the weight is done then Nazar lag jayege (evil-eye)	3	1.31
This child was conceived after long t/t for infertility so fear something goes wrong to child	2	0.88
ASHA did not help us during pregnancy so do not use govt service	1	0.44
Child of elder brother died after vaccination so no faith in govt supplies	1	0.44
Elder child died of drowning at village so fear that anything wrong will happen to child	1	0.44
Elder child had "reaction" after immunization, so lost faith in govt supplies	1	0.44
Child is too young to be taken out	1	0.44
Group II	F	% N=228
Get weight of the child done at DDU Hospital whenever go to hospital	4	1.75
Get weight of the child done at SJH or AIIMS whenever go to hospital	1	0.44
Not require get weight of the child done at private clinic	14	6.14
Group III	F	% N=228
No feedback is given about the weight and growth of child	4	1.75
No machine is available at AWC thus no weight done	17	7.46
Weight is not done regularly	17	7.46
Even if weight is done, weight does not increase	5	2.19
Group IV	F	% N=228
Have to go to work thus, no one to accompany the child	9	3.95
Help husband in household business hence cannot accompany child to AWC	2	0.88
No time to accompany the child as busy in household work	21	9.21
Take the child at work site	3	1.31
Group V	F	% N=228
Not aware of the AWC	79	34.65
Not aware of the services of AWC	85	37.28
Group VI	F	% N=228
Weight of the child done when go for immunization	6	2.63
Group VII	F	% N=228
Child suffering from hydrocephalus	1	0.44
Other child may tease/beat the child as we are from northeast	1	0.44
Other child suffering from spinal bifida, and cannot leave the child alone	1	0.44

Table 10. Reasons for not utilizing Supplementary Nutrition and Take-Home Ration

Group I	F	% N=228
Child does not like panjiri	26	11.40
Child does not like taste of the food	29	12.71
Group II	F	% N=228
Child of elder brother died after vaccination so no faith in govt supply	1	0.44
Elder child died of drowning at village so fear that anything wrong will happen to child	1	0.44
Elder child had reaction after immunization, so lost faith in govt supply	1	0.44
Group III	F	% N=228
Child is suffering from hydrocephalus	1	0.44
Other child suffering from spinal bifida, cannot leave the child alone	1	0.44
Group IV	F	% N=228
Poor quality	27	11.84
Doubt about standard of raw material used	9	3.95
Doubt if food is fresh	4	1.75

Doubt about hygiene of cooking	1	0.44
Not given regularly	1	0.44
Group V	F	% N=228
Do not require SNP	35	15.35
No use for child	21	9.21
Group VI	F	% N=228
Not aware of the services of AWC	83	36.40
Not aware of the AWC	78	34.21
Group VII	F	% N=228
Child suffering from seizures	1	0.44
We are Brahmin cannot eat food from outside	1	0.44
ASHA did not help us during pregnancy so do not use govt service	1	0.44
Group VIII	F	% N=228
No time to accompany as busy in household work	17	7.46
Have to go to work no one to accompany the child	11	4.82
Take the child at work site	3	1.32

Referral Service: Reasons for satisfaction for Referral Services was that “we get immunization done” (184) and “AWW guide where to go”. (8), (N = 184). A reason for dissatisfaction for Referral Services was that “behaviour of Govt health staff is rude so prefer to go to private clinic.” (4), (N = 4)

Table 11. Awareness for growth monitoring supplementary nutrition / take home ration and referral services provided by anganwadi among the non-users.

Service	f	% N=228
Growth monitoring service	131	57.5
Supplementary nutrition/THR	143	62.7
Referral	120	52.6

Table 11 shows that awareness for the growth monitoring services was 57.5% followed by 62.7% awareness for supplementary nutrition and 52.6% awareness for referral services provided by anganwadi among their non users. There is need of enhancing the IEC and IPC activities to increase in awareness level about the location and services of AWC among the community especially growth monitoring which is very crucial.

Reasons for not utilizing referral services

Reasons for not utilizing referral services are as follows: (Multiple reasons were given by each user. Frequency of each response is given in bracket, N = 268)

1. “ASHA did not help us during pregnancy so do not use govt service”. (1)
2. “Go to private clinic”. (176)
3. “Govt health staff is rude”. (102)
4. “No medicines in dispensary”. (88)
5. “Referrals are not honoured”. (60)
6. “Not aware of referral service”. (41)

Infant and Young Child Feeding Practices (IYCFP).

Table 12. Awareness about IYCFP among users and non-users.

IYCF component	Users		Non Users	
	Aware	% (N=228)	Aware	% (N=228)
Early initiation of breast feeding	211	92.5	210	92.1
Exclusive breast feeding for six months	224	98.2	218	95.6
Continuing of breast feeding for two years	228	100.0	224	98.2
Complementary food started with soft food six month to one year	225	98.7	221	96.9
Adult food without spices from one year	228	100.0	220	96.5
Precautions while preparing food	228	100.0	221	96.9
Feeding during and after illness	166	72.8	33	14.5
Feeding malnourished child	16	7.0	3	1.3

Table 12 shows the details of awareness about components of IYCFP

among the users and the non-users. Except for feeding the child during illness and after illness there was marginal difference in awareness among the users and the non-users. Awareness among the users about feeding the child during illness and after illness was 72.8% as compared to 33% in the non-users; this could perhaps be because this aspect is highlighted by AWW as part of nutritional and health education component of anganwadi services.

Services for pregnant women

Table 12. Awareness and utilization of services for pregnant women provided by AWC among the mother of users and non-users (for child services).

Type service for pregnant women		Users	% (N=228)	non users	% (N=228)
Supplementary Nutrition	Awareness	190	83.3	18	7.9
	Utilization	131	57.5	5	2.2
TT Immunization	Awareness	166	72.8	18	7.9
	Utilization	108	47.4	5	2.2
Referral service	Awareness	88	38.6	10	4.4
	Utilization	6	2.6	0	0.0
Nutrition and health education	Awareness	68	29.8	11	4.8
	Utilization	22	9.6	1	0.4

Though all the users were aware of and utilizing growth monitoring and supplementary nutrition services provided by AWC for the children, but their awareness about anganwadi services for pregnant women was low (83.3% for supplementary nutrition and 68% for NHE). Utilization of supplementary nutrition and NHE services for pregnant women was also low 57.5% and 9.6% respectively. Similar low awareness was also observed in non-users about anganwadi services for pregnant women (7.9% for supplementary nutrition and 4.8% for NHE), and utilization was as low as (2.2% for supplementary nutrition and 0.4% for NHE)

The study by Adarsh Sharma et al 1992⁽⁵⁾ observed that 36% expectant mothers were registered for supplementary nutrition, 77% registered expectant women were receiving supplementary nutrition and in urban projects 83% expectant mothers were utilizing the services. Study by NIPPCD 2006⁽⁶⁾ observed that maximum numbers of pregnant women (49.5%) were registered in AWCs run under World Bank-assisted ICDS projects, followed by AWCs under NGO-run ICDS projects (48.6%) and regular ICDS projects (47.2%). Interestingly, maximum coverage of pregnant women was found in tribal AWCs of regular ICDS projects (61.8%) and NGO-run ICDS projects (58.3%).

CONCLUSION AND RECOMMENDATION

Significant differences were observed in profile of user and non-user, population with years of stay less than 2 years are utilizing the services less as compared to those who have comparatively more years of stay in the area. Utilization of anganwadi services is less among families with children in age group up to 12months, lower birth order and families with relatively higher monthly income of household. Awareness about anganwadi services for pregnant women was low (83.3% for supplementary nutrition and 68% for NHE). Utilization of supplementary nutrition and NHE services for pregnant women was also low 57.5% and 9.6% respectively. Among the non-users 34% were not aware of the location of AWC and awareness level for the growth monitoring services was 57.5% and 62.7% for supplementary nutrition / Take Home Rations. Among users 23 (13%) were not aware of importance of growth monitoring and 17 (9%) were not aware about importance of SNP/THR. Awareness among the user about feeding the child during illness and after illness was 72.8% as compared to 33% in the non-user.

Active efforts are needed by the AWW to include the migrant young population with small children, the children of families with relatively higher household monthly income in the nutrition and health services for growth monitoring to enable detection of under or over-nutrition in these children and appropriate advice for corrective measures. AWW should enhance efforts to reach out to pregnant women for NHE and SNP, and highlight benefits of early initiation of breast feeding within 1hr of birth and feeding of colostrum. IEC and IPC activities should be envisaged to increase awareness regarding the services available at AWC and their importance for normal growth and development of the child from pregnancy till 6 years so that even marginalised families like recently migrated into city become aware of and utilise the

services available in the AWC.

In conclusion the people want the services of growth monitoring, advice on IYCF and health care and supplementary nutrition for their children however, they have some views on certain modalities which are different from what is provided in the programme.

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A STUDY ON FUNCTIONING OF THE NUTRITIONAL SERVICES IN ANGANWADIS FOR 0 – 3 YEARS CHILDREN UNDER ICDS PROGRAMME IN DELHI FROM PROVIDER'S PERSPECTIVE.

Community Medicine

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ABSTRACT

INTRODUCTION: Pregnant and lactating women and children under three years have high nutritional requirements due to rapid growth both physical and mental/cognitive, of the developing foetus/neonate/infant/young child. Providing a safe and hygienic environment, Anganwadi worker training, workload, status and remuneration, inadequacy and uneven distribution of staff and low prioritization of monitoring and evaluation activities are the factors which are responsible for quality of ICDS services.

OBJECTIVES: To study availability and functional adequacy of infrastructure for providing nutritional services in anganwadi of urban area

METHODOLOGY: The study was conducted at Mehrauli and Hastals Project of Delhi. The study population includes Anganwadi supervisor and Anganwadi worker of all the Anganwadis in the study areas. It was a cross sectional and descriptive type of study. Variables of study was manpower available at AWC and Infrastructure at AWC were assessed by the researcher visiting each anganwadi centre and observation of AWC/questions from Anganwadi staff. Data was collected by observational checklist and interview schedule.

RESULTS: All AWC of both project areas have been operational since five to more than 20 years. While all AWC had provision of safe drinking water, toilet facility was available in only 31.58% of AWC. Out of 57 AWCs covered in this study 21 AWC from Mehrauli have functional Dial Salter balance with place to hang it. Training regarding handling of children with handicap/disability and child nutrition in both areas was given to some AWW. Anganwadi Supervisor in Hastals reported that a panel of AWW was on ad hoc basis and 2 AWW were posted in new ICDS project from the month of data collection however in Mehrauli there was no list of on panel AWW. Mother held 'Mother and Child Protection card' was not present in any AWC. Anganwadi Supervisors were able to plot the weight correctly. All 51 AWW were able to identify correctly Weight within normal, moderately undernourished and severely undernourished range as per WHO norms. Visit of supervisors were to disseminate regular instructions and MPR and provide supportive supervision/guidance if required by AWWs.

CONCLUSION AND RECOMMENDATION: Infrastructure norms for AWC especially for space for multiple activity room and storage space may need to be different for rural and urban. Coordination between the AWW and the health staff for convergence of needed health and nutrition services including referral should be enhanced for improving health and nutritional status of the children.

KEYWORDS

ICDS, Provider's Perspective, AWW

INTRODUCTION

Pregnant and lactating women and children under three years have high nutritional requirements due to rapid growth both physical and mental/cognitive, of the developing foetus/neonate/infant/young child. Adverse nutrition-infection interaction results in a vicious cycle with serious consequences to the life of the infant/young child. Realising the need for a programme to promote adequate nutritional status and prevent under-nutrition especially in the vulnerable groups like pregnant and lactating women and pre-school children the Government of India started the Integrated Child Development Services (ICDS) as a Project in 1975 focussing on "Nutrition, Assisting Health Services. Pre-school Education".

Even after three decades of implementation of nutritional services under the ICDS programme poor nutritional status of children in India is seen. The ICDS programme faces substantial operational challenges such as:

Achieving ICDS universalization with quality:

Variations in age, gender, socio-economic status has hampered in achieving universality with quality. Responding to Public Interest petitions, the Supreme Court intervened by issuing various orders from time to time⁽¹⁾. On 28.11.01, the Supreme Court directed the government to ensure that every settlement has a functional anganwadi centre (AWC), and that ICDS is extended to all children under 6, all pregnant and lactating women and all adolescent girls. The order further extended to specify that Below Poverty Line (BPL) is no longer a criterion under ICDS to be an eligible beneficiary.

Providing a safe and hygienic environment for ICDS service delivery

Location of anganwadi centres: Various evaluation studies indicate

that the services under ICDS Scheme have delivered better quality results in those AWCs, which are located in their own premises. Most AWCs in urban areas are located in rented buildings, especially community buildings moreover budgetary allocation to rent is low with the consequence that AWCs are frequently found in small or unclean locations which thwarts their purposive function.

Construction of anganwadi centres: An improvement was found in building structure of Anganwadi Centres over the past 14 years. It was found that the percentage of AWCs housed in *kutcha* structure (38.7%) in 1992 has gone down in 2006 (19.9%). On the other hand, in 1992 only 43 per cent AWCs were found to be housed in *pucca* structure whereas in 2006, this percentage has gone up to 75 per cent. This progressive trend would have been because of provision of constructing *pucca* building of AWCs under World Bank and *Jawahar Rojgar Yojana/Nehru Rojgar Yojana*^(2,3,4). But space was found to be a problem in most of the Anganwadi Centres in urban areas. Adequate outdoor and indoor space and separate space for storage was available in only 44, 36 and 39 per cent Anganwadi Centres respectively. This situation was found to be little better in rural and tribal areas.

Toilet & Drinking water: While around 41 per cent of Anganwadis had toilet facilities, 17 per cent of these facilities were not found to be in good condition and 59 per cent AWCs were even deprived of this amenity⁽⁵⁾. The majority of AWCs obtain their drinking water from a tap or hand pump, but the water source varies substantially across state and rural-urban-tribal location. 27% AWCs do not have drinking water facility⁽⁶⁾.

Anganwadi worker training, workload, status and remuneration:

Undoubtedly, the skills of the AWW and her capacity to mobilize the community to support ICDS and recruit all children stand central to

quality service delivery and ICDS effectiveness. Too often, though, performance is constrained by poor quality of training and the pressure of a large and diverse workload. AWWs can spend up to 40% of their time on supplementary nutrition-related activities and a further 39% on preschool education⁽⁴⁾, which does not leave much time for other important ICDS activities such as growth-promotion, health and nutrition education, home visits, referral services and meeting with the community. In addition, AWWs must maintain different types of records, teach and assist in other government programmes for women and children. Low regard for important work and frequent lags in payment of honoraria contribute to dissatisfaction and lack of motivation^(5,6).

Inadequacy and uneven distribution of staff

While a general shortage of staff was noticed across the projects the uneven distribution of the staff had probably made things worse. This clearly led to poor functioning of the programme as often the workload of the concerned staff becomes so heavy that she cannot effectively deliver services in spite of her best efforts⁽⁷⁾.

Low prioritization of monitoring and evaluation activities

Given the size of the ICDS programme, monitoring and evaluation is a daunting task. The complexity, reliance on manual entries and compilations, delays and bottlenecks in the replenishment of supplies etc. has resulted in an inadequate monitoring – in the sense that information is regularly collected on inputs and outputs but the system is not oriented towards using that information to make an informed action, i.e. it is not used to improve service delivery, beneficiary recruitment or, eventually, modify programme design. A relatively small number of qualified people assigned to the monitoring and evaluation activities at almost all levels of programme implementation has further contributed in widening the gaps. Central information system for processing so much data is held back by insufficient utilization of computer networks. Software programmes are seldom used to analyse the data collected at the state and central level, except in some of the states covered under World Bank ICDS Projects.

In view of few studies addressing these issues this study will try to find out; providers' perspective on the issues of functional adequacy of infrastructure, skills for using available equipments for accurate weight and growth monitoring, efforts for universal coverage, supportive supervision available to the Anganwadi worker (AWW).

OBJECTIVES

1. To study availability and functional adequacy of infrastructure for providing the nutritional services in anganwadi of urban area.
2. To assess type of nutritional services provided and the extent of their utilization.

METHODOLOGY

The study was conducted at Mehrauli Project of South District and Hastals Project of West District. In South District CDPO of Mehrauli Project granted permission for 12 centres of Neb Sarai, 8 centres of Lado Sarai and 10 centres of Andheriya Mod. In West District CDPO of Hastals Project granted permission for areas 10 centres of Shiv Vihar and 17 centres of Vikas Nagar. All anganwadi centres present in the areas where permission was granted were covered in the present study. The study population includes Anganwadi supervisor and Anganwadi worker of all the anganwadies in the study areas. It was a cross sectional and descriptive type of study.

Background variables, manpower available at AWC and Infrastructure at AWC were assessed by the researcher visiting each anganwadi centre and observation of AWC/questions from Anganwadi staff. In case there was no AWW at the AWC the supervisor was contacted and details were collected from AWW of another AWC, as detailed by the supervisor. Information on type of building, indoor and outdoor space available and source of drinking water; availability and functional status of toilet, light, fan and furniture (table and chair/stool) were obtained by observation; In case of weighing machine the number of weighing machines, type, make, sensitivity minimum and maximum weight the balance can weigh and functional status of each weighing scale were assessed by direct observation. In case the Weighing scale was of Dial Salter which needs to be hung from a height the way the scale was hung whether it was stable etc were assessed.

For assessing skills of AWW for weighing and growth monitoring each anganwadi worker was observed while weighing the children under 3

where ever weighing scale was available. Variables taken were experience and training, knowledge of AWW about weighing child, knowledge of AWW about assessing accuracy of weighing balance, knowledge of AWW about assessing sensitivity of the weighing balance, knowledge of interpretation of growth chart, knowledge about IYCF, perceptions of the AWW on problems faced in performing duty, remedial measures taken and supportive supervision available for problem faced.

For assessing skills of anganwadi supervisor variables taken were experience and training, knowledge about weighing child, knowledge about accuracy of weighing balance, knowledge about sensitivity of the weighing balance, knowledge and interpretation of growth chart, knowledge about IYCF, Perceptions about Supportive supervision being provided for problems faced by AWW.

Data was collected by observational checklist and interview schedule. In this study two supervisors (two), fifty-seven anganwadi centres and fifty-seven anganwadi workers were covered. Data collection was done in duration of two months, April – May 2011. Data was analyzed by using Statistical Package for the Social Sciences 19 (SPSS 19) and Microsoft Office Excel 2010 and 97-2003 for windows software as follows: Descriptive statistics and Test of significance

RESULTS

This study was conducted in Delhi, in the anganwadi centres of Neb Sarai (12), Lado Sarai (8), and Andheriya Mod (10) (Mehrauli Project, South District) and Shiv Vihar (10) and Vikas Nagar (17) (Hastals Project, West District) were covered.

Infrastructure

Table 1. Infrastructure available at anganwadi centres.

	ICDS Project				Total	
	Mehrauli		Hastals			
	f	%	F	%	f	%
Number of years AWC is operational		N = 30		N = 27		N = 57
up to 10 years	11	36.67	27	100.00	38	66.67
10 years one day to 20 years	11	36.67	0	0.00	11	19.30
more than 20 years	8	26.67	0	0.00	8	14.04
AWW positioned at AWC	f	%	F	%	f	%
		N = 30		N = 27		N = 57
AWW present at AWC	26	86.67	25	92.59	51	89.47
NO AWW, AWC looked after by AWW of other AWC	4	13.33	2	7.41	6	10.53
Ownership of AWC building	f	%	F	%	f	%
		N = 30		N = 27		N = 57
Rented	29	96.67	27	100.00	56	98.25
Government girls' senior sec school	1	3.33	0	0.00	1	1.75
Availability of outdoor space for children at AWC	f	%	F	%	f	%
		N = 30		N = 27		N = 57
Available	10	33.33	0	0.00	10	17.54
Not Available	20	66.67	27	100.00	47	82.46
Location of AWC	f	%	F	%	f	%
		N = 30		N = 27		N = 57
Ground floor	26	86.67	27	100.00	53	92.98
First floor	4	13.33	0	0.00	4	7.02
Source of safe drinking water in AWC	f	%	F	%	f	%
		N = 30		N = 27		N = 57
Piped water into dwelling	18	60.00	0	0.00	18	31.58
Public tap or standpipe	0	0.00	7	25.93	7	12.28
Tube well or borehole	12	40.00	20	74.07	32	56.14
Supportive Infrastructure	f	%	F	%	f	%
Light	26	87	27	100	53	92.98
Fan	26	87	27	100	53	92.98
Table	9	30	1	4	10	17.54
Chair	30	100	27	100	57	100.00
Toilet	16	53	2	7	18	31.58

*All anganwadi centres open at 0900Hrs and Close at
*All anganwadi centres in pucca building.

Details of infrastructure available in AWC are given in **Table 1**. All AWC of Hastals Project were operational for at least five years, whereas in Mehrauli project area it ranges from five years in Andheriya

Mor to more than 20 years in Neb Sarai. Six AWC (10.53%) were without AWW in place; the services for these areas were being provided by AWW of another nearby AWC in the same locality with resultant increase in area of responsibility of such AWW; this arrangement may affect coverage and quality of service rendered by them.

While all AWC had provision of safe drinking water, toilet facility was available in only 31.58% of AWC. The study conducted by **FORCE Delhi 2007⁽⁸⁾** where only 58% AWCs had clean drinking water. Toilet facility was available in only 18 (31.58%) of AWCs; this compares well with study by **NIPPCD 2006⁽²⁾** where of 41% of AWCs with toilet facilities, 17% of these facilities were not found to be in good condition and 59% AWCs did not have toilet facilities. In the study conducted by **FORCE Delhi 2007⁽⁸⁾** 57% centres had toilets facility.

Space available for AWC activities

Table 2. Area of AWC Room

Size of AWC room	ICDS Project				Total	
	Mehrauli		Hastals		F	%
	f	% N=30	F	% N=27	F	% N=57
5.4m*7.2m	3	10	0	0	3	5.26
5.4m*5.4m	1	3	0	0	1	1.75
5.4m*2.4m	1	3	0	0	1	1.75
3.6m*3.6m	8	27	2	7	10	17.54
3m*3m	1	3	4	15	5	8.77
2.4m*3.6m	1	3	3	11	4	7.02
2.4m*3m	0	0	13	48	13	22.81
2.4m*2.4m	13	43	5	19	18	31.58
1.2m*2.4m	1	3	0	0	1	1.75
1.2m*1.2m	1	3	0	0	1	1.75

Size of AWC room is tabulated in **Table 2**. The size varies from range 5.4m X 7.2m to as small to 1.2m X 1.2m. All AWC in the study population were situated in one room of size less than proposed area. This highlights the shortage of space for all activities of the AWC like weighing children and conducting nutrition and health education sessions or preschool education. AWC in urban areas are likely to have this constraint.

Space requirement for an anganwadi centre, as per proposed infrastructure norms for anganwadi centre by Ministry of women and child development Government of India, dated 10 March 2011, for multipurpose room (room to cater 30 children for multipurpose activities) is 7m X 7m or 8m X 6m.

Storage space

Table 3: Storage space available in the AWC

Storage Space Available At AWC	ICDS Project				Total	
	Mehrauli		Hastals		f	%
	F	% N = 30	F	% N = 27	f	% N = 57
no storage space available	6	20	0	0	6	10.53
One small iron almirah	1	3	0	0	1	1.75
One small iron almirah and one iron box	2	7	0	0	2	3.51
Two large iron almirah	1	3	0	0	1	1.75
One iron box	1	3	0	0	1	1.75
shelf in wall	18	60	27	100	45	78.95
shelf in wall, iron almirah, iron box	1	3	0	0	1	1.75

***All anganwadi centres open at 0900Hrs and Close at**
***All anganwadi centres in pucca building.**

Storage space available in the AWC of the study is given in **Table 3**. Space requirement for storage in an anganwadi centre, as per proposed infrastructure norms for anganwadi centre by Ministry of Women and Child Development Government of India, dated 10 March 2011, is 3.05m X 1.5m. In Delhi since supplementary nutrition and THR (panjiri) is supplied by self-help groups on daily and weekly basis respectively, need for storage space at AWC is reduced. The study conducted by **NIPPCD 2006⁽²⁾** also highlights inadequacy of indoor and outdoor space, storage in 49% and 50% of AWCs respectively.

Balances

Three type of weighing balance were present in various distributions in

AWC, details of their specification are given in **Table 4**.

Table 4. Type of Balance present at AWC

Type of balance	Maximum weight can be measured	Sensitivity
Pan Balance	15 Kg	50gm
Dial Salter	25Kg	100gm
Adult Dial	140Kg	500gm

The number of functional weighing balance present at AWC for weighing infants, children and adults was assessed in the study; details are given in **Table 5**.

Table 5. Availability of Functional Weighing Balance at AWC

	ICDS Project				Total	
	Mehrauli		Hastals		f	%
Number Of Weight Balance At AWC	f	% N=30	f	% N=27	f	% N=57
0	9	30.00	8	29.63	17	29.82
1	21	70.00	3	11.11	24	42.11
2	0	0.00	13	48.15	13	22.81
3	0	0.00	3	11.11	3	5.26
Availability of place to hang weighing balance	F	% N=30	f	% N=27	f	% N=57
Available	30	100	0	0	30	52.63
Not available	0	0	27	100	27	47.36

UNICEF provided Dial Salter balance for weighing infants and young children, platform dial balance for weighing adults and pan balance for weighing infants were present in various combinations in different AWC. Details of distribution of three type of weighing balance were present in AWC, are given in **Table 6**. Similarly, **FORCE Delhi 2007⁽⁸⁾** observed 82.23 % AWWs reported scarcity of equipment like weighing machines in the study by. Whereas, **NIPPCD 2006⁽²⁾** observed weighing scales were available in 97 % Anganwadis of World Bank-assisted ICDS Projects, followed closely by NGO run projects 95.3 % and 85 % of regular ICDS projects, around 89 % of them were in working condition also. **Umesh Kapil et al 1996⁽⁹⁾** observed 75% per cent AWCs had Salter type weighing scales; in 9% of the AWCs, weighing scales were not in working condition and about 7% AWCs did not have any weighing scales in the study.

Table 6. Distribution of Various Weighing Balance at AWC

Project	Area	Type of Balances	f	N	%
Mehrauli	Lado Sarai	Dial Salter	8	8	100
	Neb Sarai	Dial Salter	12	12	100
	Andheria	Dial Salter	1	10	10
	Mod	No Balance	9		90
Hastals	Shiv Vihar	Pan	1	10	10
		Pan + Platform Dial	7		70
		Pan + Platform Dial + Dial Salter	2		20
	Vikas Nagar	Pan	1	17	6
		Pan + Platform Dial	5		29
		Pan + Dial Salter	1		6
		Platform Dial	1		6
		Pan + Platform Dial + Dial Salter	1		6
		No Balance	8		47

Out of 57 AWCs covered in this study 21 AWC from Mehrauli have functional Dial Salter balance with place to hang the balance, thus can weigh children up to 6 yrs but do not have any balance to weigh adults. None of AWC in Hastals had place to hang weight; however, 4 AWC in Hastals were supplied with Dial Salter balance. In Hastals 15 AWC can weigh infants and adults as they have both Pan and platform Dial Balance, 3 AWC can weigh infants as they have only Pan Balance and 1 AWC can weigh only Adults as it has only platform Dial Balance. There were 17 AWC [Mehrauli (9), Hastals (8)] where there was no weighing balance.

Action taken by AWW

Anganwadi supervisor was informed about non-functional status on weighing balance. Anganwadi Supervisor asked AWW to manage deficiency of weighing balance by rotation of weighing balance but AWW stated that rotation cannot be done as Dial Salter balance are bulky and difficult to transport even for short distances.

Action taken by Anganwadi Supervisor

Anganwadi Supervisor has already reported about the non-functional

weighing balance but it usually takes 4-6months to get it repaired/replaced, in the meantime AWW are asked to rotate functional weighing balance among them.

Table7. Availability of AWW and functional weighing balance at AWC.

AWW and functional weighing balance	Project					Total
	Mehrauli			Hastals		
	Lado Sarai	Neb Sarai	Andheria Mod	Shiv Vihar	Vikas Nagar	
Total AWC	8	12	10	10	17	57
AWW available at AWC	8	11	7	8	17	51
No AWW at AWC	0	1	3	2	0	6
AWC available with functional weighing balance	8	12	1	10	9	40
No functional weighing balance at AWC	0	0	9	0	8	17
AWC with AWW and functional balance	8	11	1	8	9	37
AWW without functional balance	0	0	6	0	8	14
No AWW and No functional Balance	0	0	3	0	0	3

It is significant to note that out of 57 AWC there was no AWC where both children of 0 to 6yrs and adults can be weighed and the weight recorded in an appropriate growth chart. In Mehrauli where Dial Salter balance are present children of 0 to 6 years age group can be weighed; but in Hastals, no AWC can weigh all children of 0 to 6 years age group due to non-availability of functional balance or place to hang the balance.

Reporting format

Records maintained at AWC were, Property register; Survey register; Attendances register; Stock; Immunization register; Referral register; Birth and Death register; Monthly progress report (MPR); Daily diary; Medicine kit; weight book; Diet register; Daily SNP register; Visit diary; Mahila mandal; Weight register; and Pregnant women register. There was variation in number of registers in Mehrauli and Hastals as weight was maintained in weight book in Hastals rather than registers as in Mehrauli. Mother and Child Protection Card were not available in any AWC.

According to WHO MGRS standards child is assessed as Above Normal (White coloured area denoting weight above +2SD); Normal (Green coloured area denoting weight between +2SD to -2SD); Moderately undernourished (Yellow coloured area denoting weight between -2SD to -3SD); Severely undernourished (Red coloured area denoting weight below -3SD).

In Hastals weight of the child is plotted on the WHO growth monitoring booklet using WHO MGRS standards but they are reporting in IAP standards. This is done by reporting those children in the white part (Above +2SD) of the WHO growth chart as Normal (IAP), those in the green part (from +2SD to -2SD) as Grade I (IAP), those in the Yellow area (between -2SD and above -3SD) as Grade II (IAP) and those falling in the red area (below -3 SD) as Grade III (IAP). Thus, there is misinterpretation of the nutritional status based on weight-for-age of children i.e. Above Normal is reported as Normal; Normal is reported as Grade I; moderately undernourished is reported as Grade II; severely undernourished is reported as Grade III; there is no reporting of Grade IV.

Supportive supervision by Anganwadi Supervisor

Anganwadi Supervisor in Hastals felt urgent need to change the reporting format in accordance to WHO MGRS standards-based M&CP card because AWW are plotting the weigh on WHO growth monitoring booklet using WHO MGRS standards but they are reporting in IAP standards.

Manpower

The details of AWWs and the training received by them in the 51 AWC with an AWW posted and in position in the AWC are given in Table 8.

In Mehrauli all AWW had received training regarding handling of children with handicap/disability and only one AWW had received training regarding child nutrition during last one year. In Hastals area only 2 AWW had received training on child nutrition and 2 AWW had on job training for providing services at AWC 21 (84%) AWW had not received any training during last one year.

Table 8. Manpower Available At AWC

	ICDS Project				Total	
	Mehrauli		Hastals			
AWW positioned at AWC	F	%	F	%	F	%
	(N=30)		(N=27)		(N=57)	
AWW present at AWC	26	86.67	25	92.59	51	89.47
Age of AWW worker in years	F	%	f	%	F	%
	(N=26)		(N=25)		(N=51)	
20 to 30yrs	4	15	7	28	11	21.57
30yrs one day to 40 years	5	19	16	64	21	41.18
40 years one day to 50 years	11	42	2	8	13	25.49
50 years one day and more	6	23	0	0	6	11.76
Education qualification of AWW	F	%	f	%	F	%
	(N=26)		(N=25)		(N=51)	
Tenth	5	19	6	24	11	21.57
Twelfth	14	54	12	48	26	50.98
Graduate	6	23	5	20	11	21.57
Postgraduate	1	4	2	8	3	5.88
Number of years AWW completed service	F	%	f	%	F	%
	(N=26)		(N=25)		(N=51)	
up to 10 years	9	35	25	100	34	66.67
10 – 20	9	35	0	0	9	17.65
more than 20 years	8	31	0	0	8	15.69
AWW belongs to same area	F	%	f	%	F	%
	(N=26)		(N=25)		(N=51)	
Yes	20	77	6	24	26	50.98
No	6	33	19	76	25	49.02
Distance of AW worker from AWC	F	%	f	%	F	%
	(N=26)		(N=25)		(N=51)	
Less than 3 Km	16	62	10	40	26	50.98
3 to 5 Km	7	27	14	56	21	41.18
6 to 8 Km	1	4	1	4	2	3.92
Type of training course attended in last one year	F	%	f	%	F	%
	(N=26)		(N=25)		(N=51)	
Handicap child	26	100	0	0	26	50.98
Child nutrition	1	4	2	8	3	5.88
No Training during last one year	0	0	21	84	21	41.18
Job Training	0	0	2	8	2	3.92

* AWC where AWW were not present are not taken in calculation for N

Supportive supervision by Anganwadi Supervisor

Anganwadi Supervisor of Mehrauli reported that there was no list of on panel AWW thus there were 4 AWC without AWW. Whereas as in Hastals one on panel AWW was on ad hoc basis and 2 AWW were posted in new ICDS project from the month of data collection thus process has been initiated to fill vacant position of AWW.

Table 9. AWW Skills of weighing child correctly

	ICDS Project				Total	
	Mehrauli		Hastals			
AWW hang the weighing scale correctly and securely at eye level	F	%	f	%	f	%
	N = 26		N = 25		N = 51	
Yes, As observed	20	77	0	0	20	39.22
No weighing scale available, But answered correctly when asked	6	23	21	84	27	52.94
No place to hang Salter balance, But answered correctly when asked	0	0	4	16	4	7.84
AWW read weight reading at eye level for hanging balance and vertical for adult dial balance	F	%	f	%	f	%
	N = 26		N = 25		N = 51	

Yes, As observed	20	77	17	68	37	72.55
No weighing scale available, But answered correctly when asked	6	23	8	32	14	27.45
AWW check for and correct zero error	F	%	f	%	f	%
Yes, As observed	20	77	17	68	37	72.55
No weighing scale available, But answered correctly when asked	6	23	8	32	14	27.45
AWW take the reading from one foot away	F	%	f	%	f	%
Yes, As observed	20	77	17	68	37	72.55
No weighing scale available, But answered correctly when asked	6	23	8	32	14	27.45
AWW take reading up to smallest fraction possible	F	%	f	%	f	%
Yes, As observed	20	77	17	68	37	72.55
No weighing scale available, But answered correctly when asked	6	23	8	32	14	27.45
* No AWW take average of minimum of two weight reading. * No AWW had knowledge about how to check accuracy of the weighing balance. * No AWW had knowledge about how to check sensitivity of the weighing balance.						

Details of skills for weighing correctly are given in **Table 9**. Out of all 51 AWW, observations for Dial Salter weighing balance was carried out in 20 AWW as hanging balance and place for hanging was available whereas knowledge was assessed in rest 31 AWW. For all the following steps in weighing the child 37 AWW with functional balance (any type) were observed and rest 14 AWW were assessed for the knowledge as there was no weighing balance. All AWW were aware of securely hanging weighing scale correctly and at eye level, taking the reading of the weight at eye level or looking at the reading from directly above without any inclination or angulations, checking and correcting zero error and taking weight up to smallest fraction. But, no AWW was either aware of or practicing taking final reading as average of two readings; checking sensitivity of weighing balance and checking accuracy at regular and frequent intervals.

In contrast **Umesh Kapil et al 1996⁽⁹⁾** observed that almost 90% of the AWWs were not aware of the correct sequence of steps required for conducting growth monitoring and nearly 75% of AWWs were not able to use the Salter weighing scales correctly. **K. Indira Bai et al 1989⁽¹⁰⁾** in their study observed that only 69% AWWs bring the pointer to zero and 54% adjust for zero error before weighing a child.

Supportive supervision by Anganwadi Supervisor

Both Anganwadi Supervisors were aware of securely hanging weighing scale correctly and at eye level, taking the reading of the weight at eye level or looking at the reading from directly above without any inclination or angulations, checking and correcting zero error and taking weight up to smallest fraction and checking accuracy at regular and frequent intervals. They used to advice the AWWs on the need for checking accuracy of the balance using an ISI standard weights/PDS ration shop ISI std weight.

But, no Anganwadi Supervisors was aware of taking final reading as average of two readings; checking sensitivity of weighing balance using an ISI standard weights/PDS ration shop ISI std of 100gm and checking for increase in weight at regular and frequent intervals. Thus, Anganwadi Supervisor were able to provide supportive supervision to AWW for weighing the child for growth monitoring but not for checking sensitivity or taking final reading as average of two reading.

Skills of plotting and interpretation of the growth chart

Table 10. AWW skills of plotting weight of the child in growth charts and growth monitoring

	ICDS Project				Total	
	Mehrauli		Hastsal			
AWW Plot weight against Child Age In Growth Card correctly	f	%	F	%	F	%
Yes, As observed	0	0.00	17	68.00	17	33.33

No growth chart available but able to mark on graphs provided by us.	20	76.92	0	0.00	20	39.22
No weighing scale present, but answered correctly and able to mark on graphs provided by us.	6	23.08	8	32.00	14	27.45
AWW Plot Weight Against Child Age In Growth Card Immediately	f	%	F	%	F	%
No growth chart/booklet available record maintained in registers	20	76.92	0	0.00	20	39.22
Yes, done on growth monitoring booklet available	0	0.00	12	48.00	12	23.53
Not done on growth monitoring booklet available	0	0.00	5	20.00	5	9.80
No balance, weight not done regularly	6	23.08	8	32.00	14	27.45
* Mother and Child Protection card was not available in any AWC.						

Details of AWW's skills for plotting and interpretation of growth card are given in **Table 10**. Mother held 'Mother and Child Protection card' was not present in any AWC. In Mehrauli record is maintained in the self-maintained registers according to IAP standards. For testing the knowledge AWW were asked to plot weight of the child on the growth charts in the M & C P Card provided by us, (see observational checklist). All 26 AWW of Mehrauli were able to plot the weight correctly but, only 20 AWW were maintaining the record in register and maintaining the record, rest 6 AWW do not have weighing machine thus not maintaining the record regularly. In Hastsal weight of the child is recorded in growth monitoring booklets based on WHO MGRS standards. The way the AWW plotted the weight in the growth monitoring booklets available and being currently used in the AWC was observed. All 25 AWW of Hastsal were able to plot the weight of the child correctly but only 12 AWW were maintaining the record regularly in the growth monitoring booklet, out of rest 13 AWCs 5 AWW were irregularly maintaining the growth monitoring booklet even with functional balance and 8 AWW do not have functional weighing machine.

Supportive supervision by Anganwadi Supervisor

Anganwadi Supervisors' were able to plot the weight correctly. Thus, Anganwadi Supervisor was able to provide supportive supervision to AWW for plotting the weight correctly whenever necessary.

Interpretation of growth patterns of weight of children
Table 11. AWW skills of interpretation of the growth card and advising the mother of the child for corrective actions and IYCFP

	ICDS Project				Total	
	Mehrauli		Hastsal			
	f	%	f	%	F	%
Weight in above normal range	13	50	0	0	13	25.49
Weight in Normal Range	26	100	25	100	51	100.00
Weight in Moderately Undernourished	26	100	25	100	51	100.00
Weight in Severely Undernourished	26	100	25	100	51	100.00
Trajectory normal range	26	100	1	4	27	52.94
Trajectory moderately undernourished	13	50	0	0	13	25.49
Trajectory severely undernourished	13	50	0	0	13	25.49
Growth flattening	26	100	25	100	51	100.00
AWW referred beneficiaries to health centre for severe malnutrition and disease	f	%	f	%	F	%
Yes, refers to local dispensary.	19	73.08	8	32.00	27	52.94
No feedback of referrals as local dispensary don't honour referrals	7	26.92	17	68.00	24	47.06

To assess AWW skills of interpretation of growth patterns of weight for age, pre marked weight for age growth patterns in the growth chart in the Mother and Child Protection Card were used. All 51 AWW were able to identify correctly Weight within normal, moderately undernourished and severely undernourished range as per WHO

norms. Trajectory within normal range and growth flattening was identified by all AWW. Though there was no prior training of AWW regarding Mother and Child Protection Card, 13 AWWs from Mehrauli were able to identify correctly weight in above normal range and maintaining trajectory while located within moderately undernourished or within severely undernourished zone as being normal for that individual child. Umesh Kapil et al 1996⁽⁹⁾ observed that 54.2% of the workers did not know about the type of intervention measures to be taken on findings of growth monitoring.

Adarsh Sharma et al 1992⁽¹¹⁾ observed that about 36.3% AWWs were not able to monitor the growth of children and the reasons were not availability of growth charts, lack of skills in filling up growth charts, and weighing scales not being in working condition

Supportive supervision by Anganwadi Supervisor

Both the Anganwadi Supervisor were neither aware of WHO MGRS standards nor they were trained to interpret the M&CP card, urgent need of training to interpret WHO MGRS standards was felt by the AWW supervisor of Hastals. Thus, Anganwadi Supervisors' were not able to provide supportive supervision to AWW for interpretation of M&CP card based on WHO MGRS standards.

Referral of severely under-nourished children and linkage with health services

Severely malnourished child was referred to local dispensary by 19 AWW of Mehrauli (all from Lado Sarai and Neb Sarai) and 8 AWW of Hastals; 7 AWW of Mehrauli (all from Andheria mod) and 17 AWW of Hastals do not refer as they felt referrals are not honoured, however they advised the parents/care givers to get a medical opinion for their children.

Reported coverage of services by the AWCs

Denominator for providing service is calculated based on the survey done by AWW in her area of responsibility. There is no provision of assessing coverage against expected number of children in the 0-6 year age group based on CBR for the district. Hence, though the services are available universally but it is been rendered only to those children who are registered in AWC, children left unaddressed may include those who need the anganwadi services the most.

Supportive supervision by Anganwadi Supervisor

Anganwadi Supervisor were not aware of importance of assessing coverage against expected number of children in the 0-6 year age group based on CBR for the district hence cannot provide supportive supervision to AWW for assessing coverage against expected number of children in the 0-6 year age group based on CBR for the district.

For assessing frequency of weighing the children 0 to 3 years, all AWC were taken, including those where there was no AWW. Out of all 57 AWC weighing of the children registered in their AWC was done regularly each month at 34 AWC (20 AWC from Mehrauli and 14 AWC from Hastals). If only those AWCs are considered where there are AWWs and functional weighing balance i.e. 37 AWC weighing of the children registered in their AWC was done regularly each month at 91.89% of AWC.

Supplementary Nutrition and Take-Home rations supplied
Table 12. Menu schedule, frequency, quantity and source of supplementary nutrition and Take-Home Rations provided at AWC in Delhi.

Day	Type of cooked food	Quantity in gms	Cooked Snack	Quantity in gms
Mon	Sweet Pudding of coarse flour (Halwa)	200	Yellow Peas boiled (Matar)	50
Tue	Namkeen Dalia	270	Black Gram boiled (Channe)	50
Wed	Vegetable Kichiri	270	Yellow Peas boiled (Matar)	50
Thr	Vegetable Pullao	270	Lobiya boiled	50
Fri	Sweet Dalia	270	Yellow Peas boiled (Matar)	50
Sat	Vegetable Kichiri	270	Black Gram boiled (Channe)	50

* Panjiri as THR 840 gms per child per week for age of 7 months to 12 months.

* Panjiri as THR 840 gms per child per 2 weeks for age of 1 yr to 3 yrs.
* Source of THR for 7 mths to 12 mths is packed panjiri supplied on weekly bases to AWC.
* Source of cooked food and snack for 1 year to 6 years is common kitchen for project in each area run by NGO.
* Site for beneficiaries to consume food is within AWC for 3 years to 6 years and less than 3 years take cooked food and snack to home
* Menu schedule present and followed in AWC

Details of Menu schedule, frequency, quantity and source of supplementary nutrition and Take-Home Rations provided at AWC in Delhi are given in Table 12. In study by NIPPCD 2006⁽²⁾ Ready to Eat (RTE) food was provided in all types of projects, maximum being in Anganwadis of urban projects (45.8%), followed by rural (33.6%) and tribal (23.5%) projects. Some Anganwadis (18.0%) were providing both cooked and RTE. Adarsh Sharma et al 1992⁽¹¹⁾ observed that about 38% urban, 29% rural and 19% tribal AWWs mentioned that the food items served as supplementary nutrition in Anganwadis were not acceptable to the community. The food was difficult to digest, caused diarrhoea, was not tasty, and sometimes not fit for consumption. In study by FORCE Delhi 2007⁽⁸⁾ in 26 per cent centres AWWs complained about irregular food supply.

As per the affidavit submitted to Honourable Supreme court on behalf of Ministry of Women and Child Development, Government of India it was stated that the children especially those in the age group of 6 months to 24 months children are not required to come to the Anganwadi Centre every day. Instead, 'Take Home Ration' has to be provided to this category of beneficiaries. But, the State Governments/Union Territories have the flexibility to select the type of food to be given to the beneficiary as part of the supplementary nutrition depending upon local availability, type of beneficiary, location of the project, administrative feasibility etc.

Supportive supervision and visit of senior staff

Table 13. Frequency of Visit of Senior Staff.

	ICDS Project				Total	
	Mehrauli		Hastals		N=57	
Frequency of visit of health staff to AWC	F	% N=30	f	% N=27	F	%
For Immunization in group of two or three AWC average once in two months	8	30.77	17	68	25	49.02
Any case is taken to local dispensary as it is situated centrally in area	12	46.15	0	0	12	23.53
No visit to AWC, immunization done at Dispensary and referrals are not honoured	0	0.00	10	40	10	19.61
No Visit of Health staff in AWC and no coordination and referrals are not honoured	10	38.46	0	0	10	19.61

* Frequency of visit of CDPO to AWC once per month *
 Frequency of visit of Anganwadi Supervisor to AWC 4 to 5 times per month

Visit of supervisor were to disseminate regular instructions and MPR and provide supportive supervision/guidance if required by AWWs.

CONCLUSION AND RECOMMENDATION

AWC should be assessed for ability to provide growth monitoring including all its components - functional weighing balance with at least sensitivity of 100gms to weigh all children; AWW skilled in weighing the children, plotting the weight in individual child based mother held M&CP cards, interpreting M&CP card correctly, advising the mother for corrective actions according to nutritional status of child and reporting format based on WHO 2006 MGR standards to report the nutritional status of children.

Anganwadi supervisors should optimally utilise available enabling provisions for ad hoc appointment of AWW, repair of equipment, or shortage of balances in a project for eg. by rotation of balance within a project if required. It is essential that the list/panel of AWWs be kept updated regularly in every project.

Measures to fulfil deficiency of weighing balance and reduce four to six months' time usually taken to replace or repair balance may need to be put in place. A single electronic balance with 100 gm sensitivity could be used instead of multiple balances for weighing different age groups. Provision of petty cash for anganwadi centre can be used for minor repairs as well as procurement of the battery used for the electronic balance.

Skills and knowledge upgradation training of AWWs should continue with focus on areas where skills are deficient. Untrained supervisors need to undergo training for growth monitoring (with focus on all aspects as mentioned earlier) on priority. Monthly Progress Report Formats need to be according to WHO 2006 MGRS standards so that correct assessment of the under nutritional status of the children can be done.

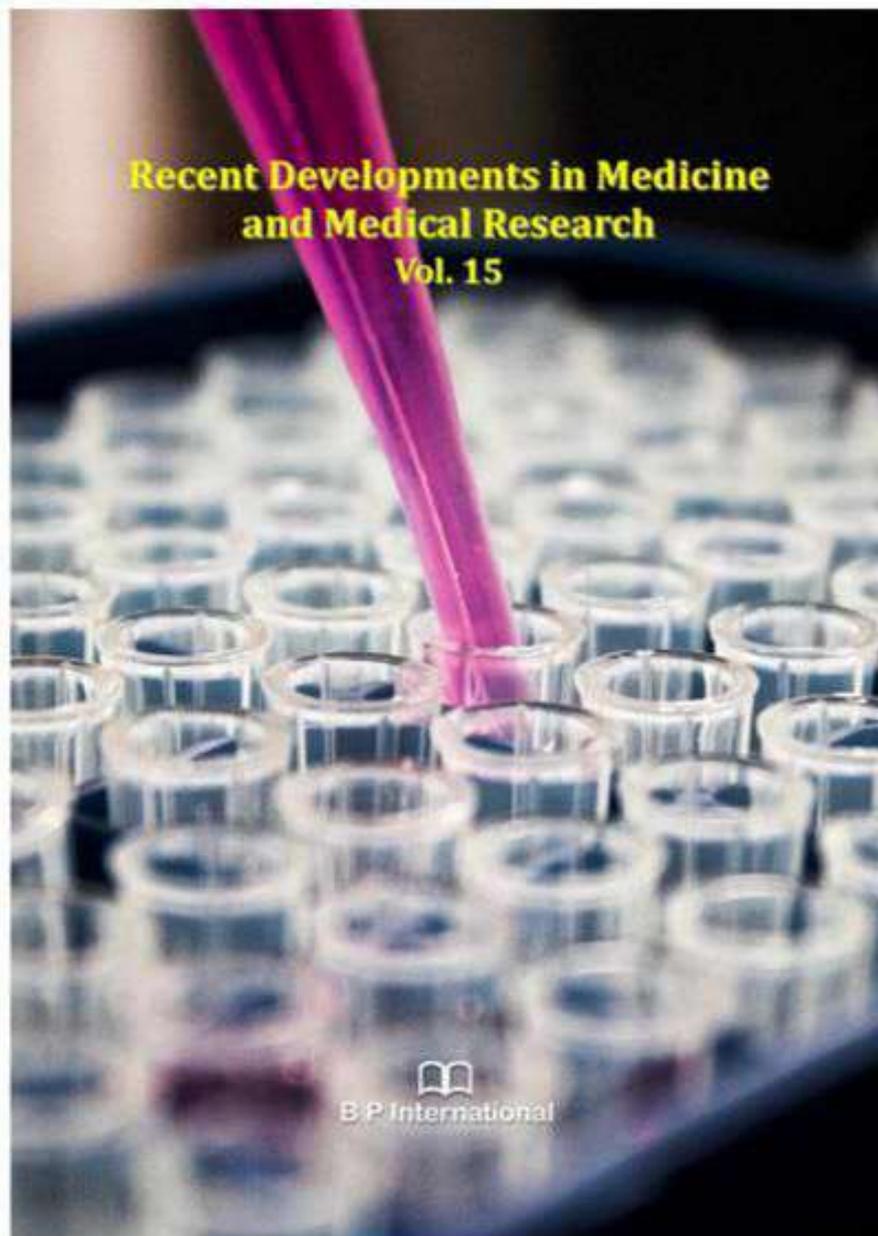
Inclusion of a column giving expected number of under 6 age children (calculated from CBR for the district) in the MPR would help in assessing the performance for growth monitoring and supplementary nutrition as a measure of universal access as per Supreme Courts directive.

Infrastructure norms for AWC especially for space for multiple activity room and storage space may need to be different for rural and urban especially large metros given the constraints of available space in such cities. There is need to explore possibility of providing dry grains through PDS for those 6-36 months aged children who need SNP accompanied with regular growth monitoring of child to ensure improvement in nutritional status of the child. AWW should provide advice and counselling to mothers for practicing components of infant and young child feeding practices and for appropriate health care; this can be done during Nutrition and Health Education session (NHEs) in urban areas and Village Health and Nutrition Day in rural areas.

Coordination between the AWW and the health staff for convergence of needed health and nutrition services including referral should be enhanced for improving health and nutritional status of the children.

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शिक्षा-पैसा : हाई स्कूल और इंटरमीडिएट, खैर इंस्टिट्यूट इंटर कॉलेज, बस्ती, उत्तर प्रदेश।

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Behavioural and psychological symptoms of dementia (BPSD) are non-cognitive manifestations of dementia that include verbal and physical aggression, agitation, psychotic symptoms (hallucinations and delusional), sleep disturbances, and wandering. These symptoms occur at some point in over 50% of patients with dementia. These symptoms are distressing to patients and troublesome to carers. Psychosocial and pharmacological management both recommended for BPSD. Antipsychotics are one of the available options. However, this is a topic of controversy whether antipsychotics should be used or not in elderly patients as they are considered to have lesser tolerability for these drugs and if used, ambiguity still remains on the drug of choice. The study 'Usefulness of Typical (Haloperidol) and Atypical Anti-psychotic (Risperidone) Drugs in Dementia with Behavioural and Psychological symptoms (Psychotic features)' funded by ICMR New Delhi, India was conducted and obtained results are discussed in this book. The book is beneficial for the academicians, clinicians, researchers, scientific community, practicing doctors and for policymaking.



S.C. Tiwari
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Usefulness of Haloperidol and Risperidone in BPSD: Comparative Study



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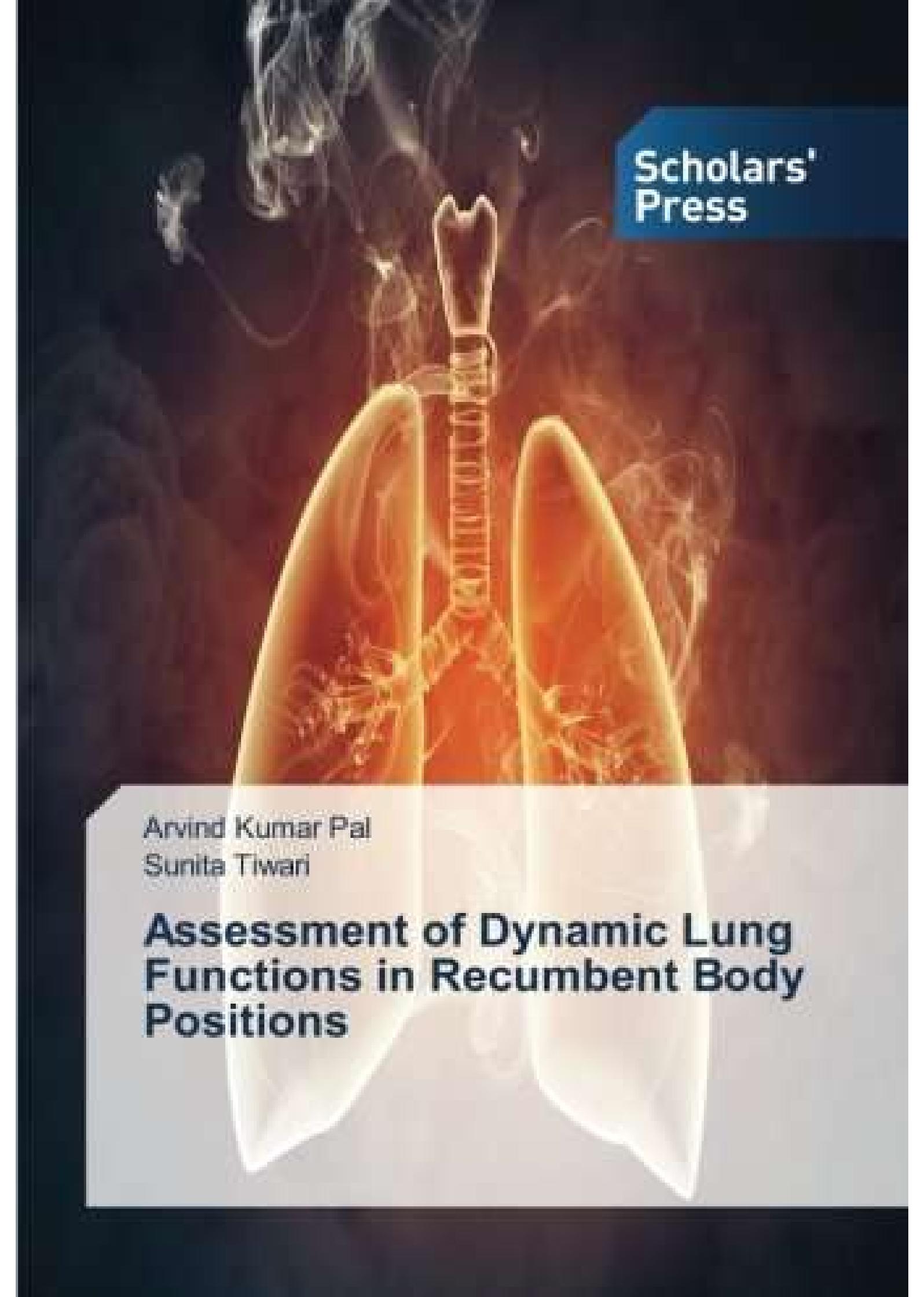
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Environmental Lead Toxicity

P.K. Singh; Rajendra Nath; Rishi Pal and R.K. Dixit

ABSTRACT

Lead is one of the most common, non-essential heavy metals present in our eco-system. Lead poisoning produces the global burden of disease and has been a recurrent problem in society for many centuries. Lead toxicity affects various physiological system and biochemical processes in living beings e.g. gastrointestinal system, cardiovascular system, respiratory system, haematological system and most important, the neurological system. The lead neurotoxicity is more prevalent in childhood [WHO, 2009]. The strategies to reduce the lead level in ecosystem have been advised by many scientific authorities from time to time. Most of them have recommended for elimination of lead from gasoline [Landrigan *et.al.*, 2007, UNEP, 2010]. There are various preventive steps which can significantly reduce the incidence of getting lead toxicity from the environment, especially in human beings.

Keywords: Lead Toxicity, Heavy Metals, Lead Poisoning, Gastro-intestinal System, Cardiovascular System, Respiratory System, Haematological System and Neurological System.

INTRODUCTION

Lead (Pb) is the commonest element found in low concentrations in the Earth's crust. It is one of the ubiquitous environmental pollutants persists

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Molecular and Functional Aspects of Muscarinic Receptors in Correlation with Anticholinergic Drugs

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Pramod Kumar Singh, Rajendra Nath, Ram Narayan,
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Abstract

The muscarinic acetylcholine receptors (mAChRs) are receptors that produce the GPCR complex in the membrane of specific neurons and other cells. It performs a key role at the end of the receptor stimulated by the neurotransmitter. Ach liberates from postganglionic neurons in a parasympathetic region of ANS. The mAChRs constitute a family of five interrelated GPCRs that come under the category of α branch of GPCRs' Class A. The five different subtypes of the mAChR family are designated as M1–M5. M1, M3 and M5 subtype receptors exhibit to pair through the Gq/11 family of G proteins, but the M2 and M4 subtype receptors particularly indicate through Gi/o family of G protein. The mAChRs play multifunctional peripheral and central roles in human physiology including regulation of muscle contraction, heartbeat, lung, secretion by gland and other functions of the CNS.

Keywords

Muscarinic receptors · Acetylcholine receptor · Anticholinergic drugs · Central nervous system · *Atropa belladonna*

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CHAPTER 6

Dynamic Auscultation

Rishi Sethi, Akshyaya Pradhan, Snigdha Boddu

INTRODUCTION

Dynamic auscultation is the technique of altering circulatory dynamics by physiological and pharmacological maneuvers and observing the effects of these maneuvers on heart sounds/murmurs.

With the advent of echocardiography and other widely available modes of noninvasive diagnosis, the fine art of clinical examination is losing its importance. However, despite all the new age tools, the technique of performing methodical clinical examination is the fundamental backbone of any training in cardiology and forms the basis of all further diagnostic tests.

Before performing and speaking about it in clinical examination, the following fundamental philosophical points of dynamic auscultation should be kept in mind:¹⁻³

- Dynamic auscultation should only be performed when we have faintly heard heart sounds or murmurs that we want to accentuate by performing some special augmentation tests. Or, we have confusion in similar sounding heart sounds or murmurs and we want to differentiate between them. So, it is the really not judicious for us to perform or to speak about dynamic auscultation when we have clearly heard and well-defined murmurs/heart sounds.
- Dynamic auscultation should be taken as part of the entire clinical picture and should not be taken as a standalone gold standard tool for making a dogmatic clinical diagnosis.

The techniques of dynamic auscultation can be broadly classified into physiological maneuvers, pharmacological maneuvers, and maneuvers that relate to simple change in posture of the body (Table 1).

PHYSIOLOGICAL MANEUVERS

Valsalva Maneuver⁴

Method

The maneuver is performed by asking patient to exhale forcefully into mercury manometer to generate and maintain a pressure of **40 mm Hg** for **20 seconds**.

Table 1: Classification techniques of dynamic auscultation

Physiological maneuvers	Pharmacological maneuvers	Simple postural changes
Valsalva maneuver	Amyl nitrite inhalation	Left lateral-MS
Sudden standing from squatting or lying down	Methoxamine/phenylephrine	Sitting up and leaning forward
Muller maneuver		Stretching of neck
Passive leg elevation		
Sudden squatting		
Isometric exercise		

Abbreviations: MS, mitral stenosis; AR, aortic regurgitation.

Practically, this can be done by asking the patient to take a deep inspiration, followed by forced expiration against a closed glottis for 20 seconds. (Examiner may place flat of hand on the abdomen to provide the patient the force, against which to strain).

There are four stages of Valsalva maneuver (Table 2 and Figure 1).

Clinical Implications

Pressure and Heart Rate Response (Figure 1)

Square-wave response: This is seen in conditions like left heart failure, mitral stenosis (MS), and atrial septal defect (ASD). During Valsalva maneuver, blood pressure increases in stage I (normally), but remains elevated in all subsequent stages due to abolished stage II and loss of overshoot in stage IV. This is seen when lungs are overloaded with fluid and this excessive volume continues to empty in the LV even during straining. So, there is little effect of fall in systemic vascular return on LV volume and hence, blood pressure (Figures 2A to C).

Physiological Changes

Stage II (Figure 3).

Stages	Blood pressure	Heart rate
1. Onset of straining (1st 10 sec)	↑ Aortic compression due to raised intrathoracic pressure	↓
2. Continued expiration (10–20 sec)	↓ Due to venous compression and decreased venous return	↑
3. End of expiration	↓↓ Due to increased capacitance of pulmonary bed	↑↑
4. Recovery 5–10 sec after stopping expiration	↑ Overshoot due to sympathetic activation	↓

Note: Normally changes in intensity of murmur are only recorded in stage 2.

Caution: Valsalva maneuver should not be performed in ischemic heart disease patients and patients of severe left ventricular (LV) outflow obstruction.

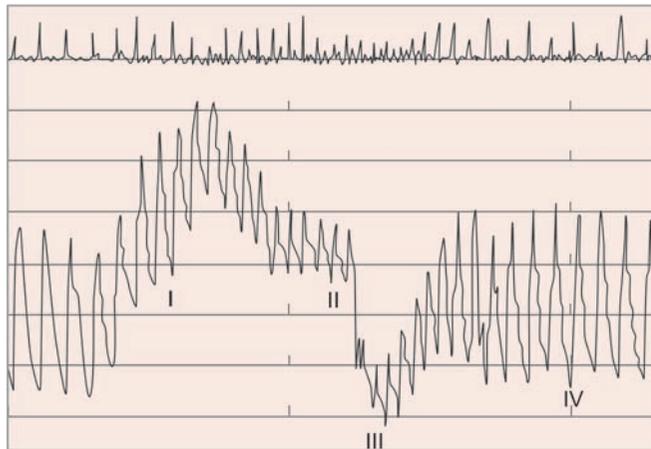


Figure 1: Pressure and heart rate response during normal and Valsalva maneuver

Response in Specific Diseases

Hypertrophic obstructive cardiomyopathy: Murmur of hypertrophic obstructive cardiomyopathy (HOCM) starts well after S1 and it has a crescendo-decrescendo pattern. Basic pathology is the dynamic obstruction of LVOT by combined effect of systolic increase in thickness bulge in LV cavity of already hypertrophied septum and systolic anterior motion (SAM) of anterior mitral leaflet (AML). Any factor which decreases LV size [left ventricle end-diastolic volume (LVEDV)], such as decreased preload, decreased afterload, and increased contractility, will increase murmur of HOCM (**Figure 3**).

Mitral valve prolapse: Basic pathology in mitral valve prolapse (MVP) is the prolapse of mitral leaflet above annulus during ventricular systole. It is said that mitral valve leaflet and chordae are too big for left ventricle; so, they prolapse into left atrium during ventricular systole when a *critical LV volume* is reached (mid-to-late systole). Click in MVP occurs in mid-late systole because of billowing of mitral valve (MV) leaflets and tensing of chordae and is synchronous with maximum prolapse of involved leaflet. Murmur usually begins with the click and then fans out up to A2.

Any maneuver which decreases LV size (LVEDP) leads to early attainment of *critical volume of LV* which causes

the mitral valve to prolapse early in the systole. This makes the click move closer to S1 and the murmur to become longer.

Rapid Standing from Squatting or Lying Posture

Method

Physiologically, effects of rapid standing from squatting or lying down posture are similar to Valsalva stage II. The patient must be in squatting position for at least **30 seconds**. The patient is asked to stand rapidly from squatting position and changes in heart sound and murmur are seen at **15–20 seconds**.

Clinical Implications

Similar to stage II Valsalva, this maneuver leads to decreased venous return, decreased LVEDV, and decreased stroke volume. These physiological changes result in narrow splitting of A2-P2, soft S3, S4, softer murmur of pulmonary stenosis (PS), aortic stenosis (AS), tricuspid regurgitation (TR), mitral regurgitation (MR), tricuspid stenosis (TS), mitral stenosis (MS), louder HOCM murmur, click of MVP moves closer to S1 and the murmur becomes longer.

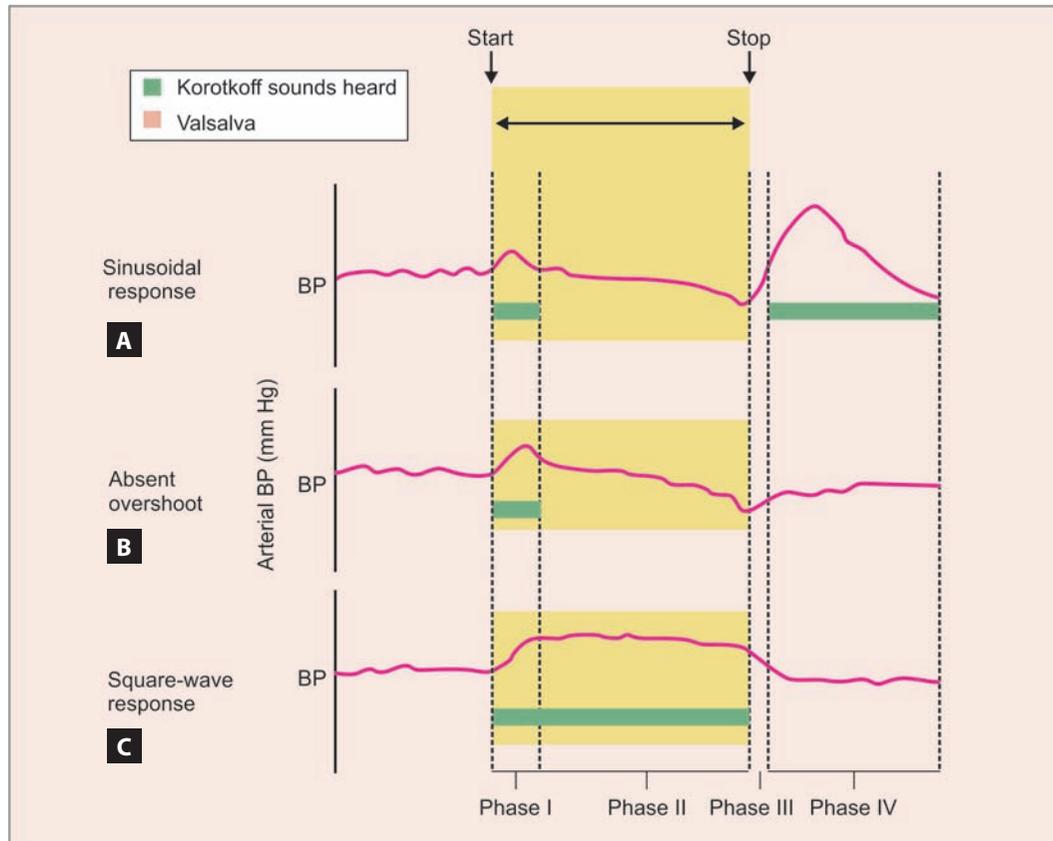
Müller Maneuver

This maneuver is commonly known as opposite of Valsalva maneuver.

Method

It is done as the patient's nares are held closed and then patient has to suck forcibly into a manometer to generate a negative pressure of **40–50 mm Hg for 10 seconds** and changes are seen in the intensity of murmur at the end of **10 seconds**.

Practically, this is done by asking the patient to inspire forcefully for **10 seconds** while the patient's nares are pinched and mouth firmly sealed.



Figures 2A to C: (A) Normal: sinusoidal response with sounds intermittent during strain and release; (B) Briefly audible sounds during initial strain phase and absence overshoot suggests only impaired systolic function in the absence of fluid overload; (C) Persistence of Korotkoff sounds throughout strain phase suggests elevated left ventricular filling pressures known as square root pattern



Figure 3: Physiological changes during stage II Valsalva maneuver and its effect on heart sounds and murmurs

Abbreviations: LVEDV, left ventricle end-diastolic volume; AS, aortic stenosis; PS, pulmonary stenosis; AR, aortic regurgitation; PR, pulmonary regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; MS, mitral stenosis; TS, tricuspid stenosis; HOCM, hypertrophic obstructive cardiomyopathy; MVP, mitral valve prolapse

Clinical Implications

This maneuver leads to increased venous return which leads to increase in right-sided murmurs, increase in A₂-P₂ gap, and increase in right ventricle (RV) S₃ and S₄.

Passive Leg Elevation or Sudden Lying Down

Method

In this maneuver, the patient is asked to lie in supine position and passive elevation of both the legs is done straightly for **15–20 seconds** or the patient is asked to

lie down from the standing posture. The changes in murmur or heart sound are noticed after **15–20 seconds**. Physiology and effects are almost similar to Muller's maneuver, but are more pronounced (**Figure 4**).

Clinical Implications

Physiologically, this maneuver leads to increased venous return, which leads to increased RV stroke volume; and after a few beats, this leads to increased LVEDV and increased LV stroke volume. The increased RV stroke

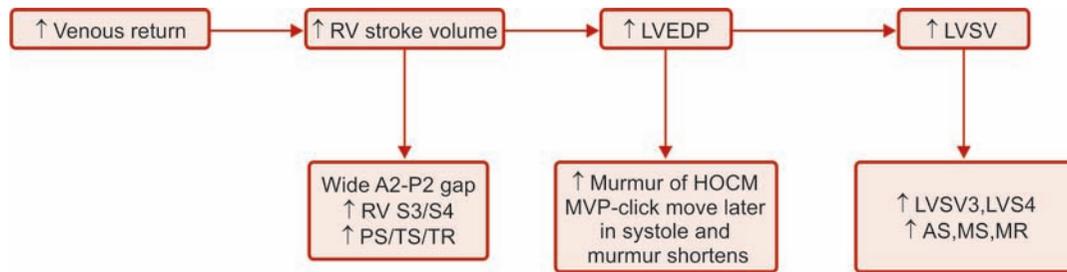


Figure 4: Physiological changes during passive leg elevation or sudden standing

Abbreviations: RV, right ventricle; LV, left ventricle; SV, stroke volume; PS, pulmonary stenosis; TS, tricuspid stenosis; TR, tricuspid regurgitation; AS, aortic stenosis; MS, mitral stenosis; MR, mitral regurgitation; MVP, mitral valve prolapse; HOCM, hypertrophic obstructive cardiomyopathy

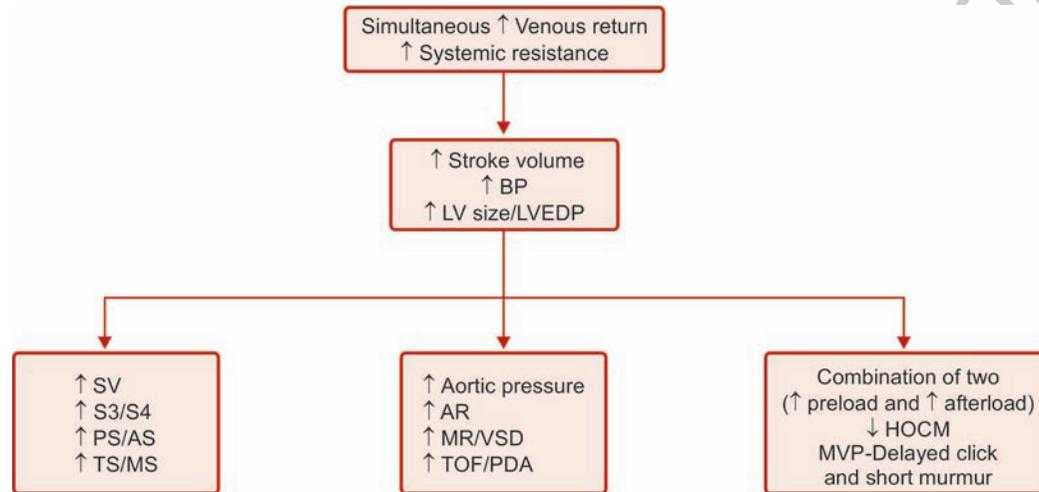


Figure 5: Physiological effects of sudden squatting and effects on heart sounds and murmurs

Abbreviations: BP, blood pressure; LV, left ventricle; LVEDP, left ventricle end-diastolic pressure; SV, stroke volume; PS, pulmonary stenosis; AS, aortic stenosis; TS, tricuspid stenosis; MS, mitral stenosis; AR, aortic regurgitation; MR, mitral regurgitation; VSD, ventricular septal defect; TOF, tetralogy of Fallot; PDA, patent ductus arteriosus; HOCM, hypertrophic obstructive cardiomyopathy; MVP, mitral valve prolapse

volume leads to widely split A2-P2, louder RV S3, S4, louder right-sided murmurs like PS, TS, and TR. The increase in LVEDV leads to softer HOCM murmur and the click of MVP moves later in systole with a shorter murmur. The increase in stroke volume leads to louder LV S3, S4 and louder left-sided murmurs such as MS, MR, and AS.

Sudden Squatting

Method

The patient is asked to squat suddenly from standing position (Valsalva maneuver to be avoided) and changes in murmur or heart sounds are heard just after squatting (Figure 5).

Clinical Implications

Physiological effect of this maneuver is simultaneous increase in venous return and systemic vascular resistance. This leads to increased stroke volume, increased blood pressure, and increased LV size (LVEDV). Increased stroke volume leads to increased S3, S4 sounds, louder murmurs of PS, AS, TS, and MS. Increased systemic vascular resistance leads to increased louder murmurs of AR, MR,

tetralogy of Fallot (TOF), ventral septal defect (VSD), and patent ductus arteriosus (PDA). Due to combination of increased preload and afterload, there is increase in murmur intensity of HOCM, click of MVP is delayed, and the murmur of MVP shortens.

Isometric Exercise

Method

To perform this maneuver, the patient is asked to tightly grip a calibrated hand grip device or handball with both the hands simultaneously and sustain it for at least **20–30 seconds** (care should be taken not to perform Valsalva maneuver). This maneuver is most useful for left-sided lesions and it should not be done in patients with coronary artery disease (CAD) and ventricular arrhythmia.

Clinical Implications

Physiologically, there is transient but significant increase in systemic vascular resistance, increase in heart rate, increase in stroke volume, increase in cardiac size, and increase in LV filling pressures. Clinical effects on heart sounds and murmurs are as follows:

- Murmur of AS is diminished due to reduction of pressure gradient across aortic valve

- Murmur of AR, rheumatic MR and VSD increases due to increase in SVR
- LVS3 and LVS4 accentuated due to increase in LV filling pressures
- Murmur of MS becomes louder due to increase in flow across valve
- Murmur of HOCM decreases due to increase in LV volume
- Click and murmur of MVP delayed due to increase in LV volume, but the murmur of MVP becomes louder.

PHARMACOLOGICAL MANEUVERS

Amyl Nitrite

Method

An ampoule of amyl nitrite (0.3 mL) is crushed into a gauze piece and the patient is asked to take 3–4 deep breaths with the gauze piece near the patient's nostril. Changes in the murmur are noticed in the **first 15–30 seconds**.

Physiologically, in the first 30 seconds, there is intense vasodilation leading to decreased arterial pressure. In the next **30–60 seconds**, there is reflex tachycardia and, therefore, increased cardiac output.

Clinical Implications

Due to decreased aortic pressure, amyl nitrite accentuates the murmurs of AS (increased gradient across aortic valve), HOCM (decreased afterload), MS (reflex tachycardia) and diminishes the murmurs of AR, MR, VSD, PDA, and TOF.

Amyl nitrite is very useful in differentiating:

- Mid-diastolic murmur (MDM) of MS vs. Austin flint murmur of AR (MS murmur is accentuated and Austin flint is diminished)
- TOF vs. isolated PS (TOF murmur is diminished and PS murmur is accentuated)
- MR vs. TR (MR murmur is diminished and TR murmur is accentuated)
- AR vs. PR (AR murmur diminishes and there is no change in PR murmur).

Methoxamine and Phenylephrine

Method

Methoxamine is administered at **3–5 mg IV (intravenous)** to increase arterial pressure by **20–40 mm Hg for 10–20 min**. Phenylephrine is administered at **0.5 mg IV** to elevate systolic pressure around **30 mm Hg for 3–5 min**. Phenylephrine is preferred due to shorter duration action.

Clinical Implications

Physiologically, there is increased systemic arterial pressure that causes reflex bradycardia and decreased

contractility and thus decreased cardiac output. They are contraindicated in chronic heart failure (CHF) and hypertension (HTN).

The effects of methoxamine and phenylephrine on heart sounds are reduced S1, louder A2, prolonged A2–OS interval and variable response of S3 and S4.

Methoxamine and phenylephrine accentuate the electrolyte-driven mobilization (EDM) (EDM) of AR, paradoxical septal motion (PSM) of MR, murmur of VSD, TOF, and continuous murmurs of PDA and arteriovenous fistula (AVF). Also, the systolic murmur of HOCM softens (increased LV size), click and murmur of MVP delayed (increased LV size). Due to decrease in cardiac output, ejection systolic murmur (ESM) of AS, functional systolic murmurs, and MDM of MS are diminished.

Clinically Dynamic Auscultation Helps to Differentiate

AS and HOCM

- Squatting (AS murmur increases, HOCM murmur diminishes)
- Valsalva/standing (AS murmur diminishes, HOCM murmur accentuates).

AS and MR

- Handgrip (AS murmur diminishes, MR murmur accentuates)
- Phenylephrine (AS murmur diminishes, MR murmur accentuates)
- Postventricular premature contractions (VPC) (AS murmur accentuates and MR murmur diminishes)
- Amyl nitrate (AS murmur accentuates and MR murmur diminishes).

MS and Austin flint

- Amyl nitrite (MS murmur accentuates and Austin flint murmur diminishes).

PS and small VSD

- Amyl nitrite (PS murmur accentuates and VSD murmur diminishes)
- Phenylephrine (PS murmur diminishes and VSD murmur accentuates).

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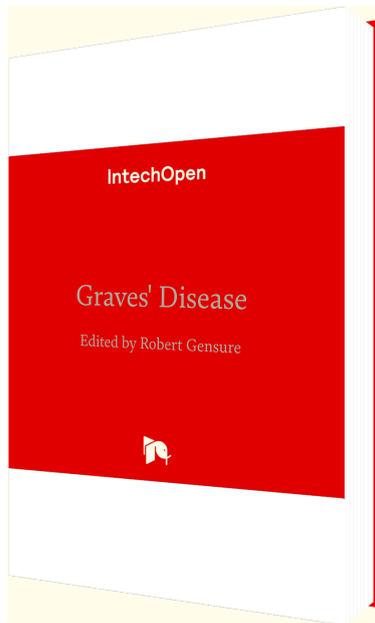
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Graves' disease is caused by autoantibodies to the thyroid gland that mimic thyroid-stimulating hormone, causing the gland to overproduce thyroid hormone. This speeds the metabolism of the patient and can lead to dangerous conditions including atrial fibrillation and heart failure. Mainstays of treatment have included antithyroid medication, surgical removal of the thyroid gland, and more recently...

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1. Graves' Disease: Clinical Significance and Management



Oral care measures in patients with Ventilator Associated Pneumonia: Review article

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Abstract

Most common nosocomial infection in Intensive Care Unit is Ventilator associated pneumonia (VAP). The risk associated is 1-3% per day of intubation, which signifies 6-20 fold increased probability of developing pneumonia than in non ventilated ICU cases. The major cause of VAP is the colonization of the oral cavity by microbes due to poor oral hygiene. Oral hygiene care like mouth rinse, gel, toothbrush, or combination along with use of suction for removing oral secretions, may reduce the risk of VAP in such patients.

Keywords: VAP, ICU, oral microbes, colonization, hygiene, risk

Introduction

Pathogenic oral microflora has a significant role in many systemic diseases like bacterial endocarditis, bacteremia respiratory problems, and ventilator-associated pneumonia (VAP) [Di Benedetto, *et al.*, 2013]. In this spectrum of diseases, nosocomial pneumonia is studied and the association between VAP and oral microbes is recognized. VAP is a nosocomial pneumonia occurring in patients who receive mechanical ventilation for more than 48 hours [Hutchins, *et al.*, 2009].

Cases with VAP have a prolonged ICU stay with a longer total hospital stay typically an extra 7-9 days [Eke *et al.*, 2012, Dennesen, *et al.*, 2003]. Increased cost of health and higher mortality are also related to VAP. In this review we have focused on the oral care preventive protocol associated with VAP [Hutchins, *et al.*, 2009].

Signs and symptoms of VAP include following: [American Thoracic Society, 1995]

1. Body temperature above 38⁰C or below 36⁰C
2. New infiltrate on chest X-ray
3. White blood count altered (above 12000 or below 4000)
4. Purulent sputum

Risk factors in the oral cavity associated with VAP include plaque formation, bacterial colonization in mouth, growth of pathogenic bacteria on teeth, certain secretions from oral cavity [Eke *et al.*, 2012]. 24 hours of admittance to an intensive care unit (ICU) can lead to bacterial colonization with *Staphylococcus aureus* which includes Methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter*, *Klebsiella*, *Escherichia coli* and *Pseudomonas* [Eke *et al.*, 2012, Dennesen, *et al.*, 2003].

VAP is related to a longer period of mechanical ventilation, excessive antimicrobial medicines and extensive hospitalization. Mortality rate linked to VAP is around 30-60%. Due to poor oral hygiene, aspiration of oral secretions is the main cause of VAP [Keyt, *et al.*, 2014]. The normal defense mechanism against pneumonia is impaired due to endotracheal tube (ET) disrupting normal mucous clearance and collection in subglottic pool due to which these contaminated secretions are aspirated in lungs [Dennesen, *et al.*, 2003, Keyt, *et al.*, 2014].

Antibiotics should be used judiciously as the resistant microbes can infect critically ill cases and ICU's [Keyt, *et al.*, 2014]. Appropriate and preventive nursing and respiratory intervention should be implemented.

Saliva plays an important role in oral clearance and has antimicrobial properties. In ICU, excessive stress leads to xerostomia which increases risk of plaque accumulation, caries and periodontal diseases [Bouadma, *et al.*, 2010]. Intraoral examination, inspecting lips and any associated pathologies in oral cavity should be done by a dental expert.

Incorporation of oral hygiene habits like brushing the teeth, tongue using soft bristle brush twice a day reduces the risk of VAP by 60%. Use of chlorhexidine 0.12% twice daily and 1.5% hydrogen peroxide is recommended for maintaining proper oral hygiene [American Thoracic Society, 1995, Keyt, *et al.*, 2014].

A proper oral care protocol should be followed in all institutions so that patient receives a comprehensive oral care. Appropriate treatment of plaque by hand scaling, aphthous ulcers, caries and oral candidiasis should be done [Bouadma, *et al.*, 2010].

Oral care recommended for VAP patients: [Dennessen, *et al.*, 2003, Keyt, *et al.*, 2014]

1. Assessment of oral cavity: Assessing lips, oral mucosa, teeth, tongue, palate and gingival for any pathologic lesions or infections.
2. Maintain salivation: Prevent xerostomia and mucositis. Use of salivary substitutes or moistening gel.
3. Prevention of caries: Use of fluoridated tooth paste. Use of mouthwash and plaque removal should be done.
4. Head elevation: Head should be lifted to at least 30⁰ as this will prevent the accumulation of salivary secretions in oral cavity, prevent the aspiration of gastric contents and prevent the pooling of oral secretion in subglottic area.
5. Use of intraoral suction: To prevent aspiration of contents to lungs.

Conclusion

Acquired pneumonia in ventilated patients causes financial crisis due to increased hospitalization and use of ventilator. Due to severity of this disease healthcare professionals should consider the risk factors associated with VAP and adopt preventive strategies.

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Dr. Manish Kumar Singh is currently working as associate professor in the Department of Anesthesiology at King George Medical University, Lucknow. He has a vast experience of teaching in the field of Medical.



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Chapter 17

Sleep and Sleep Disorders in Old Age: Assessment and Non-Pharmacological Management

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Allahabad University, India

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ABSTRACT

Sleep complaints are prevalent among older adults. Sleep quality and quantity changes with advancing age. There are changes in sleep patterns that are normal with ageing but many changes are the sign of disordered sleep. Sleep can be divided into rapid eye movement (REM) sleep and non-rapid eye movement sleep (NREM). Each has unique characteristics that are differentiated by their waveforms on the electroencephalogram (EEG) and by other physiological signals; several physiological age-related changes are thought to produce alterations in circadian rhythms. While there are numerous psychological and social factors contributing to quality and quantity of sleep, specific sleep disorders more prevalent in old age are insomnia, sleep apnea, and rapid eye movement disorder. Non-pharmacological treatment is effective in management of sleep disorders. Cognitive behaviour therapy is most effective to tackle insomnia. Cognitive behavior therapy along with meditation is beneficial for other sleep disorders and a new technique is also emerging: mindfulness.

INTRODUCTION

Sleep is a process in which important physiological changes (i.e. shift in brain activity, slowing of basic bodily functions) are accompanied by major shifts in consciousness (Baron, 2001). The pattern of sleep progression is called sleep architecture. Markov and Goldman (2006) reported two types of sleep architecture, rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. NREM sleep is

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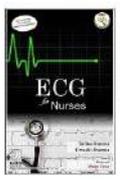
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Biomass fuel exposure and respiratory diseases in India

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Summary

One half of the world's population relies on biomass fuel as the primary source of domestic energy. Biomass fuel exposure causes a high degree of morbidity and mortality in humans. This is especially true in the context of developing countries, which account for 99% of the world's biomass fuel use. Biomass fuel consists of fire wood, dung cakes, agricultural crop residues such as straw, grass, and shrubs, coal fuels and kerosene. Together, they supply 75% of the domestic energy in India. An estimated three-quarters of Indian households use biomass fuel as the primary means for domestic cooking. Ninety percent of rural households and 32% of urban households cook their meals on a biomass stove. There are wide variations between the rural and urban households regarding the specific type of biomass fuel used. Globally, almost 2 million deaths per year are attributable to solid fuel use, with more than 99% of these occurring in developing countries. Biomass fuel accounts for 5-6% of the national burden of disease. Burning biomass fuels emits toxic fumes into the air that consist of small solid particles, carbon monoxide, polyorganic and polyaromatic hydrocarbons, and formaldehyde. Exposure to biomass fuels has been found to be associated with many respiratory diseases such as acute lower respiratory infections, chronic obstructive pulmonary disease, lung cancer, pulmonary tuberculosis, and asthma. Biomass fuel exposure is closely related to the burden of disease in India. Hopes are that future studies will examine the morbidity associated with biomass exposure and seek to



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Rajendra Prasad, Rajiv Garg & Nikhil Gupta

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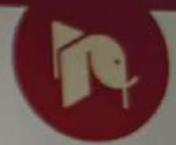
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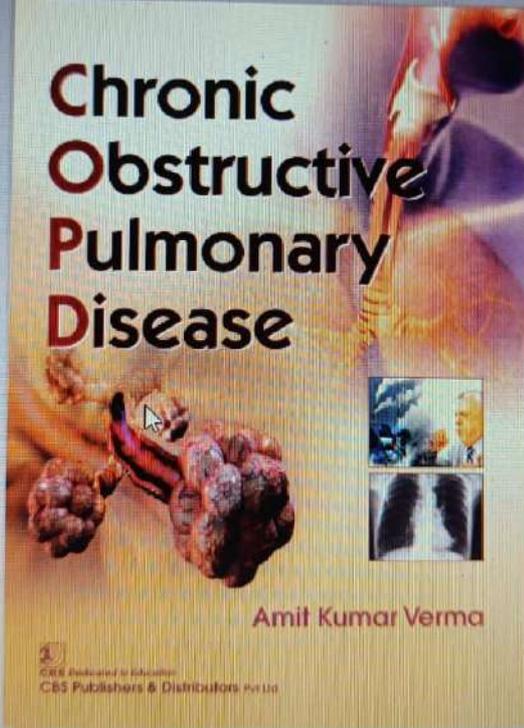
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Phenomenal rise in elderly population is bound to add to already existing enormous mental health demands. Age-related changes in sensation and perception, cognitive functions like memory orientation, calculation, and concentration etc. are significant in themselves. The ability to perform functions for self care, planning and execution are critical indicators of an individual's ability to live independently. Decline in cognitive functions hamper their activities of daily living thus, compromise their quality of life. Relationships between cognitive functioning and quality of life of Indian urban elderly have been thoroughly studied and are being presented in this book. Age, gender, education, family, occupational and socioeconomic status wise specific cognitive functions and different domains of quality of life of older adults are discussed. Quality of life of cognitively impaired elderly was found significantly poor as compared to normal group. These early detection, are important since it provides a window of opportunity for therapeutic interventions, directing clinical interventions and maximizing treatment outcome. Study provides cues for elderly care and policy making.



Rakesh Kumar Tripathi

Cognitive Functioning: Determinant of Quality of Life of Urban Elderly



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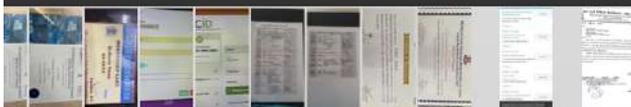
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AN EPIDEMIOLOGICAL STUDY IN XDR-TB PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND: India with a major burden of multidrug-resistant tuberculosis (MDR-TB) does not have national level data on this hazardous disease. Since 2006, emergence of extensively drug-resistant TB (XDR-TB) is considered a serious threat to global TB control. This study highlights the demographic and other epidemiological factors associated with XDR-TB in Lucknow.

METHODS: The study was conducted for a period of one year. Sputum samples were cultured using rapid, automated liquid culture system (MGIT 960). Drug susceptibility testing (DST) for Rifampicin (RIF) and Isoniazid (INH) was performed for all positive *M. tuberculosis* (*M.tb*) cultures. All MDR-TB isolates were tested for sensitivity to second-line drugs.

RESULTS/FINDINGS: In the present study it was found that the patients were mainly males who were suffering from XDR-TB visiting our tertiary center. The age group ranged from 17-52 years and was not seen in the pediatric age group. The patients mainly had pulmonary form of tuberculosis as none of the patients had extra-pulmonary tuberculosis. Most of the patients who had XDR were malnourished and had the weight between 26-45 kilograms. In the study majority of patients were on standard treatment for XDR patients as per RNTCP guidelines. One patient was defaulter and two mortalities were seen in our study. Majority of patients were from the Lucknow district.

CONCLUSIONS: The actual incidence and prevalence rate of XDR-TB in India is not available, although some scattered data is available. This study raises a concern about existence of XDR-TB in India, though small, signaling a need to strengthen the TB control program for early diagnosis of both tuberculosis and drug resistance in order to break the chains of transmission

KEYWORDS : Tuberculosis, XDR-TB, India

INTRODUCTION

Tuberculosis (TB) has existed for millennia and remains a major global health problem. It causes ill-health in millions of people each year and in 2015 was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease. [1] The upward revisions to estimates of the burden of TB disease in India for the period 2000–2015 follow accumulating evidence that previous estimates are too low. This evidence comprises of household surveys, a state-wide TB prevalence survey, studies of anti-TB drug sales in the private sector, notification data and new analysis of mortality data [2]. Globally, emergence of drug resistance is a dangerous alarm. An extremely worrisome aspect of tuberculosis is a recent rise to multi drug-resistant (MDR) and extremely drug-resistant (XDR) TB [3]. The increase in the incidence MDR and XDR tremendous challenges to the global efforts to battle tuberculosis. [4]

In 2015, there were an estimated 48,0000 new cases of multidrug-resistant TB (MDR-TB) and an additional 10,0000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment [2]. However load of MDR-TB accounting for almost 50% of world total cases carry together by India and China alone. [3] Due to their drug resistance, tuberculosis have emerged as a serious problem in the world. MDR-TB (defined as in vitro resistance to anti-tuberculous drugs, isoniazid and rifampicin) and XDR-TB (defined as in vitro resistance to isoniazid, rifampicin, any fluoroquinolones and at least one of three injectable second-line drugs) are now widely reported. The is difficult to cure and requires prolonged treatment with expensive and often toxic multidrug regimens [1].

Treatment outcomes have been significantly worse for patients with XDR TB than for patients with TB that is either drug-susceptible or

MDR tuberculosis [5–7]. In the first recognized outbreak of XDR TB, Gandhi et al [8] reported that 53 patients in KwaZulu-Natal, South Africa, who were co-infected with XDR TB and human immunodeficiency virus (HIV) survived for a median of only 16 days, with a mortality of 98%. Although some subsequent studies have reported better outcomes [9], therapeutic options for XDR TB are extremely limited because second-line drugs are less effective, more toxic, and more costly than are first-line therapies, and XDR TB strains are, by definition, resistant to the more potent of the second-line options. Although several new drugs are being evaluated for the treatment of XDR TB, none are currently available. Therefore the aim of current study is an attempt to find out the true prevalence of XDR-TB cases.

MATERIAL & METHODS

This observational study involved category II sputum positive pulmonary tuberculosis patients, aged 0 to 65 years. The cases were recruited for one year through the outdoor/indoor-patient who visited department of Respiratory Medicine, King George's Medical Sciences Lucknow, Uttar Pradesh.

After the subject provided informed consent, an interview was conducted to collect demographic, epidemiologic, and clinical information. Patients' medical records were abstracted to collect detailed information about comorbidities and treatment history. Patients were observed monthly until the completion of the prescribed treatment regimen. Treatment outcome definitions for cure, failure, relapse and default followed the guidelines of the World Health Organization.

Definitions:

- **Cure:** MDR-TB patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.
- **Completed:** MDR-TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
- **Died:** MDR-TB patient who dies for any reason during the course of MDR-TB treatment.
- **Failed:** Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events.
- **Default:** MDR-TB patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.
- **Transfer out:** MDR-TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

All patients were subjected to sputum-smear microscopy for acid-fast bacillus (AFB) and chest radiography at the time of enrollment in category II treatment for the study. All sputum specimens were subjected to culture on MGIT. The positive cultures were evaluated pattern for mycobacterial culture and drug susceptibility testing (DST). Drug susceptibility testing (DST) for Rifampicin (RIF) and

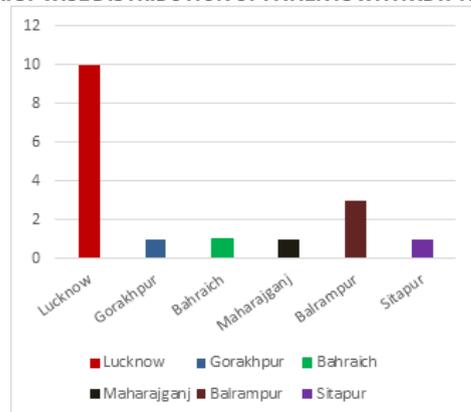
Isoniazid (INH) was performed for all positive M. tuberculosis (M.tb) cultures. All MDR-TB isolates were tested for sensitivity to second-line drugs [Amikacin (AMK), Capreomycin (CAP), Ofloxacin (OFX), Ethionamide (ETA)]. The sensitivity tests were set up with inoculum prepared from the growth of selected positive culture. The standard reference strain H37Rv was tested in addition with each batch of tests.

PARAMETERS		TOTAL
Sex	Males	13
	Females	4
Age	Range (Years)	17-52
	Average (Years)	30.24
Site of Disease	Pulmonary	17
	Extra-pulmonary	0
Weight	<26Kgs	0
	26-45Kgs	12
	>45Kgs	5
Outcome	On-Treatment	14
	Default	1
	Expired	2

RESULTS

CLINICO-EPIDEMIOLOGICAL PARAMETERS IN PATIENTS WITH XDR-TB

DISTRICT-WISE DISTRIBUTION OF PATIENTS WITH XDR-TB



DISCUSSION

XDR-TB is a serious global health threat. The emergence of XDR TB reflects a failure to implement the measures recommended in the WHO's Stop TB strategy. In the present study it was found that the patients were mainly males who were suffering from XDR-TB visiting our tertiary center. The age group ranged from 17-52 years and was not seen in the pediatric age group. The patients mainly had pulmonary form of tuberculosis as none of the patients had extra-pulmonary tuberculosis. Most of the patients who had XDR were malnourished and had the weight between 26-45 kilograms. In the study majority of patients were on standard treatment for XDR patients as per RNTCP guidelines. One patient was defaulter and two mortalities were seen in our study. Majority of patients were from the Lucknow district.

CONCLUSIONS

Extensively drug-resistant tuberculosis (XDR-TB) is a known serious health hazard in India and sub-tropical countries. There is urgent need for strengthening the clinic-epidemiological surveillance so that the diseases can be curtailed. The laboratory diagnosis is cumbersome in the XDR TB patients and laboratories must be strengthened across the country so that the early detection and timely treatment can be done.

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RESEARCH ARTICLE

Emergence of blaNDM-1 and blaVIM producing Gram-negative bacilli in ventilator-associated pneumonia at AMR Surveillance Regional Reference Laboratory in India

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Abstract

Introduction

Ventilator-associated pneumonia (VAP) may be a life threatening nosocomial infection encountered in intensive care units. Currently the emergence of carbapenem-resistant Gram-negative pathogens has become worrisome threat worldwide.

Material and methods

Endotracheal aspirates samples were collected from patients who were under mechanical ventilation for > 48 h. The bacterial isolates were identified by MALDI-TOF-MS and antibiotic susceptibility testing performed. All carbapenem resistant isolates were tested by Modified Hodge test (MHT), modified carbapenem inactivation method (mCIM), and EDTA-CIM (eCIM) and PCR were performed to detect blaIMP, blaVIM and blaNDM producing MBL genes.

Results

VAP occurred in 172/353(48.7%), 23.3% had early-onset VAP and 76.7% had late-onset VAP. Males (69.2%) were found to suffer more from VAP. Prior antibiotic therapy, CPI>6, prior surgery and tracheostomy were associated with VAP. The mortality in VAP (58.1%) contrasted with non-VAP (40%). 99/169 (58.6%) Gram-negative isolates were resistant to carbapenems. *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were common pathogens found in late onset VAP, whereas *K. pneumoniae*, *A. baumannii* and *Staphylococcus aureus* were common in early onset VAP. The PCR results

detected blaNDM in 37/172(21.5%) and blaVIM in 30/172(17.4%); 15/172(8.7%) isolates carried both genes.

Conclusion

The blaNDM-1 and blaVIM genes are the main antibiotic-resistance genes that induce resistance patterns to carbapenems in VAP, highlighting CRE strains of potential public health concern and therapeutic challenge. Diagnostic laboratories in India must get on high caution for early MBL detection as it may limit the wide dispersal of MBL genes.

Introduction

Ventilator-associated pneumonia (VAP) is one of the life-threatening nosocomial infections in intensive care units (ICUs) worldwide and accounts for 25% of all ICU infections [1]. VAP is estimated to occur in 9–27% of all mechanically ventilated patients, with the highest risk being early in the course of hospitalization. It is associated with longer hospital-stay, prolonged antibiotic usage, and increased cost of treatment, higher morbidity and with an estimated attributable mortality of 13% [2]. VAP is usually classified as either early onset, occurring within the first four days of mechanical-ventilation (MV) or late onset, developing five or more days after initiation of MV. Successful treatment of patients with VAP is a difficult and complex undertaking [3].

Microorganisms responsible for VAP differ according to the geographic areas, duration of mechanical ventilation, antibiotic dose, ventilator days, duration of ICU stay and specific patient characteristics. A number of studies have shown that Enterobacteriaceae, non-fermenters and *Staphylococcus aureus* are causative agents of VAP [1,4]. The etiology of VAP pathogens are changing over the past years, therefore early detection of pathogens and knowledge of sensitivity patterns are very crucial for better patient outcomes [5]. There is an increasing evidence of emergence of multidrug-resistant (MDR) pathogens due to extended spectrum beta (β)-lactamases (ESBL), AmpC β -lactamases (AmpC) or metallo- β -lactamases (MBLs) [6].

Carbapenemases include three types: class A (*bla*_{KPC}, *bla*_{GES} and *bla*_{IMI}), class B (*bla*_{NDM}, *bla*_{IMP}, *bla*_{VIM}, and *bla*_{SIM}) and class D (*bla*_{OXA-48} like). Recently, treatment of VAP has become challenging due to emergence of class B MBLs that have a broad range, potent carbapenemase activity and resistance to all β -lactam antibiotics but not to monobactams [7]. Development of accurate methods for the early detection of carbapenem resistant bacteria is required not only for therapy but also to monitor the spread of resistant bacteria or resistance genes in hospitals and community [8]. The multidrug resistance has been increased globally that is considered a public health threat. Several previous studies revealed the emergence of multidrug-resistant bacterial pathogens from different origins especially birds, animals, fish, and food chain which may transmitted to the human consumers resulting in severe illness [9–13].

The characterization of underlying mechanisms leading to carbapenem resistance of clinical isolates in VAP is not undertaken by most clinical microbiology laboratories for therapeutic decision-making. There is paucity of data addressing microbiological aspects particularly of MBL-producing Gram-negative bacilli among VAP patients in India. This study aimed to investigate the clinicomicrobiological profiling, antibiogram and metallo- β -lactamases (MBLs) production in VAP infections with their subsequent outcome.

Material and methods

Study site and design

A prospective hospital-based cross sectional study was conducted over a period of one year from June 2019 to May 2020 in the Department of Microbiology, Critical Care Unit (CCU), Pulmonary Critical Care Unit (PCCU) Critical Care Units and Trauma Ventilatory Unit (TVU) at King George's Medical University in Lucknow, India. The bacteriology laboratory of the Microbiology department is an Antimicrobial Resistance Surveillance Regional Reference Laboratory in India.

Ethical approval

This study was approved by the King George's Medical University U.P., Institutional Ethics Committee (Ref. code: 97th ECM II B-Thesis/P89 dated 29-07-19) and written informed consent was obtained from patients' attendants'.

Sample size

Existing literature from Indian studies suggests an incidence of VAP ranging from 13–42%, and is highly variable in different regions. The sample size (n) is calculated according to the formula: $n = z^2 \times P(1-p)/d^2$. Where: $z = 1.96$ for a confidence level (α) of 95%, $p =$ proportion (0.4) and $d = 0.06$.

Study subjects

We enrolled patients based on National Healthcare Safety Network's (NHSN) new classification definition [14] for VAP, minimum 48 h on mechanical ventilation with radiologic criteria (≥ 2 serial radiographs with at least one of the following: new or progressive infiltrate, consolidation or cavitation), systemic criteria with at least one of the following: fever ($>38^\circ\text{C}$ or $>100.4^\circ\text{F}$), leukopenia (<4000 white blood cell/mm³) or leukocytosis ($\geq 12,000$ white blood cell/mm³) and for adults ≥ 70 years old, altered mental status with no other recognized cause) and pulmonary criteria with at least two of the following: new onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, worsening gas exchange (eg, desaturations, increased requirements, or increased ventilator demands), new-onset or worsening cough, or dyspnea, or tachypnea and rales or bronchial breath sounds. Patients with pneumonia prior to MV or within 48 hours of MV were excluded.

Data collection

Detailed history, including the name, age, sex, underlying clinical condition, date of admission, history of previous hospitalization, duration of ventilation, duration of hospital-stay and demographic data of patients were obtained in a structured questionnaire format and clinical outcome of each patient was noted.

Criteria for diagnosis of VAP

The patients who fulfilled clinical and microbiological criteria (> 10 polymorphonuclear cells/low power field and \geq one bacterium/oil immersion field with or without the presence of intracellular bacteria on gram staining and quantitative endotracheal aspirate culture showing $\geq 10^5$ CFU/ml) were considered as confirmed cases of VAP cases.

Identification of VAP pathogens

Endotracheal aspirate sample was collected under all aseptic precautions in a sterile universal container and sent to the laboratory within 4 h at ambient temperature. The endotracheal samples were serially diluted in sterile normal saline as 1/10, 1/100, 1/1000 and 0.01 ml of 1/1000 dilution and quantitative culture was performed on 5% sheep blood agar and MacConkey agar. After incubation at 37°C in a 5% CO₂ incubator for 24 h, colony count was done and expressed as number of colony forming units per ml (CFU/ml). The number of CFU/ml is equal to number of colonies on agar plate × dilution factor × inoculation factor. All isolates were identified by MALDI-TOF MS (bioMérieux) and antibiotic susceptibility testing was performed and interpreted as per the Clinical and Laboratory Standards Institute (CLSI) guidelines [15].

Antimicrobial susceptibility testing

Based on the CLSI guidelines, for the Enterobacteriaceae members and non-fermenters, the antibiotics used were amikacin (30 µg), ampicillin (10 µg), amoxicillin-clavulanate (10 µg), aztreonam (30 µg), cefepime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), ceftazidime-avibactam (30 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), tetracycline (30 µg), co-trimoxazole (30 µg), gentamicin (10 µg), tobramycin (10 µg), imipenem (10 µg), meropenem (10 µg), ertapenem (10 µg), piperacillin-tazobactam (10 µg). For *Pseudomonas spp.*, amikacin (30 µg), aztreonam (30 µg), cefepime (30 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), co-trimoxazole (30 µg), gentamicin (10 µg), tobramycin (10 µg), imipenem (10 µg), meropenem (10 µg), ertapenem (10 µg), piperacillin-tazobactam (10 µg), co-trimoxazole (30 µg) and ceftazidime (30 µg) were tested. In multidrug resistant isolates colistin MICs were tested by broth microdilution (BMD). For the Gram-positive pathogens, penicillin, erythromycin, clindamycin, penicillin B, ceftazidime (10 µg), linezolid, amikacin (10 µg), levofloxacin (5 µg), tetracycline (30 µg), co-trimoxazole (30 µg) and gentamicin (5 µg) were tested by disc diffusion method and vancomycin MICs were tested by E-strip Test. Ceftazidime (30 µg) disc was used as surrogate marker for methicillin-resistant *Staphylococcus aureus*. The carbapenem resistance was screened from meropenem and/or imipenem disc (HiMedia Laboratories, India). The quality control strains used in the study were *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923) and *Pseudomonas aeruginosa* (ATCC 27853).

Phenotypic test for detection of Metallo Beta Lactamase

Modified Hodge test. An inoculum of 0.5 McFarland standard of *E. coli* ATCC 25922 was prepared in saline and then diluted with saline up to 1:10 dilutions. MHA plate was inoculated with the above-prepared inoculum with a sterile cotton swab. Meropenem disc was applied to 10 µg at the center of the MHA plate. After that test organism was streaked with help of a sterilized wire loop in a straight line out from the center to the periphery. Plates were incubated at 37°C for 24 hours. The appearance of a cloverleaf type indentation or flattening at the intersection of the test organism and *E. coli* ATCC 25922 within the zone of inhibition of the carbapenem susceptibility disc is positive Modified Hodge test [16].

mCIM (Modified Carbapenem Inactivation Method) testing. Using a sterile inoculating loop, isolates were emulsified from a fresh cultured overnight blood agar plate in a tube containing 2 ml of tryptic soy broth (TSB). 10 µg MEM disc (BD BBL Sensi-disc susceptibility test disc) was added into the above TSB inoculum and incubated. The MEM disc was removed from the TSB inoculum with a 10 µl loop wire and then the disc was placed on the previously *E. coli* ATCC inoculated MHA plate. MHA plate was then incubated in for 18–24 h at 37°C. The zone diameter of 6–10 mm was considered as carbapenemase producer. All isolates that were mCIM positive were tested for eCIM test [15].

EDTA-modified carbapenem inactivation method. For each isolate to test eCIM, TSB tubes were prepared. 20 μ l of the 0.5 M EDTA was added to the TSB tube. An increase in zone diameter (mm) \geq 5 was considered as metallo- β -lactamase producer [15].

DNA extraction and PCR amplification of *bla*_{IMP}, *bla*_{VIM} and *bla*_{NDM} genes

DNA extraction was done by boiling method [17]. Monoplex PCR was performed to detect *bla*_{IMP}, *bla*_{VIM} and *bla*_{NDM} responsible for MBL production using the primers as described in Table 1. PCR amplification was done in a DNA thermal cycler (Model-Bio-Rad C1000 Touch TM Thermal Cycler) with a final volume of 25 μ l master mix consisting of 12.5 μ l of 2X universal PCR master mix, 2 μ l of primers (5–10 μ M) of each forward and reverse primers, 5.5 μ l of nuclease-free water and 5 μ l of DNA template. The initial denaturation temperature was at 95°C for 15 min, followed by 30 cycles of DNA denaturation at 95°C for 30 sec. The primer annealing was carried out at 59°C for 1.5 min, and primer extension was carried out at 72°C for 1.5 min. After the last cycle, a final extension step was carried out at 72°C for 10 min. After that, amplification products were electrophoresed on 1.5% agarose gel and visualized using UV transilluminator at 260 nm.

Statistical analysis

Statistical analyses within the study were performed using the SPSS, Version 20 (SPSS Inc., Chicago, IL, USA). Chi-square test was used to compare categorical variables where ever applicable and *p*-value less than 0.05 were considered significant.

Results

Incidence and characteristics of patients with VAP

Out of the 353 MV patients, 172(48.7%) met clinical and microbiological criteria and were considered cases of VAP. 55(15.6%) samples met microbiologically criteria, but cases did not meet clinical criteria and were considered as non-VAP. Early-onset VAP was found in 40 (23.3%) patients and late-onset VAP in 132(76.7%) patients. Most common affected age group was 41–60 years with mean age 46.85 \pm 18.13 and range 19–89 years. 119(69.2%) patients were male and 53(30.8%) were females and difference was statistically significant (*p* = 0.026).

Risk factors in VAP and Non-VAP patients

On univariate analysis, VAP showed significant association with prior surgery (*p* = 0.009), CPI score >6 (*p*<0.001) and previous antibiotic therapy (*p*<0.001). Tracheostomy showed significant association with late-onset VAP (*p* = 0.025). The proportion of tracheostomy cases was significantly higher in late VAP as compared to early VAP (36.4% vs. 17.5%). Late VAP cases as compared to early VAP cases had significantly higher ventilation time (10.02 \pm 4.27 vs. 5.75

Table 1. Primer sequences and their amplicon sizes used in amplification of MBL genes.

Gene	Primer Sequence (5'-3')	Product size (bp)	Ref
NDM-1F	CACCTCATGTTGAATTCGCC	984	Kaase M et al. 2011 [18]
NDM-1R	CTCTGTCACATCGAAATCGC		
VIM-F	GATGGTGTGTTGGTCGCATA	390	Poirel L et al. 2011 [19]
VIM-R	CGAATGCGCAGCACCAG		
IMP-F	GGAATAGAGTGGCTTAAYTCTC	232	Poirel L et al. 2011 [19]
IMP-R	CCAAACYACTASGTTATCT		

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± 2.47 days) and duration of hospital stay (21.29 ± 10.93 vs. 15.35 ± 5.85 days). The risk factors have been summarized in [Table 2](#).

Causative agents of early-onset and late-onset VAP

187 isolates were recovered from 172 VAP patients; the most common pathogen was *Acinetobacter baumannii* (29.4%) followed by *Pseudomonas aeruginosa* (24.1%), *Klebsiella pneumoniae* (24.1%) and *Staphylococcus aureus* (7.5%). Most common agents in early-onset VAP cases were *K. pneumoniae* (36.4%), *A. baumannii* (20.5%), *S. aureus* (20.5%), and while in late-onset VAP were *A. baumannii* (32.2%), *P. aeruginosa* (29.4%), *K. pneumoniae* (20.3%) and *E. coli* (5.6%) [Table 3](#). Of the included cases, 15 (8.7%) showed the polymicrobial growth [Table 4](#).

Antibiotic resistance patterns in VAP patients

Out of 169 Gram-negative isolates recovered, 144 (85.2%) were multi-drug-resistant; as they were resistant to more than three groups of antibiotics. 99/169 (58.6%) Gram-negative isolates were resistant to carbapenems. Among Gram-positive organisms, 13(92.9%) isolates were MRSA but all isolates were sensitive to linezolid and vancomycin. 21.4% isolates of *S. aureus* showed MIC 0.5 $\mu\text{g/ml}$ and in 78.6% MIC was 1 $\mu\text{g/ml}$. The colistin MIC of the isolates ranged from 0.25–2 $\mu\text{g/ml}$ and no resistance was seen. The antibiotic resistance pattern of isolated organisms has been summarized in [Table 5](#).

Table 2. Correlation of demographic and risk factors in VAP and Non-VAP patients by univariate analysis.

SN	Variable	Total cases (n = 244)		Non-VAP (n = 57)		VAP (n = 187)		Chi-square	
		n	%	n	%	n	%	χ^2	'p'
1.	Mean age \pm SD (Range)	46.85 \pm 18.13 (19–89)		49.25 \pm 17.93 (19–82)		46.08 \pm 18.18 (19–89)		1.132	0.259
2.	Age (Years)							2.101	0.717
	18–25	35	7	12.7	28	16.3			
	26–40	60	12	21.8	48	27.9			
	41–60	75	20	36.4	55	32.0			
	61–80	51	15	27.3	36	20.9			
	>80	6	1	1.8	5	2.9			
3.	Sex							4.975	0.026
	Females	79	26	47.3	53	30.8			
	Male	148	29	52.7	119	69.2			
4.	Smoking	86	17	30.9	69	40.1	1.501	0.220	
5.	Alcohol	41	9	16.4	32	18.6	0.141	0.707	
6.	Diabetes	30	7	12.7	23	13.4	0.015	0.902	
7.	Hypertension	81	18	32.7	63	36.6	0.276	0.599	
8.	Liver disease	18	6	10.9	12	7.0	0.883	0.347	
9.	Lung disease	39	7	12.7	32	18.6	1.012	0.314	
10.	Renal disease	22	8	14.5	14	8.1	1.954	0.162	
11.	Neurological	11	2	3.6	9	5.2	0.230	0.631	
12.	Surgery	109	18	32.7	91	52.9	6.799	0.009	
13.	Tracheostomy	68	13	23.6	55	32.0	1.382	0.240	
14.	Heart disease	13	6	10.9	7	4.1	3.611	0.057	
15.	CPI ^a Score ≥ 6	186	15	27.3	171	99.4	146.569	<0.001	
16.	Previous Antibiotic history	62	12	6.7	50	29.1	30.421	<0.001	

^aCPI score- Clinical pulmonary infection Score.

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Table 3. Proportion of pathogens isolated from early-onset and late-onset VAP patients (n = 172).

SN	Organisms	Total of isolates recovered (n = 187)	Early VAP (n = 44)		Late VAP (n = 143)	
			No.	%	No.	%
1	<i>Acinetobacter baumannii</i>	55	9	20.5	46	32.2
2	<i>Pseudomonas aeruginosa</i>	45	3	6.8	42	29.4
3	<i>Klebsiella pneumoniae</i>	45	16	36.4	29	20.3
4	<i>Escherichia coli</i>	12	4	9.1	8	5.6
5	<i>Proteus mirabilis</i>	8	0	0.0	8	5.6
6	<i>Pseudomonas putida</i>	2	0	0.0	2	1.4
7	<i>Enterobacter hormaechei</i>	1	1	2.3	0	0.0
8	<i>Citrobacter freundii</i>	1	0	0.0	1	0.7
9	<i>Staphylococcus aureus</i>	14	9	20.5	5	3.5
10	<i>Candida albicans</i>	3	2	4.5	1	0.7
11	<i>Candida tropicalis</i>	1	0	0.0	1	0.7

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Performance of phenotypic methods for carbapenamase producers

The phenotypic methods showed that 66/99(66.6%) carbapenam-resistant isolates were phenotypic producer of carbapenamases by the MHT while 58(75.3%) were detected by mCIM/eCIM test as MBL producers (Fig 1A and 1B). The sensitivity and specificity of the MHT was 76.9% and 44.7% respectively. The sensitivity and specificity of mCIM/eCIM test was 96.2% and 83% respectively considering PCR as the gold standard Table 6.

Genotypic methods for carbapenamase producers

The results of amplified genes by the PCR (Fig 2A and 2B) showed of the 99 isolates, 37/172 (21.5%) contained *bla*_{NDM} and 30/172(17.4%) had *bla*_{VIM} gene. 15/172(8.7%) isolates harbored both *bla*_{NDM} and *bla*_{VIM} genes and these all were found in late-onset VAP cases. None of the isolates harbored *bla*_{IMP} gene (Table 7). NDM was more common in early-onset VAP while VIM in late-onset VAP cases. Verona integron metallo beta-lactamase (VIM) type MBL was associated with more deaths than NDM type MBL and patients with MBL negative organisms had a lesser mortality.

Clinical outcomes

While assessing for an outcome, mortality in VAP patients (100, 58.1%) was higher compared to non-VAP (22, 34.3%). The most common cause of the death was septic shock with multisystem organ failure. 59(34.3%) patients with VAP and 31(56.4%) non-VAP patients had recovered.

Table 4. The distribution of poly-microbial isolates from VAP patients.

S.No.	Organism	No. of isolates (n)	Percentage (%)
1.	<i>Acinetobacter baumannii</i> + <i>Pseudomonas aeruginosa</i>	4	26.6
2.	<i>Acinetobacter baumannii</i> + <i>K. pneumoniae</i>	4	26.6
3.	<i>Pseudomonas aeruginosa</i> + <i>K. pneumoniae</i>	3	20
4.	<i>Acinetobacter baumannii</i> + <i>Candida albicans</i>	2	13.2
5.	<i>Pseudomonas aeruginosa</i> + <i>Candida albicans</i>	1	6.8
6.	<i>Escherichia coli</i> + <i>Candida tropicalis</i>	1	6.8
	Total	15	100

<https://doi.org/10.1371/journal.pone.0256308.t004>

Table 5. Antibiotic resistance pattern of bacteria isolated from VAP patients.

Drugs	<i>A. baumannii</i> (n = 55)	<i>P. aeruginosa</i> (n = 45)	<i>K. pneumoniae</i> (n = 45)	<i>E. coli</i> (n = 12)
Ampicillin	-	-	-	100
Amoxy-clavulanic acid	-	91.8	-	91.7
Amikacin	84.8	48.9	78.4	41.7
Tobramycin	80.4	75.6	88.2	33.3
Gentamycin	88	82.2	80.4	36.4
Ciprofloxacin	90.2	46.7	96.1	91.7
Levofloxacin	95.6	91.4	92.2	83.3
Aztreonam	-	50	90	75
Ceftriaxone	96.7	-	93.8	90
Cefoxitin	-	-	93.8	90
Cefazolin	-	-	100	100
Ceftazidime	-	62.1	-	-
Piperacillin-tazobactam	66.3	53.3	92.2	66.7
Imipenem	85.9	57.8	66.7	50
Meropenem	65.2	48.9	70.6	50
Ertapenem	-	-	56	40
Colistin	0	0	0	0
Tigecycline	0	0	0	0

<https://doi.org/10.1371/journal.pone.0256308.t005>

Discussion

VAP refers to pneumonia caused by bacterial agents developed in patients who are mechanically ventilated for duration of more than 48 h. It is a critical public health issue related to significant morbidity, mortality and enhanced cost of care [20].

In our study, the incidence of confirmed VAP was 48.75%. Existing literature from Indian studies suggests an incidence of VAP ranging from 13–42%, and is highly variable in different regions [21]. Incidence rate reported in the developing countries is 25–35%, while in developed countries is 15–17% [22]. Majority of patients were in age group of 40–60 years with preponderance of male sex (69.2% or 199/172), similar findings have been published in various studies [23]. It appears due to the difference in the rates of admission and enrollment. In present study, late-onset VAP (76.7%) was more common than early-onset VAP (23.3%). Few

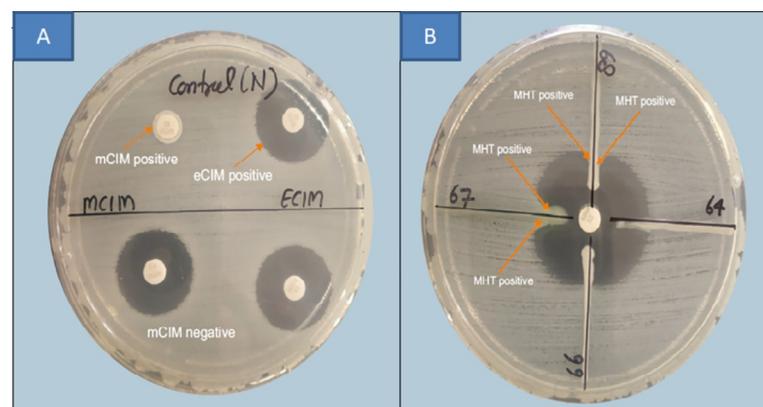


Fig 1. A: Isolate positive for mCIM/eCIM test (isolate with *bla_{NDM}* gene). B: Isolate showing clover-leaf shaped pattern in Modified-Hodge test.

<https://doi.org/10.1371/journal.pone.0256308.g001>

Table 6. Sensitivity and specificity of different phenotypic methods in relation to PCR among carbapenem-resistant isolates from VAP patients.

	PCR				Sensitivity	Specificity	PPV	NPV	Diag. accuracy
	Positive		Negative						
	No.	%	No.	%					
MHT +ve	40	76.9	26	55.3	76.9	44.7	60.6	63.6	61.6
MHT -ve	12	23.1	21	44.7					
eCIM +ve	50	96.2	8	17.0	96.2	83.0	86.2	95.1	89.9
eCIM -ve	2	3.8	39	83.0					
mCIM +ve	51	98.1	26	55.3	98.1	44.7	66.2	95.5	72.7
mCIM -ve	1	1.9	21	44.7					

Abbreviations: MHT, modified Hodge test; eCIM, EDTA-modified carbapenem inactivation method; mCIM, modified carbapenem inactivation method; PPV, positive predictive value; NPV, negative predictive value; VAP, ventilator-associated pneumonia; +ve-positive.

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studies conducted in India showed late-onset VAP in 34–60% cases and early-onset VAP in 20–40% cases [24]. In contrast, a study conducted in Pondicherry, India observed early-onset VAP in 72.2% patients [25]. We also observed higher mortality in VAP patients 100/172 (58.1%) compared to non-VAP 22/55(40%).

There are some factors that make the patients vulnerable to develop VAP. The present study identified prior surgery, CPI score >6, previous antibiotic therapy and tracheostomy were associated with VAP compared to non-VAP. The proportion of tracheostomy cases was significantly higher in late-onset VAP as compared to early-onset VAP. Patients with late-onset VAP had higher ventilation time and duration of hospital stay. Previous antibiotic treatment is a well-known risk factor for VAP [26]. However, few observational studies found antibiotic treatment to be protective against early-onset VAP [27]. The study in a Europe, demonstrated that tracheotomy was independently associated with decreased risk for VAP which is contrasting to our findings [28].

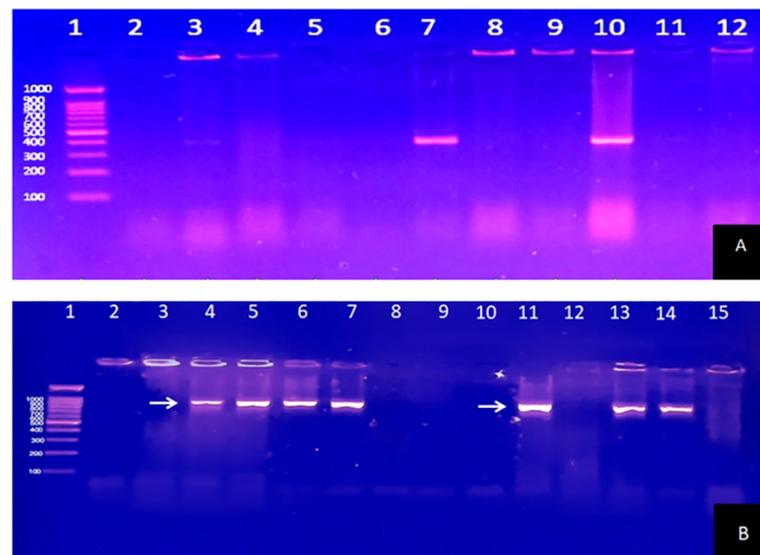


Fig 2. A: Agarose gel electrophoresis of products obtained by PCR of amplified DNA. Lane 1: 100 bp DNA ladder; Lane 2- Negative control; Lane 9-Positive control *bla_{VIM}* (390bp); Lane 10: Isolates positive for *bla_{VIM}* gene (390bp). B: Agarose gel electrophoresis of products obtained by PCR of amplified DNA. Lane 1: 100 bp DNA ladder; Lane 2: Negative control; Lane 4: Positive control for *bla_{NDM}* gene (984bp); Lane 5, 6, 7, 11,13 and 14: Isolates positive for *bla_{NDM}* gene (984bp).

<https://doi.org/10.1371/journal.pone.0256308.g002>

Table 7. Metallo- β -lactamases producing Gram negative isolates from VAP patients.

	Total (n = 99)	<i>bla</i> _{VIM} +ve		<i>bla</i> _{NDM} +ve		<i>bla</i> _{VIM+NDM} both +ve		<i>bla</i> _{IMP} +ve	
		No.	%	No.	%	No.	%	No.	%
<i>A. baumannii</i>	37	18	48.6	15	40.5	8	21.6	0	-
<i>P. aeruginosa</i>	24	3	12.5	5	20.8	1	4.2	0	-
<i>K. pneumoniae</i>	27	8	29.6	13	48.1	6	22.2	0	-
<i>E. coli</i>	5	0	0.0	3	60.0	0	0.0	0	-
<i>P. mirabilis</i>	2	1	50.0	1	50.0	0	0.0	0	-
<i>Pseudomonas spp.</i>	2	0	0.0	0	0.0	0	0.0	0	-
<i>Enterobacter hormaechei</i>	1	0	0.0	0	0.0	0	0.0	0	-
<i>Citrobacter freundii</i>	1	0	0.0	0	0.0	0	0.0	0	-
	99	30		37		15		0	

<https://doi.org/10.1371/journal.pone.0256308.t007>

In present study, Gram-negative bacteria were found as causative agents of VAP which is similar to what has been reported in few studies [29,30]. Gram-positive bacteria are common agents of VAP in developed countries but have also been reported in few Indian studies [31]. In accordance to other Asia studies [23], multidrug-resistant *A. baumannii* was the predominant bacteria in VAP cases followed by *P. aeruginosa* (24.1%), *K. pneumoniae* (24.1%) and *S. aureus* (7.5%). Most common agents in early-onset VAP were *K. pneumoniae* (36.4%), *A. baumannii* (20.5%), *S. aureus* (20.5%), and while in late-onset VAP were *A. baumannii* (32.2%), *P. aeruginosa* (29.4%), *K. pneumoniae* (20.3%) and *E. coli* (5.6%). But the probable cause for this difference could not be explained. The results of our study showed mono microbial infection in the majority of patients and 15(8.7%) patients had polymicrobial infection which can result in poor prognosis [32].

Knowledge of the susceptibility of pathogens to antimicrobial agents is urgently required, since understanding of the pattern of antibiotic resistance may aid in treatment of VAP infection. In present study, the majority of isolates from both early-onset and late-onset VAP were multidrug resistant (85.2%), carbapenem-resistant (58.6%) and resistant to typically recommended for empirical initial therapy for VAP. In the study, tigecycline and colistin showed promising efficacy followed by piperacillin/tazobactam combination and the imipenem. Among these isolate, the MIC values for colistin ranged from 0.25–2 μ g/mL and for tigecycline ranged from 0.125–2.0 μ g/mL. Similar to other studies [5], we observed that MRSA and MSSA isolates were 100% sensitive to vancomycin and MIC ranged from 0.5–1 μ g/ml. The incidence of MDR pathogens was quite high in our study; investigators have stated that MDR is usually a consequence of management based on empirical broad spectrum antibiotics. Thus, appropriate and judicious use of antibiotic to treat VAP, empirically, timely awareness and intervention can potentially reduce VAP and thus suffering in these patients [33]. The widespread use of over the counter antibiotics in India have led to huge selection pressure and MDR problem is likely to get substantially worse in the foreseeable future [25].

Carbapenem resistance in Gram-negative bacteria is an emerging worldwide challenge in the critical care settings. World Health Organization (WHO) in 2017 included carbapenem resistant Enterobacteriaceae (CRE), carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *A. baumannii* in the highest priority category [34]. The understanding if isolate is carpapenamase producer has significant epidemiological implications for monitoring local epidemiology and also lead to more effective treatment of infections [35]. In recent years, numerous genotypic and phenotypic assays for detecting carbapenemases have been developed. The advantages of phenotypic assays compared to genotypic tests are that they are substantially less expensive than genotypic tests [36]. The overall sensitivity and specificity of

mCIM test in this study was 98% and 44.6% respectively, and of MHT was 76.9% and 44.7% respectively. Our results showed that the mCIM is more accurate compared to MHT to detect MBLs. Here, we showed mCIM/eCIM had excellent sensitivity for the detection MBLs, sensitivity was 96.2% and the specificity was 83%. Our results are consistent with previous studies [35]. It is possible that new or truncated carbapenemase genes might not be identified consistently with the phenotype.

In general data on the dissemination of antimicrobial genes on India is scarce, especially regarding the prevalence of MBL genes among VAP. Worrying, in our study is that 58.6% of VAP patients had high resistance to carbapenems. Of the 172 isolates, 21.5% exhibited the presence of *bla*_{NDM} genes and 17.4% exhibited the presence of *bla*_{VIM} gene. 8.7% isolates harbored both *bla*_{NDM} and *bla*_{VIM} genes. None of the isolates contained *bla*_{IMP} gene. Our study is in accordance to previously published ICMR report in which NDM was the most prevalent carbapenemases across the Indian AMR network [37]. In the present study, *bla*_{NDM} was harbored by 15 isolates of *A. baumannii*, 13 *K. pneumoniae*, five *P. aeruginosa*, three *E. coli* and one *P. mirabilis*. All the isolates showed high resistance against all antibiotics, except colistin and tigecycline. In another similar study, the most common MBL subtype was *bla*_{IMP} which is contrasting to our findings [38].

A. baumannii plays a major role in VAP and acquired MBL is emerging as one of the important mechanisms of resistance [6]. In present study, 45.4% isolates of *A. baumannii* were MBL producers, 32.7% were VIM positive, 27.2% were NDM positive and 14.5% were positive for both. Many other studies reported higher NDM positivity (60–80%) rate among *A. baumannii* isolates of VAP patients [39]. In a similar study on molecular analysis showed that *A. baumannii* and *P. aeruginosa* isolates were positive for VIM gene, whereas IMP was not detected in any of the isolates [40]. In a laboratory based study, 100 MDR isolates from ICU harbored *bla*_{IMP} (89%), *bla*_{VIM} (51%) and *bla*_{NDM-1} (34%) [41]. There is evidence that multiple clones of metallo-beta-lactamase of *P. aeruginosa* are circulating in India [42]. A study from Pune, India reported VIM-type in 40% and NDM-type in 10% carbapenem-resistant *P. aeruginosa* isolates. This study corroborates with our findings in relation to NDM, while for VIM positivity rate is lesser than our study [43]. In the present study, *K. pneumoniae* harbored NDM (28.8%), VIM (17.7%) and 13.3% were positive for both VIM and NDM gene whereas *E. coli* only three isolates carried NDM gene. Contrary to our findings, a study from North Indian corporate hospital reported NDM gene to be more prevalent in *E. coli* than *K. pneumoniae* [37]. In present study VIM type MBL was associated with more mortality compared other MBL. The exact cause of this could not be identified. Understanding the mechanisms causing carbapenem resistance in Gram negative bacteria has important clinical implications and results in different prevention measurements and individualized antibiotic therapy. Infection control committees in hospitals should ensure robust antibiotic stewardship programs and must focus on eliminating or minimizing the incidence of VAP through preventive techniques like VAP bundle, hand hygiene, proper suctioning methods and regular fumigation of ICUs and disinfection of ventilators.

Conclusions

To the best of our knowledge this is the first analysis of carbapenem-resistant Gram-negative bacilli carrying multiple MBL genes responsible for VAP in India. This study shows the high prevalence, diversity of patterns and coexistence of MBL genes in the Gram negative isolates from VAP patients pose risks of possible transmission to the environment, other animals and human. MBL production in VAP patients and its association with mortality is worth investigating in the future.

Supporting information

S1 Raw images. Raw images used in Figs 1 and 2.

(PDF)

S1 File. Data used in the manuscript.

(XLSX)

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— Fundamentals of —
PERIODONTOLOGY

RAMESHWARI SINGHAL



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Fundamentals of **PERIODONTOLOGY**

RAMESHWARI SINGHAL

Fundamentals of Periodontology is a comprehensive, up-to-date, and user-friendly textbook designed to provide undergraduate students a platform to prepare for academic and competitive examinations as well as help busy dental clinicians upgrade their knowledge and give their patients the highest level of periodontal care. In addition, this book serves as a scientifically sound and practical clinical tool for postgraduate students, private practitioners, and periodontists.

Highlights

- Provides comprehensive coverage of essential topics in periodontics
- Specific learning objectives are defined clearly at the beginning of each chapter for better orientation of the topic
- Complex concepts are simplified and given in bullet points for easy understanding
- Salient points which are academically important are marked with an asterisk (*)
- Practical tips and related studies are given in special boxes for quick recall
- Features flowcharts, tables, clinical pictures, radiographs, and line illustrations to create visual memory of the science and practice of periodontics
- Offers detailed illustration of surgical techniques with step-by-step clinical photographs
- Includes recent concepts and emerging trends in diagnosis and treatment of various periodontal conditions

Rameshwari Singhal is currently serving as Associate Professor in Department of Periodontology, King George's Medical University, Lucknow. She is an academician, teacher, and researcher besides being an excellent dental surgeon. She has high-impact peer-reviewed indexed articles to her credit and has delivered lectures both nationally and internationally at scientifically acclaimed platforms.

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प्लेडलेट्स की कमी

भांतियाँ एवं समाधान

डॉ. ए. के. त्रिपाठी

Dental Implant Supported Thumb Prosthesis with Friction Fit Retention System

Mahimaa Gupta, BDS, Saumyendra V. Singh, MDS, Deeksha Arya, MDS, Brijesh Mishra, MCh, Rishabh Keshri, BDS, Pooran Chand, MDS

ABSTRACT

Introduction: An amputated thumb causes aesthetic deficit and functional loss. Reconstruction can be surgical or prosthetic. A small residuum leaves little scope for rehabilitation with suction-retained prosthesis. Prosthetic management requires implant placement or distraction osteogenesis to be successful.

This report presents the use of bone-anchored dental implants to support a prosthesis for rehabilitation of an amputated thumb.

Case Description: Satisfactory osseointegration of a dental implant placed in the amputated right pollex of a 24-year-old woman was achieved, after a two-stage surgical procedure. A healing abutment, which is normally placed transitionally after second-stage surgery, was modified to create a permanent friction fit coping. This was used to retain the silicone thumb.

Discussion and Conclusions: The study to some extent established off-the-label use of dental implants in rehabilitating amputated digits. Also, the friction fit retention system proved to be a cost- and armamentarium-effective method of retaining thumb prosthesis for cases with small residuum.

Clinical Relevance: This report describes a procedure for two-stage surgical placement of an osseointegrated dental implant in an amputated thumb with fabrication of prosthesis, which was effectively retained by a modified healing abutment. (*J Prosthet Orthot.* 2022;34:e103–e108)

KEY INDEXING TERMS: amputation, CAD-CAM, cost-effective, healing abutment, silicone

Digit amputation is one of the more common injuries of the upper limbs.^{1,2} Aesthetic embarrassment to the patient is immense, with psychosocial implications. Impairment in hand function can occur, leading to decreased grip and inability to perform precise movements and engage in certain tasks.^{3,4}

There are several reconstructive and rehabilitative techniques available for such patients, varying from adhesive retained silicone prosthesis, transplantation surgeries, and bionic fingers.^{5,6} Each technique has its own attendant advantages and disadvantages.

With the advancement of microsurgical techniques, many centers offer autologous reconstruction of the digit and replantation. However, when this fails or when replantation is not an option due to the mechanism of injury, techniques such as finger pollicization or toe-to-hand transfer offer good reconstructive alternatives. Manrique et al.⁷ reported that, in circumstances when these options are not feasible and patients desire improved

digit functionality and aesthetics, an osseointegrated implant-supported finger prosthesis is an option.

Li et al.⁸ wrote that implantation of an osseointegrated percutaneous prosthesis provides a reconstruction alternative for thumb amputation without sacrificing donor tissues. The concept of osseointegration can be defined as direct anchorage of an implant into the skeleton by induction of bone healing at the implant surface.⁸

One of the first such reported cases was a two-stage reconstruction aimed at support of thumb prosthesis from the first metacarpal through an osseointegrated titanium implant described by Lundborg et al.⁹ Thus, the successful use of osseointegrated implants with differently designed abutments for anchorage of prosthesis has been frequently reported.

The purpose of this case report is to describe the rehabilitation of an individual with a thumb amputation, using staged surgical placement of an osseointegrated dental implant and a simple but innovative friction fit design for prosthesis retention.

CASE DESCRIPTION

A 24-year-old unemployed woman reported to the department to have a new thumb prosthesis made. A history of trauma from a chaff cutting machine during childhood, which led to right thumb amputation, was elicited. The patient reported getting a suction fit thumb prosthesis made 2 years back, which was aesthetic but unretentive. As a result, the patient stated a clear desire for a snug-fitting new prosthesis.

Clinical examination revealed constant flexion of proximal interphalangeal joint of the right index finger, probably caused

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by the same trauma (Figure 1A). Skin over the residuum was thickened, firm, and sensate. Radiographic examination revealed that the thumb was amputated through the first metacarpal with a tiny piece of proximal phalanx. Metacarpophalangeal joint was preserved and functional.

The patient was right-handed. Functional deficit involved reduced ability to grasp objects and pinch. Adduction, opposition, extension, and abduction of the pollex were affected. However, as the trauma had occurred a long time ago, the patient had adapted to these deficits. The primary goal for which the patient had reported was aesthetic rehabilitation with a well-fitting prosthesis. She had no history of any systemic disorder.

The case was planned in coordination with Department of Plastic Surgery. All available treatment options were explained to the patient. She refused any treatment that would cause donor site deficit. Considering her desire, opinion, and the small residuum, an implant-retained thumb prosthesis was decided upon as the treatment of choice. Written informed consent was obtained from the patient. The possibility of aesthetic and functional deficit remaining after rehabilitation was explained. Possible complications of the procedure were communicated. Her blood investigations were normal.

The plan was to place a titanium dental implant in the metacarpal for prosthesis retention. Cone beam computed tomography (CBCT) revealed that the bone was 39.1 mm in length and



Figure 1. A, Amputated thumb. B, Cone beam computed tomography of amputated thumb.

10.5 mm in width (at the widest region, Figure 1B). Considering the topography of the metacarpal (it shows a definite taper from base upwards), a 4.5-mm diameter \times 14-mm length Cowell SLA-SH dental implant (Seoul, South Korea) was selected. Two-stage implant surgical procedure was planned and explained to the patient. Although this would lengthen the duration of treatment compared with the single stage, chances of osseointegration of the submerged fixture were higher.

TECHNIQUE

Surgery was performed in operatory with strict asepsis under local anesthesia. The right thumb digital nerve was anesthetized with 2% lignocaine without epinephrine. Skin incision was made at the implant site, and full thickness flap was elevated. The position and angulation of osteotomy was guided by radiographs to ensure parallelism to the long axis of the metacarpal. Sequential drilling with progressively larger drill sizes was done at low speed in the presence of a coolant to create an appropriately sized osteotomy. Next, the implant was manually torqued into a marginally subcrestal position. A satisfactory torque of 40 N-cm was attained following which cover screw was placed (Figure 2).

Radiographs were taken in palmar and lateral views to verify correct placement of implant. Peri-implant connective tissues were reduced to a thickness of approximately 2 mm to prevent implant movement, and flaps were repositioned. Nylon sutures were placed with pressure dressing, which was repeated after a week. Postoperative medication consisted of an anti-inflammatory analgesic (ibuprofen) and an antibiotic (amoxicillin and clavulanic acid) regimen for 7 days. Healing was uneventful, and sutures were removed after 2 weeks. Instructions were given for operated site hygiene, cold fomentation, and watching out for warning signs such as pain, oozing, or wound dehiscence.

At the 4-month follow-up, radiographs revealed satisfactory osseointegration of implant. There was no inflammation, pain, or other complication (Figure 3A). Second-stage surgery was scheduled. An incision was given in the region of the cover screw. The cover screw was located, removed, and replaced with a healing abutment (2HS4572; Cowell Dental Implant, Seoul, South Korea) of 4.5-mm diameter and 12-mm length. The dimension

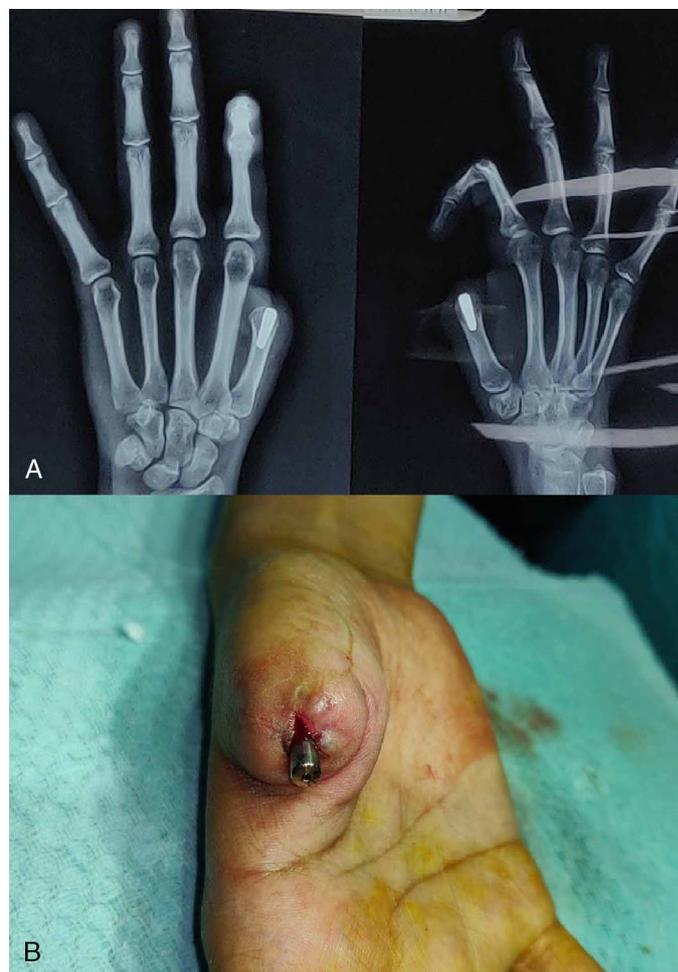


Figure 3. A, Radiograph at 4 months, lateral and palmar view. B, Second stage surgery, healing abutment placed.

of the slightly tapered abutment was chosen so as to project clearly out of the residuum for utilization in retaining the prosthesis. A shorter abutment would have been less retentive for the prosthesis, and a longer one would have created an unfavorable implant prosthesis ratio. Sutures were placed and patient instructed to avoid contact with the operated area until their removal after a week (Figure 3B).

The patient was recalled for making an impression of the residuum (implant-level impression) after 3 days of suture removal. A special tray was made in the shape of a cylinder with the help of modeling wax (Pyrex Modeling Wax, Pyrex Polykem). A transfer coping was connected to the implant, and an open-tray impression was made with additional silicone impression material (3M ESPE, St Paul, MN). An implant analog was connected to the transfer coping, and a model poured in type 4 die stone (Kalrock; Kalabhai, Mumbai, India).

Then, the healing abutment was modified to be used as an attachment for friction fit prosthesis. Its undercuts and taper were removed with the help of highly compressed, fine-grain carbide burs and finish achieved with the help of silicon rubbers (Vitality Laboratory Rotary Instruments Kit). A metal alloy coping designed with friction fit over the altered healing abutment was fabricated



Figure 2. Implant with cover screw.

(Figure 4). A white, heat-polymerized acrylic housing was prepared over the coping as an interface between the metal coping and silicone thumb. Several fins were made in the housing to make it mechanically retentive to the prosthesis (Figure 5). A properly textured and characterized wax pattern of the right thumb was sculpted in modeling wax (Pyrex Modeling Wax; Pyrex Polykem) over the acrylic housing on the residuum model. Then, the modified abutment was connected in situ for trial of the wax thumb on the patient.

After some minor modifications, the pattern—acrylic housing—metal coping assembly was again seated on the residuum model (on the healing abutment), invested and dewaxed to create a two-part mold (superior and inferior). The acrylic housing was cleaned thoroughly, and the platinum primer (G611; Technovent Ltd, South Wales, United Kingdom) was applied to improve its adhesion to silicone. Separating media was applied; the mold space was packed with intrinsically colored medical grade silicone (Technovent Ltd, South Wales, United Kingdom), which was processed conventionally. Extrinsic characterization helped achieve lifelike appearance of the prosthesis.

OUTCOME

A well-retained and stable prosthesis was obtained. The range of movement as assessed by Kapandji rule of 10, wherein the patient was asked to touch 10 specific finger areas with the tip of the thumb, was 8.¹⁰ The ability of the patient to pinch and grasp objects was improved, with limited improvement in overall mobility. Patient-assessed aesthetic outcome was 9 on a visual analog scale of 10 (Figure 6). However, on greater abduction, a slight opening at the prosthesis margin could be seen.

Maintaining proper hygiene of the peri-implant tissues with a soft brush, lukewarm water, and soap at least once a day was emphasized.¹¹ Follow-up was done on day 7 and day 30 of delivering the prosthesis. From then on, the patient has been followed up uneventfully at 3-month intervals. More than a year has elapsed since delivering the prosthesis. Radiograph taken at 12 months of baseline revealed no significant changes in implant-bone interface.

DISCUSSION

Digit amputations may be caused by work-related accidents, road traffic accidents, animal bites, and systemic diseases including

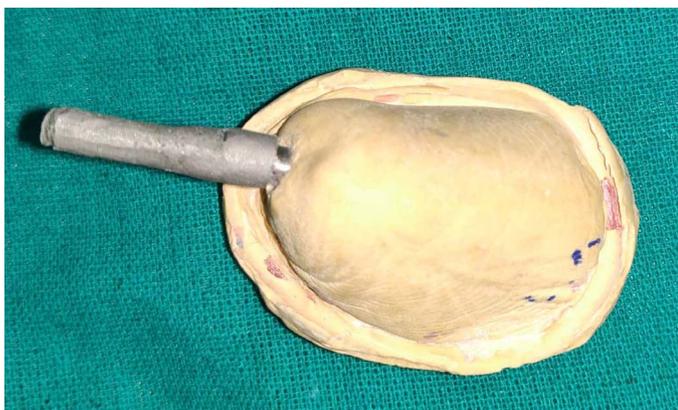


Figure 4. Coping over altered healing abutment.



Figure 5. Acrylic housing incorporating coping in (A) lateral and (B) superior views.

diabetes. The thumb is an important part of the hand used to perform daily tasks including pinch, grip, grasp, and precision handling. From a functional standpoint, it is the most important digit, performing the movements of opposition and apposition.

Amputation of the first digit can have a negative functional, aesthetic, and psychological impact. Reconstruction or rehabilitation is definitely desirable. Surgical replantation is most desirable but not always possible. Autologous transplantation or reconstruction is often complex, financially demanding, and comprises multiple procedures.¹² Such digits can be compromised in shape and size and therefore lead to dissatisfaction.¹³ Distraction osteogenesis can effectively increase functional length of the amputated digit, but apart from a long treatment procedure, possible sequelae include joint stiffness and nerve injury.¹⁴

It has been established that patients benefit from socket type of prostheses based on suctional retention. However, such prosthetic digits are not always stable, especially when the residuum

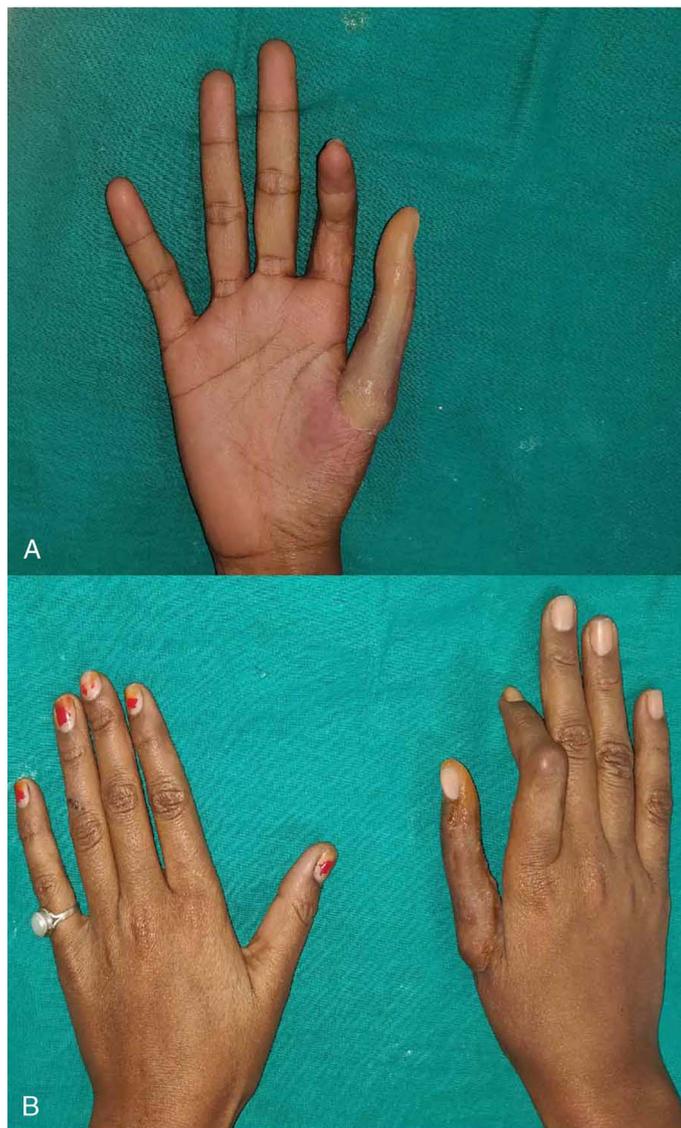


Figure 6. Finished prosthesis: (A) ventral and (B) dorsal view.

is small. A split ring is sometimes added to the socket-type thumb prosthesis at prosthesis-residuum junction to gain added retention and camouflage margin, but retention achieved is questionable, especially when the residuum is compromised in size.¹⁵ Prosthesis retention by means of osseointegrated titanium fixtures has been established as a viable solution in such cases.¹⁶

The concept of osseointegration has been applied in craniofacial reconstruction for many years, with few studies reporting prosthetic implant use for hand reconstruction. Osseointegration has also been defined as direct attachment of an implant to the bony residuum by formation of bony tissue around the implant, without growth of fibrous tissue at bone-implant interface. This allows reconstruction of the missing digit(s) when autologous tissue is not available, or when the patient desires to undergo a less complicated and invasive surgical intervention. High grip and pinch strengths, with good Jebsen Hand Function Test scores, have been reported with implant-supported prosthesis.⁷

Manurangsee et al.⁴ reported a two-stage reconstruction procedure with osseointegrated titanium implants in three patients fixing a finger prosthesis to the proximal phalanx. The first stage included implantation of the titanium fixture into the medullary canal of the proximal phalanx. After a 3-month rest period to allow the fixture to firmly osseointegrate, a skin-penetrating abutment was connected to the fixture, to which the prosthesis was attached. They reported minimal skin problems, some tactile sensibility, improved motor function, better comfort, and good cosmetic results as outcomes of the rehabilitation.⁴

Data published by Li et al.⁸ showed that osseointegrated thumb prostheses wearers achieved 66% grip strength and 71% lateral pinch strength when compared with hand function of the unaffected side. These results were comparable to great toe-to-thumb transfers, which had grip strength of 77% and pinch strength of 67%, compared with the normal side. The osseointegrated implant-retained thumb prosthesis has been reported to offer better aesthetic and functional results compared with adhesive or suction-retained prosthesis, and allow some pressure perception and tactile sensation, facilitating surface and texture distinction.¹⁷

Specific titanium fixtures are in use for retaining finger and toe prostheses.⁹ However, these are costly and difficult to obtain, in contrast to dental titanium counterparts. Further, the shape and dimensions of the metacarpal is suitable for placing a dental implant. The Cowell sand-blasted, large grit-etched, super hydrophilicity activated surface treatment (SLA-SH) dental implants were selected for this off-the-label purpose because this surface design has been reported to accelerate osseointegration and maximize bone implant interface.¹⁸

Retention is a deciding factor in the success of any prosthesis, and various mechanisms have been used to retain the artificial digit. O ring attachment systems have been used, but they add to the cost of treatment.¹⁹ A cast silver palladium two-bar system screwed to the implant body was used to retain an osseointegrated thumb prosthesis. Clips in an acrylic substructure were incorporated in the prosthesis. The clips had a snap fit on the bar. However, this system was bulky and not cost-effective.²⁰

Friction fit retention has been defined as a form of fastening between two tight-fitting mating parts that produce a joint by friction after the parts are pushed together. It was used in this study because of being cost-effective, by virtue of the healing abutment being modified as the friction fit component for retaining the coping. The healing abutment is an essential part of the armamentarium needed for rehabilitating any dental implant patient, as it aids in proper healing and attachment of peri-implant soft tissues. Costly retentive systems such as the O ring, bar, and clip were not needed. Fins were created in the acrylic substructure to provide added retention to the silicone toe, preventing accidental separation.

Areas of concern for such prosthesis include hygiene maintenance of the peri-implant area, where it is common to observe accumulation of debris and exfoliated cells. If cleaned improperly, this may lead to inflammation, infection, and implant failure. Further, the response of dental implants to a foreign environment and different sets of microorganisms needs further study.

Other issues can include failure of implant osseointegration, mechanical implant failure, implant failure due to overload, and cost compared with suction-retained thumb prosthesis. Persons with diabetes, smokers, and individuals who perform major heavy manual labor may not be good candidates for such rehabilitation. Silicone prostheses are subject to wear and tear, needing replacement.¹³

CONCLUSIONS

Dental implant-supported friction fit retained thumb prosthesis offers a retentive, functional, cost-effective, and convenient outcome.

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Dating

DENTAL TECHNIQUE

Technique to prevent fracture of a partial auricular prosthesis mold

Saumya Kapoor, MDS,^a Saumyendra V. Singh, MDS,^b Deeksha Arya, MDS,^c and Pooran Chand, MDS^d

Partial auricular defects are a result of certain congenital disorders, trauma, or tumors. The loss of an ear, an organ aiding in acoustics and esthetics, affects social behavior and psychology.¹ Management of such defects can be either surgical or prosthetic, depending on the patient's age, medical and financial circumstances, and the condition of the residual tissue. When surgical reconstruction is not indicated, a prosthesis is the best management option. The procedure for fabricating a complete silicone auricular prosthesis normally involves a 3-piece stone mold to facilitate characterization, prevent prosthesis tearing on retrieval, and prevent mold fracture.² Direct printing of a virtually designed prosthesis by using a high-resolution 3D silicone printer has been described.³ The technique reproduces major and minor anatomic surfaces of the prosthesis and has also been applied to nasal prosthesis fabrication.⁴ However, the current scope of characterization is restricted with these techniques, limiting the esthetics of the prosthesis. The initial cost associated with digital equipment is another disadvantage, and the accuracy and applicability of digital technology for facial prosthesis fabrication is still unclear.⁵

One of the difficulties faced during fabrication of a partial auricular prosthesis with the 3-piece stone mold technique is fracture of the elevated part of the mold, which fits into the natural concha and triangular fossa

ABSTRACT

One of the difficulties faced during the essential and demanding step of fabricating a mold for a partial auricular prosthesis is the fracture of its most elevated part, which engages the remnant concha and triangular fossa region, because of the presence of excessive convolutions and undercuts. This technique describes a 4-part mold for a partial auricular prosthesis in which the most elevated portion is poured separately, thereby preventing mold fracture. (J Prosthet Dent 2019;■:■-■)



Figure 1. Partial auricular defect.

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Figure 2. Partial auricular pattern.

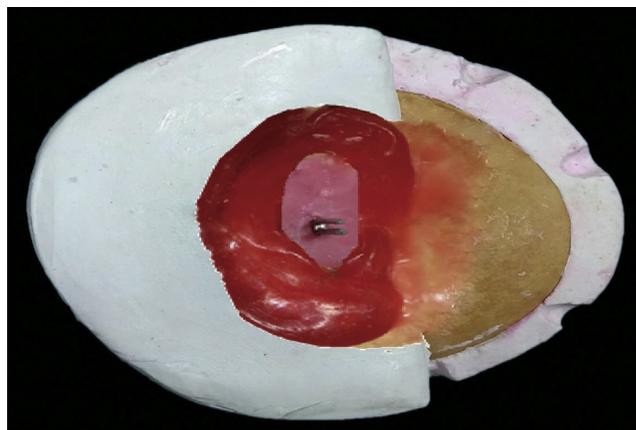


Figure 3. First, second, and third parts of mold poured.



Figure 4. Four-part mold separated.



Figure 5. Separated acrylic resin third part of mold with dowel pin.

region. The region has extreme convolutions and undercuts that are susceptible to fracture. The technique developed provides a straightforward and rapid method of preventing mold fracture and uses materials available in a dental laboratory.

TECHNIQUE

1. Make an impression of the residual auricle (Fig. 1) with the surrounding tissue by following conventional methods and pour it in die stone (Kaldent; Kalabhai Karson Pvt Ltd). Fabricate the pattern by following conventional steps (G-120; Factor II Inc) (Fig. 2).
2. Create the first 2 parts of the mold in the conventional manner using white die stone (Orthokal; Kalabhai Karson Pvt Ltd), involving the base and helix region of the wax pattern.
3. Apply a thin layer of separating medium on the first 2 parts of the mold and any portion of the partial ear model which is not to be covered by silicone.
4. Mix autopolymerizing resin (Rapid Repair Cold Cure; DPI) in the advised ratio and allow it to reach the doughy consistency. Pack this material into the concha and triangular fossa region to form the third part of the mold.
5. Place a double dowel pin with a single head (Dental Die Pin; Nebula Industries Co, Ltd) in the doughy acrylic resin such that only the head of the pin is in the resin (Fig. 3).
6. Make the fourth and final pour with white die stone (Orthokal; Kalabhai Karson Pvt Ltd), covering the protruding sleeve of the dowel pin, the remaining wax pattern, and the first, second, and third parts of the mold to the requisite thickness.
7. Follow the regular dewaxing protocol and separate the parts of the mold (Fig. 4). The acrylic resin third pour will have the dowel pin (Fig. 5), while the sleeve will be encased in the fourth part of the mold. This allows accurate duplication of the concha region in acrylic resin without the risk of fracture of a stone mold. The acrylic resin can be easily positioned in its designated place and indexed to the fourth pour by the dowel pin.



Figure 6. Prosthesis in place.

8. Proceed with packing and polymerization, separating and joining the third and fourth mold parts as required (Fig. 6).

DISCUSSION

This article details a technique for facilitating the fabrication of a 4-part partial auricular prosthesis mold. Part of the mold engaging the concha region is fabricated in autopolymerizing resin. The advantage of using autopolymerizing resin lies in providing rigidity and strength in the vulnerable concha region of the mold, thus preventing the fracture of the mold in this area and facilitating the retrieval of an intact prosthesis. Preservation of the mold is ensured for future prosthesis remakes. The dowel pins allow accurate positioning of the fourth part of the mold to the acrylic resin index.

Limitations of this technique include an increase in the number of steps and the additional time and armamentarium required to fabricate the mold.

SUMMARY

The article describes a time-efficient and convenient method for preventing the fracture of a partial auricular prosthesis mold by pouring the conchal and triangular fossa portion in autopolymerizing resin, thereby converting the conventional 3-part auricular prosthesis mold into a 4-part mold.

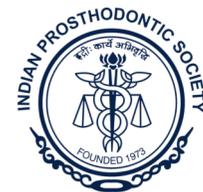
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Medknow

Mechanically retained functional prosthetic rehabilitation of partial lip necrosis: A rare clinical report

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Abstract

Prosthetic rehabilitation plays a crucial role in restoring patients with facial defects to normalcy. Although comprising a small proportion, lip defect plays a pivotal role in drastically diminishing the quality of life of the patient, both functionally and socially, with dwindling confidence and self-esteem. Patients may experience speech impairment, uncontrolled drooling, and unesthetic appearance. In addition, constant exposure of tissues to air leads to drying and crusting of lips. This rare case report of a patient with partial lip necrosis describes her functional, mechanically retained prosthetic rehabilitation, which improved phonetics, esthetics, and function without the need of additional retentive features, increasing convenience and ease of use by the patient and at the same time cutting down cost.

Keywords: Functional rehabilitation, lip necrosis, mechanically retained, silicone

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INTRODUCTION

Prosthetic rehabilitation plays a crucial role in restoring patients with facial defects to normalcy. Although comprising a small proportion, lip defect plays a pivotal role in drastically diminishing the quality of life of patients, both functionally and socially, with dwindling confidence and self-esteem. Lip defects could be of congenital, surgical, or traumatic etiology. Lip cancers constitute 1.4% of oral cancers.^[1] Cases of loss of lip due to necrosis are hardly reported. Normally, surgical reconstruction is the primary treatment rendered for lip defects. Vascularized pedicle flaps from the iliac crest, scapula, fibula, radial forearm, and temporalis are utilized for reconstruction.^[2,3] Surgical rehabilitations, though desirable, are not always feasible for reasons such as compromised tissue bed and risk of

tumor recurrence. In such cases, prosthetic rehabilitation plays a fundamental role in rehabilitation.^[4]

Importance of lower lip defects in speech disarticulation has been elucidated by Robinson and Niiranin.^[5] Other problems experienced include uncontrolled drooling, unesthetic appearance, and constant exposure of tissues to air, leading to drying and crusting. As lips play a fundamental role in consonant phonemic production, reduction in speech intelligibility occurs, especially with bilabial and labiodental phonemes.^[6] Comparatively favorable prosthetic outcome is impeded by tissue resiliency, continuous lip movement, limitations of fabrication material, paucity and inadequacy of anatomical undercuts, and variable patient compliance. Various modes of retention include use of adhesives,

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implants, or intraoral prosthetic attachment with magnets. This report discusses the fabrication of mechanically retained silicone inferior lip prosthesis.

CASE REPORT

A 35-year-old female patient was diagnosed with central hemangioma of the mandible about a year back [Figure 1], for which, sodium tetradecyl sulfate was injected into the lesion thrice. Although the lesion subsided, posttreatment necrosis developed involving the right part of the lower lip with some involvement of the upper lip extending up to the ala of the nose. Surgical reconstruction was not immediately advisable because of questionable vascularity of recipient site, and the patient was referred to the department of prosthodontics for prosthetic management. The chief complaint of the patient was unesthetic appearance and drooling of saliva due to partially absent lower lip [Figure 2].

A preliminary combined intraoral and lower lip impression was made with irreversible hydrocolloid impression material (Zelgan; Dentsply, Gurgaon, Haryana, India)

and poured in type III stone (Keldent; Kalabhai, Mumbai, Maharashtra, India), taking care to record the lip without distortion or displacement. This was achieved by increasing the flowability of alginate and loosely confining the lip part of the impression. This was followed by fabrication of a custom tray in acrylic resin (Pyrax; Pyrax Polymers, Roorkee, Uttarakhand, India) with a double spacer. This tray was used for secondary intraoral impression [Figure 3] in addition silicone (Elite HD; Zhermack, Badia Palesine, Italy) and poured in white die stone (Orthokal, Kalabhai, Mumbai, Maharashtra, India) [Figure 4]. One-millimeter thick polyvinyl chloride (PVC) thermoplastic sheet (Soft-tray sheets; Ultradent, South Jordan, Utah) was adapted on the remnant lower lip model to aid in the retention of the trial pattern, which was sculpted in wax on the model and evaluated on the patient in subsequent appointments. The PVC thermoplastic sheet was extended over the entire lower lip till the commissures on either side, till the shadow of mentolabial sulcus externally, and upto the labial vestibule internally, to aid in mechanical retention. This would also facilitate camouflage of future prosthesis margin in areas which are less remarkable.

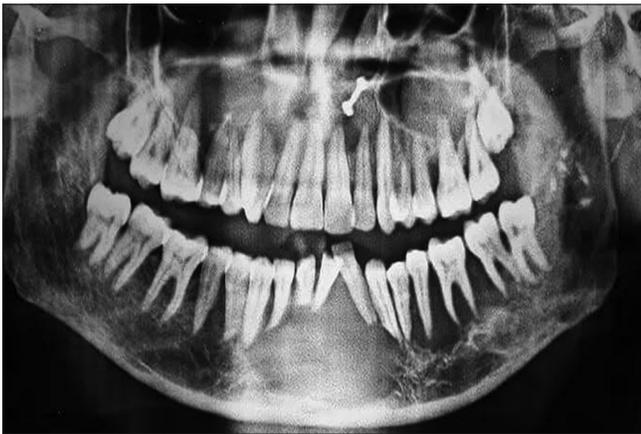


Figure 1: Central hemangioma of the mandible



Figure 2: Postoperative view after lower lip necrosis



Figure 3: Combined intra- and extraoral secondary impression



Figure 4: Model of lip defect

The wax pattern was modified to develop profile, shape and merge margins of prosthesis with natural tissue, and imitate wrinkles, skin creases, etc. [Figure 5]. To further improve the adaptation and retention, a wash impression was made in light body addition silicone (Elite HD; Zhermack, Badia Palesine, Italy) on the wax pattern itself. This relined wax pattern was again poured in white die stone (Orthokal, Kalabhai, Mumbai, Maharashtra, India) followed by marginal sealing, thinning, and merging with adjacent tissues [Figure 6]. This pour formed the first part of the mold into which keys were made for indexing. A three-part mold was necessary to achieve better characterization of different lip parts and removal of prosthesis without tearing. The second and third pours were preceded by careful application of separating media. For second pour, the boxed 1st part of mold was poured up to the inner lip line; keys were again made in this pour, followed by the third pour which was made to cover both previous pours. Dewaxing was carried out at 100°C for 5 min. The mold was cleaned properly [Figure 7]. Shade matching was done with the help of a digital spectrophotometer (Orthokal, Kalabhai, Mumbai, Maharashtra, India), and an appropriately colored

matched silicone (Technovent M511; Technovent Ltd.) was placed on to the different parts of the mold after applying a silicone-releasing agent (Orthokal, Kalabhai, Mumbai, Maharashtra, India) and polymerized as per instructions. Prosthesis was removed from investment [Figure 8] and finished and extrinsic staining was done, where required. Prosthesis was delivered to the patient 18 months back [Figure 9], who was satisfied by improved esthetics, lessened drooling, and enhanced speech intelligibility and retention, as recorded on the 3-monthly recall appointments. However, interruption of seal between prosthesis and movable soft tissues of the lip and cheek, sometimes resulted in margin show-through. Furthermore, extension of the prosthesis over the entire lip slightly increased the contour of the remaining natural portion of the lower lip.

DISCUSSION

Lip is a tactile organ which contributes not only to the process of articulation but also in creating oral seal. Its importance in attractiveness, identification of an individual,



Figure 5: Pattern: frontal and profile views

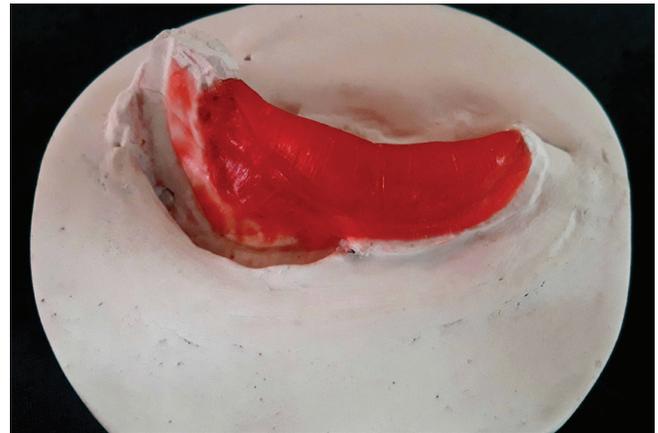


Figure 6: First part of the mold



Figure 7: Three-piece mold



Figure 8: Retrieved prosthesis from the mold



Figure 9: Final prosthesis after extrinsic coloring: frontal and profile views

and communication is undeniable. Any lip deficiency naturally leads to speech impairment and drooling of food and saliva.^[6] The prominent location makes it impossible to be missed by the eye. Therefore, a meticulous and swift correction of the defect is imperative to the patient's psychological well-being.

Restoration of such a defect poses a challenge in obtaining proper coloration, texture, and masking the margins of the prosthesis. Mobility of the tissues neighboring the defect compounds the problem. Engaging anatomical undercuts is not always feasible. Possible methods to mask margins include extending border beyond the midline, placement of margins in natural depressions, and thinning the margin. As described earlier, this prosthesis covered the entire lower lip to use the commissures and mentolabial sulcus for margin masking, increasing the retention of the prosthesis. However, the risk of making a bulky lip with this technique cannot be denied.

Another possible complication is salivary influx, breaking prosthetic seal, as well as causing show-through of margin while speaking, sucking, and smiling. Some methods utilized for retention of lip prosthesis include resin-retentive elements bonded to anterior mandibular teeth – Cheng *et al.*,^[7] placement of ball attachments on obturator's labial surface for retaining the upper lip – Oki *et al.*,^[8] and use of magnets and micro extracoronary resilient attachment (ERA) attachments – Zeno *et al.*^[4,9] Mukohyama *et al.*^[10] used lip plumper-like intraoral devices to correct mandibular lip posture skewed by marginal mandibulectomy.

Use of attachments is justifiable when no other retentive mean remains as these would have their own set of complications on the hard tissue to which the lip is anchored, make insertion and use complicated, and be

more feasible for the upper lip which is less mobile than the lower one. Gaining retention by increasing prosthesis surface area to intraoral sulcus and mentolabial sulci and extending coverage over the entire lip can be explored. Any deficiencies in retention experienced due to tissue mobility and salivary ingress may be supplemented by adhesives, though this was not done here, as a matter of patient preference (she wanted to avoid the added expenditure involved).^[11] However, such prosthesis can only be possible if about half of the lower lip is present.

CONCLUSION

Prosthetic rehabilitation plays a crucial role in the correction of lip defects where surgical reconstruction is not feasible, particularly in the rare case of necrosis described in this report. The prosthesis enhanced esthetics and aided functional and psychological recovery of the patient. This clinical report describes step-wise fabrication of the prosthesis, which was solely mechanically retained, was convenient to use, was economical, and was easy to fabricate.

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Conflicts of interest

There are no conflicts of interest.

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Spectacle Cord-retained Oculo-Orbital Prosthesis

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ABSTRACT

Retention of an orbital prosthesis plays a key role in treatment success and patient acceptance as does aesthetics. Though numerous retentive aids are available such as implants, adhesives, etc, the cost, surgical aspect, difficulty of use and allergic potential may compromise efficiency. This report describes the case of an 11-year post-enucleation poor retinoblastoma patient, in whom an unfavourable defect leads to a major prosthetic challenge (from point of view of retention and camouflage). This report describes a simple, economical, and user-friendly approach to obtain satisfactory retention and camouflage for such patients with spectacle cords and customised spectacles.

Key Words: *Oculo-orbital prosthesis, Spectacle, Cord.*

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INTRODUCTION

A facial defect compromises an individual's life by introduction of elements like facial disfigurement, social stigma, psychological strain, and economical predicament. Hence, successful rehabilitation plays an integral role in acclimatisation of patient to a more normal life. An inconspicuous prosthesis plays a major role in restoring aesthetics; and equally significant is the achievement of retention. Inadequate retention is associated with patient distress, prosthesis neglect, and discardment. Multiple methods have been described in literature to achieve adequate retention for orbital prosthesis including use of adhesives, magnets, stud attachments, and implants.¹⁻⁶ While some methods have expense as a limitation; for others, surgical intervention is the major pitfall.

In childhood, retinoblastoma is one of the most frequently encountered tumors.⁷ It is managed predominantly with the help of enucleation and adjunctive radiotherapy and chemotherapy. Enucleation creates a volume deficit, which is managed with the placement of both implant and prosthesis.⁸ Failure of early prosthesis wear can contribute to development of socket contracture, which constitutes an integral component of the post-enucleation socket syndrome (PESS).⁹ Management of socket contracture depends on severity of the condition including techniques like anterior lamellar repositioning, mucous membrane grafting, and free vascularised radial forearm flap.^{9,10}

CASE REPORT

An 11-year male patient reported to the Department of Prosthodontics with the chief complaint of unaesthetic facial appearance, due to loss of left eye. He had been diagnosed with retinoblastoma of left eye about two years back, which was managed by enucleation surgery and chemotherapy. At post-surgery, as a result of not wearing an ocular prosthesis/conformer, patient developed PESS and presented with fused upper and lower eyelids for prosthesis fabrication. He was referred to the Department of Plastic Surgery for creation of a favourably sized defect for prosthesis retention and aesthetics. Unfortunately, the surgeon removed both upper and lower eyelids, and covered the socket defect with a split thickness graft, leading to a large unaesthetic non-retentive defect (Figure 1a). For the lack of existing terminology, the prosthesis thus fabricated, and has been termed an oculo-orbital prosthesis.

A conventional impression of the defect and surrounding tissues was made with irreversible hydrocolloid impression material (Zelgan; Dentsply Pvt. Ltd.) and poured in type IV stone (Kalstone; Kalabhai). This was followed by adaptation of a 2 mm thick PVC thermoplastic sheet (Sof-tray sheets; Ultradent Products Inc) on the model to facilitate process of pattern trial by enhancing adaptability. A stock ocular prosthesis matching to the contralateral eye in terms of colour, shape and size of sclera and iris, was selected. Its position was adjusted anteroposteriorly, mediolaterally, and superioinferiorly with respect to normal gaze of the contralateral eye. Pattern was fabricated in clay and sculpted in accordance to the normal contralateral eye with subsequent modifications to obtain desired life-like contour and skin texturing by creating skin folds and stippling.

This was followed by thinning and merging of the margins with adjacent tissues.

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Investing of the pattern was done with addition of acrylic stump (Pyrax; Pyrax Polymers Ltd.) on the iris to avoid displacement of the ocular component of the orbital prosthesis, as displacement often leads to altered gaze of the prosthetic eye after processing. Dewaxing procedure was carried out at 100°C for 5 minutes. A digital spectrophotometer (e-skin; Spectromatch Ltd.) was utilised for shade matching. Colour-matched Room Temperature Vulcanising (RTV) medical-graded silicone material (Technovent M511; Technovent Ltd) was packed in the investment mould. Post-polymerisation, the prosthesis was deflasked, retrieved, and finished. Extrinsic staining was done for correction of any deficiencies and natural hair were stitched over upper and lower eyelids of the silicone prosthesis using 23 gauge syringe needle.

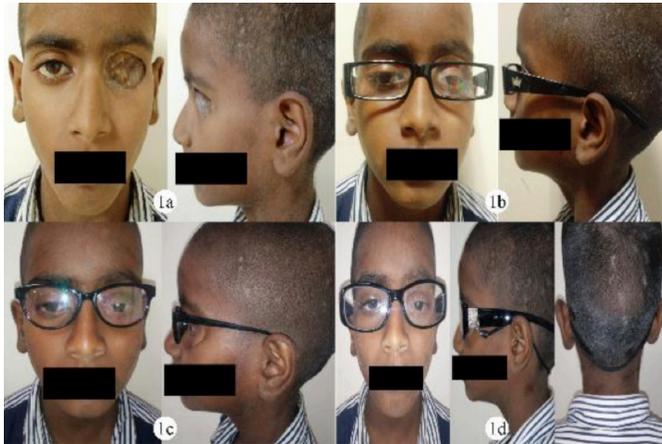


Figure 1: (a) Pre-rehabilitation frontal and profile views. (b) Mismatched spectacle 1 frontal and profile views. (c) Mismatched spectacle 2 frontal and profile views. (d) Matched spectacle with cord and prosthesis *in situ*: frontal, profile and back views.

To obtain optimum camouflage and retention, customised spectacles with elastic black nylon spectacle cord were utilised (Cord diameter was 0.3 cm and length 58.5 cm). The cord was fastened in proportion to the pressure needed to obtain a stable retentive comfortable prosthesis. For camouflage of the defect prosthesis margins (unfavourable surgical outcome left little place for their concealment), spectacles were used for the patient with wide rimmed frames. The importance of spectacle design in camouflage can be appreciated from Figures 1a through 1d. While spectacles in Figure 1b lead to lateral margin show through, the ones in Figure 1c revealed superior margin of the prosthesis. Spectacles in Figure 1d concealed the margins from all aspects. The spectacle shape was chosen to coincide with prosthesis shape, with its bridge as close as possible to the nose. The spectacle temple was chosen to be wide enough to create camouflage in lateral view. Photochromatic lenses were used for obscuring the prosthesis in daylight (Figure 1d).

Prosthesis was delivered to the patient. At the subsequent follow-up visits (now 1 year), patient and guardian expressed satisfaction with improved aesthetics, adequate retention and ease of wear.

DISCUSSION

Inter-disciplinary communication plays a major role in successful prosthesis rehabilitation. Proper case planning with involve-

ment of both the surgeon and prosthodontist is needed. Clear communication and understanding of factors, such as creation/preservation of undercuts for prosthesis retention, partial/split thickness flap coverage of denuded areas, minimum size and shape of defect necessary for satisfactory prosthetic rehabilitation and/or need of extra retentive mechanisms such as implant placement, is essential. Selection of mode of retention of a prosthesis is dependent on a multitude of factors like defect size and undercut presence, patient's economic status, and aesthetic prominence of the site. Retention for an orbital prosthesis can be obtained through inclusion of anatomical undercuts with conformer/acrylic resin template relined by a resilient denture liner, spectacle retained prosthesis, use of stud attachment, magnets, adhesives and implants.¹⁻⁶

In this patient, no functional undercuts were present, which could be utilised to obtain retention. Since the patient was from poor economic strata and had already undergone debilitating surgeries, implants were not a feasible option. Literature has delineated increased incidences of soft tissue infections and higher hygiene maintenance requirements with implant placement.^{5,6}

Adhesive serves as an expensive alternative, which require frequent applications and good manual dexterity on the part of the patient, which becomes more problematic in a paediatric patient. Routine adhesive usage is conducive to allergic responses and may simultaneously also impair prosthesis external pigmentation.^{3,4}

In conventional spectacle retained prosthesis, an acrylic shim is utilised to obtain anchorage from the spectacle due to absence of direct bond of silicone with it.⁹ This can hamper the aesthetics due to increased visibility of acrylic shim. In addition, it can introduce an element of difficulty in prosthesis insertion and removal, due to varying path of insertion of the prosthesis and spectacle. Further, the shim takes up additional space, which the concerned defect could not accommodate. Above difficulties can be ameliorated by the use of magnets or studs in the spectacle.^{3,4} However, due to limited depth of this defect and cost, these were not feasible options. In addition, magnets exhibit loss of attraction over time and corrosion.³

In this report, positive pressure created by the spectacle and elastic cord, was used for prosthesis retention. Eye-wear cords are nylon extensions with adjustable plastic loops at their end. They are readily available and are an economical retentive aid, affordable even by impoverished patients. The aesthetics of the prosthesis is not compromised by black cords, being camouflaged within scalp hair. They do not demand great manual dexterity from the patient and, therefore, can be used by the very young or old. They can be removed at any desired time and there is negligible likelihood of any allergic reaction.

Aesthetics and retention are two fundamental elements for a successful facial prosthesis, which needs good team-work between the surgeon and prosthodontist. Surgically created

unfavourable defects such as the one presented, pose a major prosthodontics challenge. This report describes the fabrication of an oculo-orbital prosthesis with spectacle and cord aided camouflage as well as retention, to meet this challenge in an economical and patient-friendly manner.

PATIENT'S CONSENT:

The written informed consent has been obtained from the guardian of the patient.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SG, SVS: Contributed to prosthesis design, fabrication and manuscript preparation.

NS: Contributed to manuscript preparation.

DA, PC: Contributed to literature review.

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Improving the Prognosis for Phthisis Bulbi Patients

Sir,

Prosthetic rehabilitation of patients with phthisis bulbi is challenging, primarily due to reduced prosthetic space and corneal sensitivity. Sensitivity can cause difficulty in prosthesis fabrication; and inability of the patient to wear the prosthesis¹ (Figure 1a). Surgical techniques to minimise sensitivity have their own complications.^{2,3} Therefore, a prosthetic technique, aimed at gradual desensitisation, and improving the esthetic outcome in cases of phthisis bulbi has been being discussed.

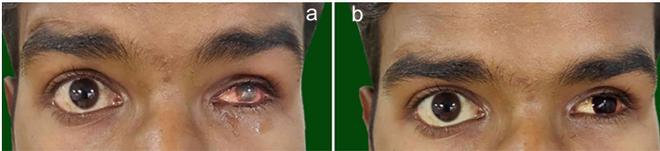


Figure 1: (a) Excessive corneal sensitivity associated with the phthisical eye. (b) Contact lens given to the patient for gradual desensitisation.

A 24-year male patient was referred for left prosthetic eye fabrication, who had presented with a history of trauma resulting in phthisis bulbi. Testing with a cotton wisp showed that the patient had sensitivity in this eye. To start with, a coloured rigid glass permeable (RGP) contact lens (Elite, Everclear) matching patient's contralateral iris colour (Figure 1b) was selected. Patient was told to wear the contact lens for brief time periods initially. The time of wear was increased gradually until two weeks.

After this, patient's affected eye was examined again for sensitivity. As the tolerance had improved, an ocular impression was made after anaesthetising the affected eye. Had excessive sensitivity been persistent, patient would have been instructed to increase lens wearing time for another two weeks. Impression was poured in type III dental stone (Kalabhai Kalstone, Karson Pvt. Ltd., Mumbai), to create a two-half mold, then wax was poured in this mold to fabricate a wax pattern for the prosthesis. Carving and contouring of the wax pattern was done to simulate the lost eye. After this, try-in was done to assess for fit, contour, comfort, size, support and movement. Acrylisation of the wax pattern was done in heat-cured tooth coloured acrylic resin (Heat Cure, Pyrax Polymers, India), matching the shade with the sclera of unaffected eye.

Margins were ascertained to be thin to avoid an over-bulging prosthesis. Prosthesis was checked for fit and contour, following which it was relined with permanent heat-cured soft reliner (Molloplast B, Detax, Germany) after reducing 1 mm

circumferentially to improve retention and reduce discomfort (Figure 2a). Iris position was determined on scleral shell according to conventional techniques (Figure 2b). This portion of the prosthesis was formed with the initially used contact lens, which was adhered with cyanoacrylate to the shell, in previously determined position. Monopoly syrup was used to protect the surface and contact lens. After this, the final prosthesis was delivered (Figure 2c).



Figure 2: (a) Margins of the prosthesis trimmed and relined with a permanent soft liner. (b) Iris positioning. (c) Final prosthesis with contact lens as the iris.

Use of contact lens introduced an inceptive stimulus to gradually desensitise the patient. Using same contact lens as iris in the prosthesis, provided superior esthetics by minimising risk of a bulging over-contoured prosthesis, pre-empting excessive thinning of scleral shell, which can lead to fragility and show through. Use of permanent soft liner at the margins of the prosthesis, reduced discomfort and aided retention. However, this approach is technique-sensitive and time-consuming, with additional cost of the lens.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

NS: Conceptualisation, investigation, writing the original draft.

SVS: Formal analysis, methodology, writing, reviewing and editing.

DA: Supervision, validation, and visualisation.

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Rehabilitation of a Complex Oro-Facial Defect by Modified Prosthetic Approach

Saumyendra V. Singh, Himanshi Aggarwal, Vinit Shah, Pradeep Kumar and Deeksha Arya

ABSTRACT

Loss of part of the face is associated with physical disability, social isolation and immense psychological trauma. Proper rehabilitation of such a patient is a challenging yet satisfying task for a maxillofacial prosthodontist. Facial prostheses are commonly fabricated of silicone because of many favorable properties, though it predisposes to fungal growth. This report is of a patient with history of uncontrolled diabetes and associated invasive fungal infection, leading to a complex oro-facial defect, which was rehabilitated successfully with a silicone facial prosthesis lined by a material more resistant to fungal growth along with a cast partial obturator. Other design and procedural modifications were also made to suit the needs of the case. Wise selection of materials, keeping in mind the properties of materials, is important in successful rehabilitation.

Key Words: Prosthetic rehabilitation. Oro-facial defect. Silicone. Fungal infection. Uncontrolled diabetes.

INTRODUCTION

Face is associated with a person's identity and individuality. Loss of part of the face is associated with physical disability, social isolation and psychological trauma. Depending on the extent of defect and time of presentation, it may be possible to use a surgical reconstructive approach for congenital facial defects. However, those resulting from trauma or oncological surgical excision are mainly restored using a prosthetic approach.¹

Among the facial defects, the loss of an eye causes profound functional and psychosocial disability.² Orbital exenteration is a radical surgery which involves removal of the entire contents of the orbit and associated periorbital structures, leaving the patient with a devastating functional and cosmetic state. Fabrication of an orbital prosthesis is demanding because of the complexity of replicating contours of tissues and accurate positioning of the iris.

Since the first mention of facial prosthesis in literature by Ambroise Pare in 1575 to the present, methods of fabrication and choice of prosthetic materials have evolved a lot. At present, silicone elastomers are the commonly preferred prosthetic material for fabrication of a facial prosthesis, though it has several undesirable properties, including proneness of fungal growth.³

This case report is about the prosthetic rehabilitation, using silicone prostheses lined by vacuum formed

polyvinyl chloride and a cast-metallic obturator. The defect involving left orbit and maxilla resulted from road-side accident in a patient complicated with uncontrolled diabetes and associated invasive fungal infection.

CASE REPORT

A 47-year female with mid-facial fractures (due to road traffic accident) 2 years back was referred to the Unit of Maxillofacial Prosthetic Rehabilitation. At that time, the patient developed soft tissue necrosis with discharge oozing from left facial region, followed by loss of vision from left eye. Culture of discharge had confirmed fungal infection secondary to bone necrosis. Orbital exenteration had to be performed along with excision of all necrotic tissues, leaving the patient with a complex defect. No reconstruction of the defect was performed because of the patient's systemic condition.

On examination, the patient presented with an oro-facial defect (Figures 1 and 2), classified as Class III Subclass F according to Okay *et al.*⁴ On evaluation, the orbital defect was lined by healthy tissue and presented with moderate tissue undercuts. It was decided to rehabilitate the patient with a cast partial removable prosthesis for the intraoral defect and an orbital prosthesis after taking patient consent.

Impressions, surveying, mouth preparation and metal framework designing of the intraoral defect (Aramany class II) was done conventionally.⁵ The cast partial denture had an antero-posterior palatal strap type of major connector, with occlusal rests and minor connectors planned in a quadrilateral design configuration (Figure 3). Effectiveness of obturation of defect was confirmed by asking the patient to sip water with no leakage noted from the nasal cavity. Maintenance and care instructions were reinforced and prosthesis reevaluated at post insertion appointments.

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Figure 1: Intraoral defect communicating with the sinus in the maxillary left 2nd premolar-1st molar region.



Figure 2: Orbital defect.



Figure 3: Cast removable partial denture to obturate the intraoral defect.



Figure 4: Clay pattern.



Figure 5: Final orbital prosthesis, camouflaged with large spectacle frame and tinted glasses.

The orbital defect impression was made after blocking undesirable undercuts with damp gauze, using addition silicone putty relined by light body impression material and poured in type III stone (Orthokal, Kalabhai Karsons Pvt Ltd, Mumbai, India). A 1mm thick polyvinyl chloride (PVC) sheet (Softray sheets; Ultradent Products Inc.) was adapted to the model using a vacuum former (Model P105-U02; Ultradent Products Inc.) as a base for pattern fabrication. For ocular part of the prosthesis, a stock eye matching in contour and colour of contralateral eye was selected and positioned on the PVC base. The orbital pattern was then carved in modeling clay (Funclay, Nara Factory Co., Ltd, Bangkok, Thailand) onto the PVC base and skin creases were sculpted to mimic the contralateral region. Clay offered advantage of easy manipulation over usage of wax for the purpose. Finally, eyelids were carved in modeling clay. The pattern was tried on the patient for adequacy of fit, proper positioning of prosthesis margins and accurate reproduction of contours and creases in harmony with adjacent and contralateral structures (Figure 4). A spectacle frame, wide enough to camouflage the margins of the prosthesis, was selected at this stage. The finalized pattern was invested in stone after ensuring that the margins of the prosthesis were feathered and merged with surrounding tissues. This was followed by heating the clamped mold in a water bath to remove the clay. The PVC base was retained in the mold with the intention to retain it as the base of the final silicone prosthesis. Maxillofacial prosthetic silicone material (Maxillofacial Rubber M511, Technovent Limited, South Wales, U.K) was intrinsically pigmented and packed in the de-waxed mold, which was then cured at 100°C in the oven. After curing, the prosthesis was carefully retrieved and tried on the patient. The prosthesis was further characterized using external stains. The finalized prosthesis was delivered to the patient. Edge adhesive (G604, Technovent Limited, South Wales, U.K) was used at the margins of the prosthesis. Tinted glasses were placed in the spectacles to camouflage the prosthesis (Figure 5). The patient was educated in maintenance and care of prosthesis and importance of periodic follow-up. The patient was satisfied with the esthetics, though some looseness of the prosthesis was noted after 1 year, probably because of tissue remodelling.

DISCUSSION

Oro-facial defects are difficult to rehabilitate with a constant dilemma between reconstructive surgery and prosthetic rehabilitation options. Albeit, in certain cases, reconstructive surgery may be less feasible like in the present case, as the patient may be predisposed to risk of infection and/or graft rejection/failure. Also, some lesions have a high recurrence rate and need to be left uncovered for regular examination to rule out recurrence.

Oro-facial defect can be restored by fabricating a conjoint prosthesis. However, such prosthesis is difficult to fabricate and demands increased manual dexterity from the patient in insertion and removal of the prosthesis. We, therefore, preferred to restore the oral and facial defects separately to simplify the manipulation and maintenance of both prostheses, by utilizing intraoral and extraoral tissue undercuts separately, eliminating the need of complex and expensive attachment systems or demanding fabrication procedures.

The orbital prosthesis was fabricated adapting a PVC sheet as the base of the pattern, providing a more durable foundation which would adapt to the undercuts meant to be used for the retention of the final prosthesis.⁶ A wax base is rigid and would, therefore, have to be relined in the undercut areas. The PVC base gave an estimate of the retentiveness of the prosthesis at the trial stage itself. The pattern for orbital prosthesis was carved in modeling clay as it offers the advantage of ease of sculpting, eliminating the need of using a flame and providing superior replication of skin creases. In this case, we preferred the stock eye for ocular component of the prosthesis as it simplified the procedure. As favorable tissue undercuts were present, only edge adhesive was used to camouflage the margins of the prosthesis.

PVC sheet complies with the ideal biological properties of non-irritating, non-allergic, non-toxic; and most importantly, for this case, non-supportive to microbial/fungal growth.⁷ The patient was followed up at 1 year for a fungal culture. The orbital prosthesis was satisfactorily

camouflaged using tinted glasses with wide frame, carefully chosen for the purpose.

The restoration of an oro-facial defect is often the toughest challenge to the prosthodontist. On the other hand, rehabilitating the patient on social front is immensely satisfying. Careful modification of basic principles and skillful selection of materials and techniques can render satisfactory results, restoring the patient's appearance and confidence significantly.

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Correspondence

Novel technique for fabrication of pneumatic ocular prosthesis

Reasons for loss of an eye include irreparable trauma, intraocular malignancy and prevention of sympathetic ophthalmia. Other indications include phthisis, microphthalmia, and improvement of cosmesis [1]. Surgical procedures in the removal of an eye are classified into 3 general categories: evisceration, enucleation, and exenteration, which is followed by fabrication of an ocular prosthesis.

The goal of any ocular prosthetic procedure is to facilitate return of the patient to society with a more acceptable appearance. Often surgical treatment might leave an ocular socket with enormous volume for rehabilitation. An ocular prosthesis of such a large size has enhanced weight, which may lead to ectropion and sagging with decreased prosthesis mobility. It might also cause discomfort to the patient. Various techniques have been proposed for fabrication of light weight/pneumatic prosthesis using lost-wax technique [2] or styrofoam [3]. In this article, an alternative procedure for fabrication of pneumatic prosthesis, using an acrylic shim, has been detailed.

Following impressions, iris-disk placement and final wax pattern try-in, invest and de-wax the wax pattern in the usual manner. Adapt a layer of baseplate wax (Modelling Wax, DPI) on the mold surface in both halves of the flask (Fig. 1). Make 2–3 4 × 4 mm slots holes in the baseplate wax in each half, taking care to locate stops on flat surfaces rather than undulating ones. Pack autopolymerising resin (RR Cold Cure, DPI) in between the baseplate wax and close flask to let acrylic set. After about 30 mins, separate the flask and remove the resin shim with stops (for accurate repositioning) (Fig. 2). Remove baseplate wax layers.

Apply separating media (Cold Mould Seal, DPI) onto the mold. Mix appropriate color matched heat polymerising resin (Heat Cure, DPI) with iris and place in respective flask halves, in dough stage. Place



Fig. 1. Baseplate wax adapted on both halves of flask and slots created for acrylic stop for acrylic shim fabrication.



Fig. 2. Acrylic shim fabricated.



Fig. 3. Two halves of the prosthesis obtained after polymerization.

cellophane sheets as separating media on top of each half of dough. Place resin shim in between cellophane sheets and close flask halves. Acrylize, remove cured halves (Fig. 3) and approximate them with thin layer of autopolymerising resin after removing the shim. Finish, polish and deliver final prosthesis conventionally.

The technique suggested here is a relatively easy, simple and cost-effective method of fabrication of custom pneumatic ocular prosthesis. It helps in controlling the amount of hollowing achieved. The weight of the ocular prosthesis fabricated by this technique is much less. In this instance reduction of weight was about 2.79 gm or 24% [Fig. 4] than conventional solid ocular prosthesis. However, this technique has



Fig. 4. Weight difference between pneumatic and solid prosthesis.

certain drawbacks as well. It is technique sensitive with increased number of steps, making it time consuming. The approximated margins may be a potential source of leakage, discolouration and irritation.

A simplified, accurate method of fabrication of a hollow, light-weighted ocular prosthesis for patients with large ocular defects or sagging lower eyelids is presented.

Source of support

None

Conflicts of interest

None

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Fabrication of Silicone Prosthesis for an Amputated Pollex with Kapandji Score 8: A Case Report

ANSHULIKA SINGH¹, MAYANK SINGH², SAUMYENDRA V SINGH³, POORAN CHAND⁴, DEEKSHA ARYA⁵

ABSTRACT

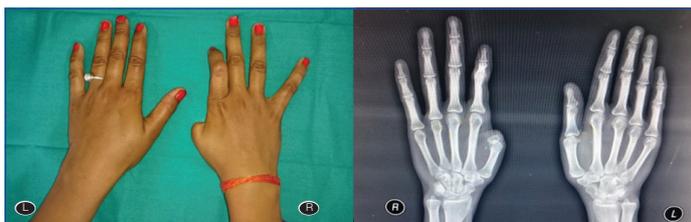
Amputations are most commonly seen due to the accidents, congenital malformations and diseases. Regardless of the cause of the loss of the part of the body, an amputation results in aesthetic, physical and psychosocial damage to an individual. An amputation can be surgically treated but in some cases where patient reports to the prosthetist, when the damage is irreversible, it can be treated with prosthetic replacements of the lost part. A prosthetist acts as an important link in helping such patients in regaining the lost confidence by rehabilitation. Prosthetic management of an amputated thumb aims to deliver a well-fitting silicone prosthesis that can mimic the opposite thumb as closely as possible, with good range of movement without dislodgement. This case report presents rehabilitation of the amputated thumb with minimal residual thumb in a conventional way along with restoring the range of movements with evaluation of the range of movement without the use of an extra retentive aid.

Keywords: Prosthetic rehabilitation, Retentive aid, Trauma

CASE REPORT

A 20-year-old female patient reported to the Department of Prosthodontics, with a chief complaint of missing thumb of right hand [Table/Fig-1]. History revealed the patient had lost her pollex in a traumatic injury when she was 1½-year-old.

Physical and antero-posterior radiographic examination of right hand revealed amputated thumb at proximal phalanx [Table/Fig-1]. The index finger was osseointegrated at the interphalangeal joint of distal and middle phalanx in the flexed position because of an attempt to reattach the distal phalangeal portion at the time of injury. The patient was naturally not able to straighten the index finger [Table/Fig-1]. The skin of the amputated finger was completely healed.



[Table/Fig-1]: Pre Rehabilitation clinical and radiographic view.

The rehabilitation of her thumb was challenging due to level and site of amputation. The patient was informed about both possible treatment options-surgical reconstruction and prosthetic rehabilitation. But, due to surgical trauma and financial constraints, the patient agreed to prosthetic rehabilitation. So, thumb prosthesis was planned for the patient. As the patient was unwilling for any surgery, implant retained prosthesis was ruled out. Mechanical retention with devices such as Velcro strap would be quite discernible for pollex location. Therefore, glove type thumb prosthesis with retention aided by an incorporated wire in the silicone prosthesis was planned to work in harmony with the flexed osseointegrated index finger of the right hand.

Patient was informed about the procedure and her consent was obtained. An impression of the right amputated thumb stump was made using irreversible hydrocolloid impression material (Zelgan) and poured with Type-III dental stone (Kalstone, Kalabhai Pvt., Ltd., Mumbai, India) to obtain the working model [Table/Fig-2]. Then

1 mm reduction was done all around the thumb stump to enhance fit to the elastic silicone prosthesis. After that, an impression of the patient's left thumb was made with alginate and poured in molten modelling wax (Link dental modelling wax no. 2, MDM Corporation, Delhi, India). This wax pattern of the left thumb was adapted to pollex stump model [Table/Fig-2] and the borders were merged with the area adjacent to the defect site. A 20 gauge silver wire was incorporated into the wax pattern as an aid for mechanical retention of the prosthesis. It was adapted at the root of the stump extending upto the metacarpophalangeal joint of the index finger, attaching to a ring worn on the index finger [Table/Fig-3]. Fabrication of silicone prosthesis with incorporated wire to aid in retention is hardly documented. Anatomic crease lines were carved to give a more natural appearance. Then, the wax pattern was tried on the patient's hand [Table/Fig-3]. Along with the shape and size, the fit, orientation, emergence and borders of the pattern were evaluated.



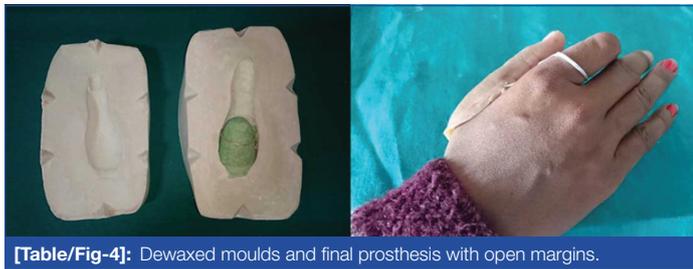
[Table/Fig-2]: Working model and wax pattern adapted to the thumb stump.



[Table/Fig-3]: Silver wire try in for wax pattern and the wax pattern tried on the patient's hand.

The pattern was then invested in a two piece mould made using type I dental stone. The two piece mould was made by pouring the dorsal and palmer halves separately. The first pour

enscoring the palmer half was made with type 1 dental stone, at slight angle. Keys were made into the first piece of mold and separating media was applied on the surface. This was followed by pouring the second half of the mold with type 1 dental stone. After the investment was set, dewaxing was done and moulds were obtained [Table/Fig-4]. The correct position of wire element was ascertained in the mold.



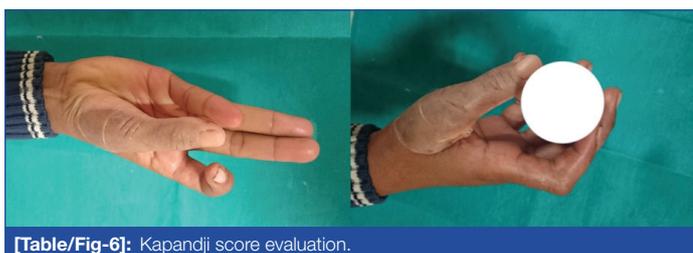
[Table/Fig-4]: Dewaxed moulds and final prosthesis with open margins.

Appropriate shades were matched for both the dorsal and the palmer surfaces with the help of digital spectrometer. The pigments were quantitatively measured, mixed with the heat temperature vulcanising silicone and added to the dewaxed mould. Surface tension releasing agent was applied to the mold surfaces. The molds were compressed and the curing process was performed according to the manufacturer's instructions. After curing, the prostheses was removed gently, trimmed and finished. The shade was evaluated and extrinsic colouring done to match the exact colour of the patient.

The prosthesis was inserted and retention was attempted by attaching the silver wire to a ring worn on the index finger. With this mode, prosthetic retention was good but on movement of the thumb the margins of the prosthesis opened up [Table/Fig-4]. So it was planned to cut the silver wire and medical adhesives were used for retaining the prosthesis [Table/Fig-5]. This also resulted in good retention and range of movement with a score of 8 as assessed with the help of Kapandji's rule of 10 [1], where the patient was asked to touch ten specified areas of 4 fingers with the tip of the thumb. For assessment of the opposition of the thumb Kapandji score was used as a tool, based on where the tip of their thumb touches the patient's hand [Table/Fig-6]. The patient was also asked to hold boxes of varying diameter to check for the grip [Table/Fig-6]. Post delivery the patient was instructed to remove the prosthesis daily and clean it with isopropyl alcohol, also asked to clean the underlying skin. A 6-month follow up for assessing the maintenance was planned for the patient.



[Table/Fig-5]: Post Rehabilitation final prosthesis.



[Table/Fig-6]: Kapandji score evaluation.

DISCUSSION

Pollex is an important part of hand used to perform daily tasks including pinch, grip, grasp, and precision handling [2]. From

functional standpoint it is the most important digit which performs the movements of opposition and apposition [3].

The patient is not able to perform various functional activities with the loss of thumb. The immediate loss of grasp, strength and security and the aesthetic impact may cause a great psychological trauma [4]. The thumb may be lost due to traumatic injuries or may be congenitally absent.

Traumatic amputation of thumb puts the patient through great aesthetic and psychological trauma, besides inability to perform functional movements, various gripping and opposing actions. To overcome these problems efforts are made to restore the lost thumb surgically or prosthetically. The first choice for treating amputated digits generally is surgical reconstruction while prosthetic rehabilitation may be considered in unsalvageable cases or in surgical reconstruction failure [5]. Options such as solitary digit transfer, bone lengthening or ray transposition allow for surgical reconstruction of lost digits achieving function and patient acceptance [6]. Prosthetic options include implant retained prosthesis which aids in higher degree of functional movements and aesthetics. Implant retained silicone finger prosthesis allow some pressure perception and tactile sensation, facilitating surface and texture distinction [7]. Tip pinch grip score can be used to determine the grip strength with marked pinch gauge, where the patient is asked to place the thumb under the gauge with the pulp of the index finger on top and dial facing upwards. This formed an O-shape whilst the other fingers are flexed [8]. However, there might be problems associated with loss of integration of these implants. Many patients do not agree to undergo surgery for implant or reconstruction due to surgical trauma, time consuming procedure and cost factors. Prosthetic replacement with mechanically retentive silicone prosthesis can serve as an acceptable option. This is non-invasive, less expensive and has good patient acceptance.

Similar case reports have been published for prosthetic rehabilitation of amputated finger/s [4,8], but rehabilitation has been without attempt at incorporation of wire. In the cases where stump length is severely reduced, there is associated difficulty in retention of the prosthesis. In such cases, where the patient is unwilling/unsuitable for osseointegrated implants, wire incorporation in silicone prosthesis might aid in retention.

CONCLUSION

This thumb prosthesis was designed to be fabricated with a silver wire incorporated, which would be attached with a ring to be worn on the index finger as an extra retentive tool since the pollex stump was very small. But due to problems like open margin and dislodgement of the prosthesis during movement of the residual stump or finger, the wire was cut and detached from the ring. Also, disadvantages such as show through of wire, susceptibility of silicone to tear from the portion where wire was emerging and difference in flexibility of the two materials, were expected with the prosthesis if the wire was retained. In the present case, since the disadvantages of using a wire to aid in mechanical retention was more, so medical adhesives were used to retain the prosthesis. Kapandji score was used as an assessment tool for evaluation of the functional movement and results with a good range of movement, without dislodgement were seen. This was achieved without any extra retentive element on the residual pollex stump of very small size.

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Custom-Soldered, Double-Ring Retained Silicone Finger Prosthesis

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ABSTRACT

Introduction: Accomplishment of adequate retention in prosthesis is vital to patient comfort. The purpose of this article is to present a technique of fabrication of a nonimplant, nonadhesive retained silicone finger prosthesis for a short, flabby residual digit.

Materials and Methods: To achieve adequate retention in this compromised clinical scenario, two rings were used: one on the residual finger and the other on the adjacent finger, which were soldered at accurate orientation using a custom-made putty index.

Results: Retention of the prosthesis was found to be satisfactory and alleviated the apprehension of the patient regarding surgical placement of implants.

Conclusions: The technique described in this report provides an effective, reversible, and straightforward method of managing the compromised situation. The double-ring technique offers a nonsurgical alternative to rehabilitation of patients with compromised residual digits. (*J Prosthet Orthot.* 2019;31:159–162)

KEY INDEXING TERMS: silicone, finger prosthesis, small, flabby/compromised residual digit, double-ring, prosthesis

Partial or total amputation of fingers can be attributed to various reasons including trauma, burns, congenital absence, and malformations. Loss of a digit results in impairment of function and compromised aesthetics, causing reduced self-confidence and disengaged social behavior.^{1,2} Also, the influence of hand gestures on the body language of an individual cannot be underemphasized.³

The course of treatment depends on the level of amputation, soft tissue condition of the residual digit, and patient preference. In case of a compromised residual digit as presented in this case report, the benefits of microvascular reconstruction of the missing digit or osseointegrated implant retained prosthesis is well recognized. However, these treatment options are irreversible, expensive, and may be associated with postoperative complications.

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This report presents an attempt to fabricate a conventional custom silicone prosthesis for a compromised residual finger with modifications to retain the prosthesis without any invasive technique.

CASE DESCRIPTION AND METHODS

HISTORY

A 35-year-old male farmer reported to this department with the chief complaint of unaesthetic appearance of right hand due to missing fifth digit lost due to trauma 1 year ago. On examination, the fifth digit of the right hand was missing at a level just distal to the proximal joint. The residual digit was covered by healthy skin with no signs of scarring or pigmentation. No sensory disturbances were observed (Figure 1).

The patient was aware that he was the subject of a case study, that information about him including photos related to the case was being published, and that he had been given an opportunity to review the submitted manuscript. A written consent was signed by the patient.

MATERIALS AND METHODS

An impression of the residual digit was made along with the adjacent finger in irreversible hydrocolloid material and poured in high-strength dental stone. The impression of the residual digit alone was not made as it caused distortion of the anatomic form of the residual digit at the area of junction with the adjacent ring finger.

The residual digit was separated from the adjacent finger by cutting with a fret saw (Figure 2). The dorsal and ventral sides of the residual digit were labeled, and uniform 2-mm circumferential reduction of the residual digit was done up to the metacarpophalangeal joint.

An irreversible hydrocolloid impression of the little finger of the normal hand was made, and modeling wax was poured into it.



Figure 1. Residual digit.

The patient was instructed to slightly flex the interphalangeal and the metacarpophalangeal joints during impression making. The residual digit was oriented and inserted into the poured molten wax finger.

Once the wax hardened, the wax finger was removed, inspected, and altered for appropriate fit, orientation, anatomy, details, and contour (Figure 3).

Then, the pattern was invested in high-strength dental stone using a two-pour technique (Orthocal), dewaxed, and made ready for packing of silicone. Shade matching was done using a digital spectrophotometer. Silicone material was mixed according to color code and packing was done. Curing of the prosthesis was done for 90 minutes at 100°C.

The cured prosthesis was retrieved and tried on the patient. It was decided to use silver split rings with adjustable diameter for retention. Adequate retention was not achieved using a primary retentive finger ring on the residual digit. Therefore, it was decided to use another ring (secondary retentive ring) on the adjacent finger, which was welded to the primary ring.

The orientation of the prosthesis and the rings was determined on the patient's hand (Figure 4). The rings were joined in correct spatial position using sticky wax (Figure 5). Their



Figure 2. Residual digit model.



Figure 3. Wax pattern trial.

position was preserved on a putty index. The rings were soldered in this position (Figure 6).

To achieve accurate color matching, extrinsic staining of the prosthesis was done. The prosthesis was inserted along with the soldered double ring (Figure 7).

RESULTS

Retention of the prosthesis was found to be adequate and the patient was satisfied.

DISCUSSION

Retention is one of the most important aspects in designing a finger prosthesis. Silicone stretches and grasps the residual digit

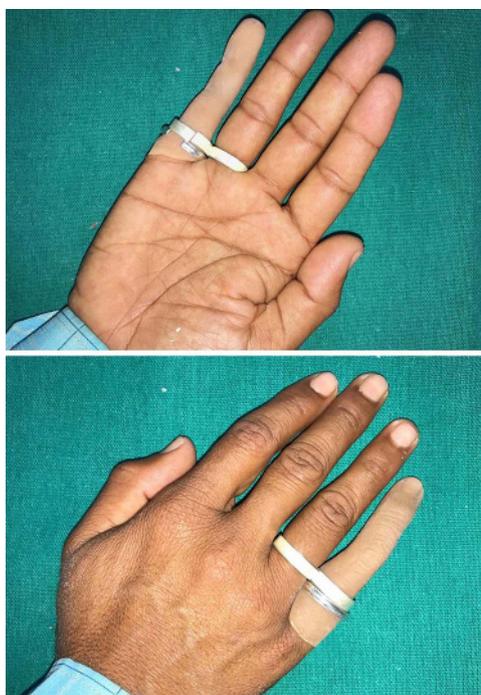


Figure 4. Prosthesis before extrinsic staining.



Figure 5. Oriented double rings.

with positive pressure. This requires the residual digit to have firm, bony content and at least 1.5 cm in length.⁴

With reduction in the length of the residual digit, the contact area of the silicone is reduced. This diminishes the gripping effect of silicone. The reduced length of the residual digit, along with excessive redundant fibrous tissue in this case, compromised the retention, even with the use of adhesives.



Figure 6. Double-ring index.

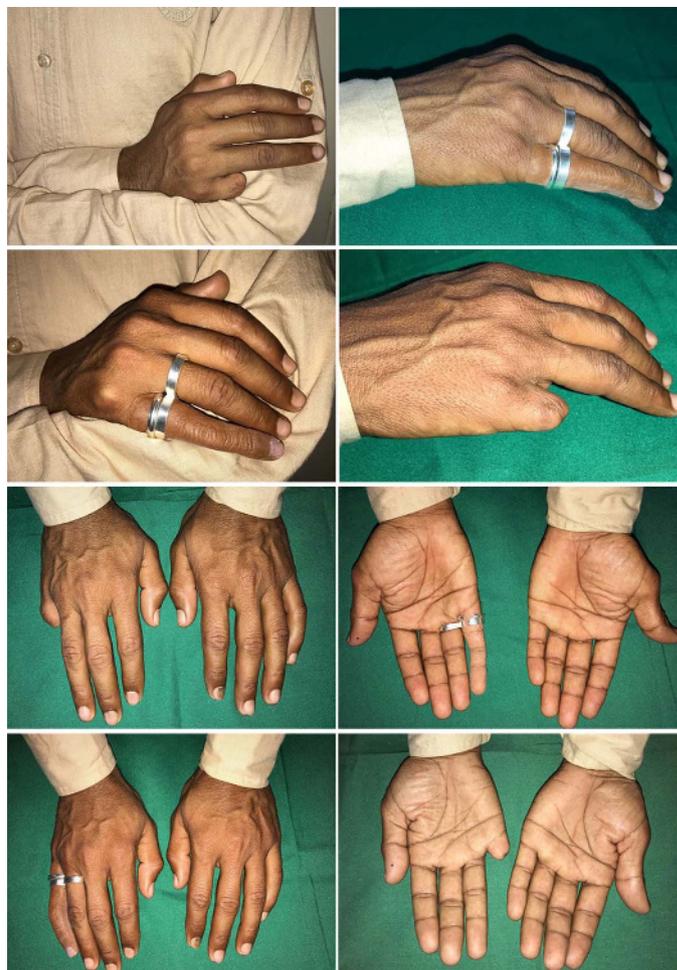


Figure 7. Final prosthesis from different views.

The use of adhesives are associated with prosthetic complications like discoloration and tear at the margins,⁵ reduction in the bond strength of acrylic polymer-based adhesives on contact with water,⁶ difficulty in removal of adhesive from the surface of the skin, and increased likelihood of fungal infection. The adoption of implants for retention, although preferred in such a case,⁷ is not readily accepted by many patients. The adverse consequences⁸ of implant surgery such as infection,⁹ loosening of implant due to trauma,¹⁰ increased expenses, and heightened time of treatment makes it unacceptable for some patients, such as the participant in this report.

Accordingly, modifications in the treatment plan were made during different stages of treatment. Uniform, anatomical reduction of the residual digit diameter was done to achieve a positive grip on the residual digit. Making the impression of the contralateral normal finger provided a provisional wax pattern. The contour of this pattern was improvised such that it resembled that of the opposite finger. This method was more predictable and immediate than carving out a new prosthesis from scratch.

The secondary ring used on the ring finger provided required retention. Soldering the rings using putty index was an important step in maintaining orientation of the rings.

CONCLUSIONS

Despite the challenges presented in this case, a satisfactory outcome was observed without the use of adhesives. This signifies that basic prosthetic principles, with some reworking, can be of great caliber in managing such a case.

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Learning Objectives

- Topical antibacterial, antiviral, and antifungal agents.
- Acne vulgaris.
- Psoriasis.
- Alopecia.
- Pigment disorders.
- Sunscreens.

Introduction

Skin is the largest organ of the body, with a surface area of 1.6 to 1.8 m², and acts as a barrier to the external environment. It permits and limits inward and outward movement of water and electrolytes across it. It provides protection against various microorganisms, toxic substances, and ultraviolet (UV) radiation, and also acts as a source of vitamin D. The various layers of skin play the role of barriers for drugs diffusion.

The stratum corneum is the outermost lipophilic keratinous layer, which consists of dead cells that shed every 4 weeks. It is considered to be a part of the epidermis and the main barrier for absorption of drugs.

Other layers of the epidermis such as the stratum lucidum, stratum granulosum, stratum, spinosum, and stratum basale consist of viable cells intercalated with neutrophils, lymphocyte, Langerhans cells, melanocytes, drug-metabolizing enzymes, and transporter proteins (OATP, MDR, P-glycoprotein).

The dermis is located between the epidermis and the subcutaneous tissue and consists of collagen, elastin, sweat glands, sebaceous glands, hair follicles, and blood vessels. It is the main site of absorption of drugs into the systemic circulation through the capillary plexus.

The hypodermis or subcutaneous tissue is well vascularized and consists of loose connective tissue and adipose tissue.

Factors Affecting Cutaneous Drug Absorption

Topical agents are available in the form of sprays, powders, lotions, creams, ointments, pastes, and aerated

foams. Their absorption across the skin depends on various factors.

1. Molecular mass of drug—Smaller molecules can cross the skin barrier easily, and topical drugs with molecular weight above 500 Da are usually not absorbed.
2. Region of skin the drug is applied—Thickness of the stratum corneum varies in different regions of the body, as it is easily permeable in face, axilla, scrotum, and scalp.
3. Drug concentration—Drug penetration increases with the rise in drug concentration gradient.
4. Dosing schedule or duration of contact—It affects the amount of available drug to be absorbed.
5. Condition of skin (normal or with disease)—Burns, abrasions, wounds, and skin diseases increase the absorption of drugs.
6. Type of vehicle (water- or oil-based, newer liposomes, and microgel)—Vehicles may vary in terms of drug release rate and moistening/drying effect on the stratum corneum. Lipophilic agents are readily absorbed than hydrophilic ones.

Principles of Selection of a Topical Formulation

Topical dermatologic formulations are classified as creams, lotions, ointments, gels, tinctures, pastes, aerosols, powders, wet dressings, and foams. Their selection depends upon various factors such as the type of disease and the main aim of drug application.

1. Acute inflammation—Drying preparations such as lotions and tinctures are preferred.
2. Chronic inflammation—Diseases with xerosis and scaling are best treated with lubricating preparations such as ointments and creams.
3. Retard evaporation—Ointments are the best option to prevent evaporation from skin.
4. Skin with hairs—Gels, lotions, tinctures, foams, and aerosols are preferred, as they are convenient.
5. Intertriginous areas (in axilla, anogenital region, skin folds of the breasts and digits)—Vanishing cream ("oil in water"-type emulsion) is preferred, as it does not cause maceration and disappears quickly.

Topical Antibacterial Agents

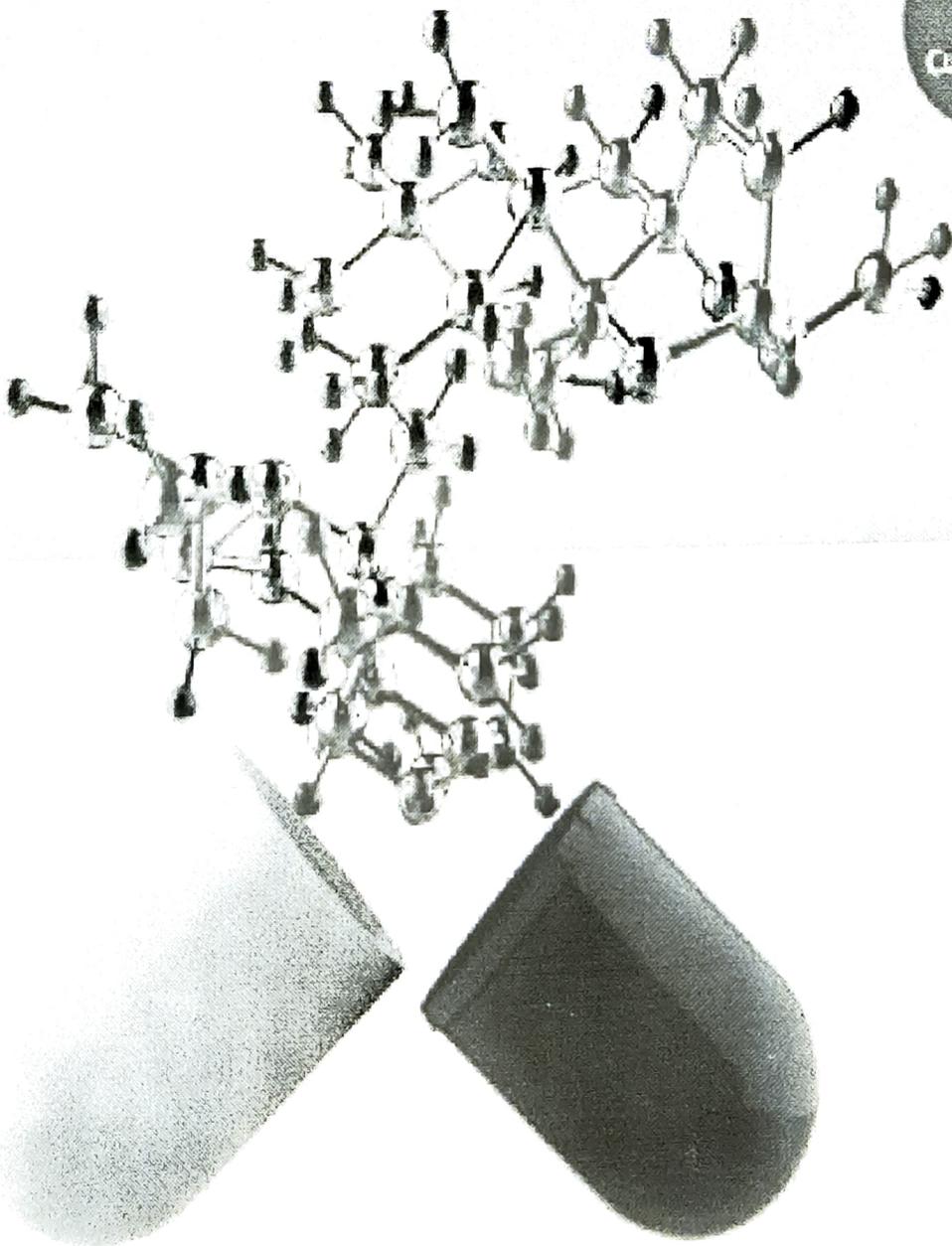
Antimicrobial agents are used topically for several common skin infections such as folliculitis, cellulitis, fasciitis, abscesses, and impetigo (Table 87.1). Bacitracin

Education

Textbook of Pharmacology

Prasan R. Bhandari

Based on
CBME
Curriculum



 Thieme

Study of oxidative stress biomarkers in chronic obstructive pulmonary disease and their correlation with disease severity in north Indian population cohort

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ABSTRACT

Background: Oxidant-antioxidant imbalance forms a prime component in pathogenesis of chronic obstructive pulmonary disease (COPD). Studies of oxidative stress markers in South Asians were sparse. **Methods:** One hundred and eighty COPD patients and eighty healthy nonsmokers were enrolled in the study. Serum malondialdehyde (MDA) and iron levels were estimated for oxidative stress. Three antioxidant markers evaluated-catalase, superoxide dismutase (SOD), and serum copper. Patients on antioxidant therapy and with sepsis and chronic illness were excluded from the study. **Results:** The mean age of COPD patients was 59.29 ± 10.3 years. Serum levels of MDA and iron were significantly higher in COPD patients compared to controls (5.21 ± 1.9 vs. 0.71 ± 0.29 nmol MDA/ml, $P = 0.0001$ and 69.85 ± 85.49 vs. 79.32 ± 24.39 $\mu\text{g/dl}$, $P = 0.0001$, respectively). Mean level of all antioxidant enzymes catalase, SOD, and copper were significantly diminished in cases when compared to control population ($P = 0.001$). Levels of MDA and iron were found to be significantly elevated in higher Global Initiative for Chronic Obstructive Lung Disease (GOLD) classes (III, IV) when compared to lower GOLD Classes (I, II). The levels of serum antioxidants were significantly depleted in higher GOLD grades too. COPD patients who were male and smoked had significantly higher levels of oxidants and depleted antioxidant levels compared to female and nonsmoking compatriots. Serum MDA levels negatively correlated with forced expiratory volume 1 s and forced vital capacity ($r = -0.19$ and $r = -0.21$, $P \leq 0.01$). The presence of a cough significantly correlated with higher levels of MDA and iron ($P = 0.001$). The levels of MDA negatively correlated with SOD and catalase levels. **Conclusion:** Oxidative markers (MDA and iron) are higher whereas antioxidants (catalase, copper, and SOD) are significantly reduced in patients of COPD. Serum MDA levels correlate with lung functions and disease severity.

KEY WORDS: Chronic obstructive pulmonary disease, malondialdehyde smoking, oxidative stress

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide.^[1,2] The disease is characterized as chronic irreversible inflammatory damage, predominantly in small airways, and lung parenchyma.^[3] The pathogenic triad of

COPD consists of oxidative stress, protease-antiprotease imbalance, and inflammation, of which oxidative stress forms prime component.^[4] Oxidative stress affects airways by myriad mechanisms including mucus hypersecretion,

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damage to airway epithelium, neutrophil influx, airway inflammation, and increased apoptosis.^[5] Several processes lead to oxidative stress-related tissue damage, primary among them is lipid peroxidation which leads to the formation of various lipid hydroperoxides and aldehydic products.^[6-8] Many markers of oxidative stress have been shown to have direct correlation among themselves and severity of airway obstruction represented by forced expiratory volume 1 s (FEV₁).^[9] Simultaneously, other studies have highlighted the deficiency of native antioxidant defense mechanisms of lungs in COPD. The important naturally occurring antioxidants in body include glutathione system, catalase, and superoxide dismutase (SOD) system.^[10,11] Trace elements such as iron, zinc, and copper have also been proposed to be involved in oxidant-antioxidant cycle in COPD.^[12] Markers of oxidant-antioxidant imbalance can be studied from blood, exhaled breath, sputum, and bronchoalveolar lavage.^[13,14] However, large studies regarding oxidative stress in COPD patients in Asian Indians are sparse. The present study was designed to study the serum markers oxidant-antioxidant imbalance in COPD patients and their association with disease progression or severity.

METHODS

Study subjects

Patients of COPD presenting to outpatient, indoor, and intensive care unit in the Department of Respiratory Medicine were studied from August 2014 to August 2015. Healthy nonsmoker subjects with no pulmonary, cardiovascular, or oncological disease, inflammation, infection, and neurological dysfunction that could influence the oxidative status were enrolled as controls. COPD was defined according to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria.^[1] The lung functions were analyzed using Mir Spirolab II spirometer and the patients with COPD were selected and grouped into mild, moderate, severe, and very severe severity group according to the GOLD criteria. Subjects with history of tuberculosis, bronchial asthma, diabetes mellitus, hypertension, lung cancer, cardiovascular, renal diseases, chronic hepatic failure, and prior antioxidant intake were excluded from the study. The study was approved by local ethics board and performed in accordance with ethical standards outlined in the Declaration of Helsinki. Detailed written and informed consent was taken from all subjects.

Markers of oxidative stress

Malondialdehyde (MDA) was estimated according to the method of Stocks and Dormandy.^[15] The levels were estimated as nmol MDA/ml.

Estimation of catalase was done by the method described by Aebi.^[16] Activity of catalase was estimated as U/ml.

Estimation of SOD was done by the method of McCord and Fridovich^[17] and measured in U/ml.

Statistical analysis

The results were presented in mean \pm standard deviation and percentages. The Chi-square test was used to compare the categorical variables. The unpaired *t*-test was used to compare two discrete variables. The one-way analysis of variance was used to compare more than two discrete variables. Pearson correlation coefficient was calculated to find the direction of association between two discrete variables. The $P < 0.05$ was considered statistically significant. All the analyses were carried out using SPSS 16.0 version (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 180 patients of COPD were enrolled in the study. Eighty age- and sex-matched healthy nonsmoker controls were taken for comparison. The mean age of our study population was 59.29 \pm 10.3 years. Baseline demographic, clinical, and biochemical features are enumerated in Table 1. Majority of the subjects in our study population were male. Out of 180 COPD patients about two third (67.8%) were smokers and majority of smokers (69.7%) had smoking index in between range of 100–500. majority of the patients were in GOLD Class 2 (40.6%) and almost half of subjects had a duration of illness <5 years. Cough and breathlessness were predominant symptoms in study patients. Mean PCO₂ levels were elevated as was mean total leukocyte count.

Results of biomarker analysis of the study are presented in Table 2. MDA levels, which is a marker of oxidative stress, were significantly higher in COPD patients than controls (5.21 \pm 1.9 vs. 0.71 \pm 0.29 nmol MDA/ml, $P = 0.0001$) [Table 2 and Figure 1b] and serum iron levels were also significantly elevated in patients vis-à-vis controls (169.85 \pm 85.49 vs. 79.32 \pm 24.39 μ g/ml, $P = 0.0001$). On the contrary, mean level of antioxidant enzymes catalase (0.13 \pm 0.12 U/ml), and SOD (10.57 \pm 7.71 U/ml) were significantly diminished in cases compared to control population and the levels of serum copper were also significantly diminished in cases (63.33 \pm 54.04 vs. 102.02 \pm 10.88 μ g/ml, $P = 0.0002$); [Table 2 and Figure 1a, c and d]. Among patients of COPD, the serum level of all biomarkers of oxidative stress (MDA and serum iron) was significantly higher in males compared to females [$P = 0.0001$, Table 3]. Consequently, the antioxidant levels (catalase and SOD) were correspondingly, significantly lower in male population vis-à-vis female cohort ($P = 0.0001$). All these data point toward a greater oxidative and anti-oxidative imbalance in males when compared to their female COPD counterparts.

Among patients with COPD, the mean levels of serum biomarkers of oxidative stress (MDA and serum iron) were significantly higher in smokers compared to nonsmokers ($P = 0.0001$). Consequently, the antioxidant levels (catalase, SOD, and copper) were significantly lower in

Table 1: Baseline demographic, clinical, and biochemical parameters of study subjects

	Cases	Controls	P
Age (years)			
50	28 (15.6)	28 (35)	0.13
50-60	72 (40)	32 (40)	
61-70	61 (33.9)	16 (25)	
>71	19 (10.6)	4 (5)	
Male sex, n (%)	136 (75.6)	56 (70)	0.55
COPD GOLD stages			
1	7 (3.9)	NA	
2	73 (40.6)		
3	60 (33.3)		
4	40 (22.2)		
Smokers	122 (67.8)	NA	
Pack years (mean±SD)	17.56±13.83		
Smoking index			
<100	12 (9.8)		
100-500	85 (69.7)		
501-1000	22 (18.0)		
>1000	3 (2.5)		
Symptoms			
Cough	134 (74.4)	NA	
Breathlessness	180 (100)		
Pedal edema	85 (47.2)		
Fever	87 (48.3)		
Clubbing	12 (6.7)		
Duration of illness years		NA	
<5	85 (47.2)		
5-10	64 (35.6)		
>10	31 (17.2)		
Arterial blood gas analysis (mean)			
pH	7.37±0.07	NA	
PCO ₂ (mmHg)	51.72±15.41		
PO ₂ (mmHg)	60.49±12.37		
Biochemical parameter			
Hemoglobin (g %)	13.08±2.06	NA	
Total leukocyte counts (/mm ³)	12,700±4927.86		
Serum sodium (meq/L)	137.15±5.37		
Serum potassium (mmol/L)	3.96±0.81		
Serum urea (mg/dl)	42.07±15.93		
Serum creatinine (mg/dl)	1.06±0.37		
Serum bilirubin (mg/dl)	0.77±0.032		

GOLD: Global initiative for Chronic Obstructive Lung Disease, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, NA: Not available

Table 2: Comparison of biomarkers between cases and controls

Markers	Cases (n=180)	Controls (n=20)	P ^a
MDA (nmol MDA/ml)	5.21±1.95	0.71±0.29	0.0001*
Catalase (U/ml)	0.13±0.12	1.05±0.45	0.0001*
SOD (U/ml)	10.57±7.71	37.03±5.93	0.0001*
Iron (µg/dl)	169.85±85.49	79.32±24.39	0.0001*
Copper (µg/dl)	63.33±54.04	102.02±10.88	0.002*

^aUnpaired t-test, *Significant. MDA: Malondialdehyde, SOD: Superoxide dismutase

smoking population vis-à-vis nonsmoking cohort ($P = 0.0001$ for former two and 0.01 for latter). All these data corroborate with a greater oxidative and anti-oxidative pathway imbalance in smokers. However, nonsmoking COPD patients still have significantly higher values of oxidative markers compared to their non-COPD counterparts.

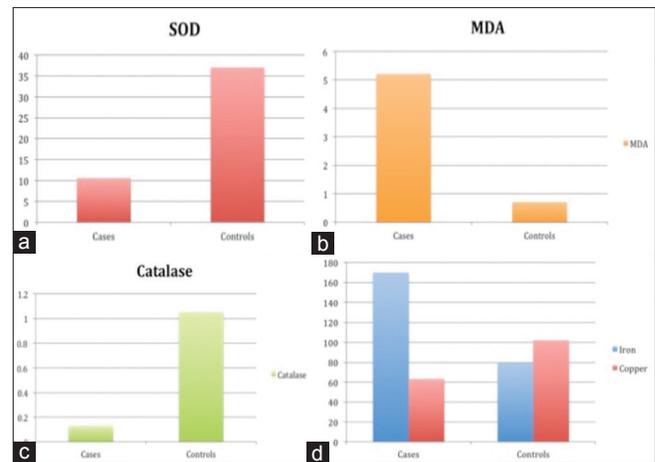


Figure 1: Distribution of biomarkers among chronic obstructive pulmonary disease patients (cases) and controls, (a) superoxide dismutase levels (in U/ml) were significantly decreased in cases ($P = 0.0001$), (b) serum malondialdehyde levels (in nmol MDA/ml) were significantly higher in cases ($P = 0.0001$), (c) serum catalase levels (U/ml) were significantly diminished in cases ($P = 0.0001$), (d) serum iron levels (&# 956; gm/dl, blue bars) were significantly higher ($P = 0.0001$) in cases and serum copper levels (&# 956; gm/dl, red bars) were significantly lower in cases ($P = 0.002$)

The serum levels of oxidative stress marker MDA were found to be significantly elevated in higher GOLD Classes (III, IV) when compared to lower GOLD Classes (I, II). There was a similar significant pattern of prevalence higher serum iron levels in higher GOLD class and vice versa. The levels of serum antioxidants (catalase and SOD) diminished significantly in higher GOLD grades when compared with lower grades.

There was no difference in oxidative stress markers according to site of enrolment – outpatient, inpatient, or intensive care setting. This implies that oxidative stress is prevalent at all stages of COPD. Similarly, there was no significant difference in distribution of antioxidant enzymes the different care setting from which the patients were enrolled. However, serum copper levels tended to be lower in an outpatient setting compared with other two setting with difference reaching borderline significance ($P = 0.08$).

Of the various symptoms, the presence of cough significantly correlated with higher levels of MDA and iron ($P = 0.001$). On the contrary, it predicted lower levels of catalase, SOD, and copper. Cough also more frequent in high COPD severity grades than lower grades ($P = 0.04$). This could explain the relationship of cough and higher levels of oxidative stress in the study. The levels of MDA correlated positively with number of pack years and increasing age ($r = 0.24$, $P = 0.02$ and $r = 0.15$, $P = 0.01$). The levels of catalase and SOD negatively correlated with age ($r = -0.14$, $P = 0.05$ and $r = -0.23$, $P = 0.001$). MDA levels had also negative correlation with FEV₁ and forced vital capacity (FVC) ($r = -0.19$, $P = 0.01$ and $r = -0.21$, $P = 0.004$; [Table 4]). Levels of other markers did

not significantly correlate with pack-years, duration of illness, and age.

The levels of MDA had negative correlation ($r > 0.50$, $P < 0.01$) with catalase, SOD, copper [Figure 2a and b]. Catalase also had negative correlation with iron and copper and positive correlation with SOD. SOD levels positively correlated with copper and inversely with iron.

DISCUSSION

The study results support the oxidant and antioxidant imbalance theory of COPD. Lungs are exposed to high levels of free radicals. Production of reactive oxygen species has been found directly linked to oxidation of

proteins, DNA, and lipids, which may cause direct lung injury or may induce a variety of cellular responses through the generation of secondary metabolic reactive species. Membrane lipids are highly susceptible to free radical damage which is found to be highly detrimental to the functioning of the cell. MDA is a product of lipid peroxidation and an indirect measure of free radical activity in body. As free radical injury increases lung function decreases. Oxidative stress is reported to play an important role in the pathophysiology of COPD. The aim of the present study was to evaluate the oxidant-antioxidant imbalance in healthy nonsmoker controls and COPD group. The levels of oxidative markers such as MDA were significantly higher in COPD patients when compared with controls. Similarly, the levels of antioxidants – catalase and SOD were significantly reduced in patients of COPD. Various studies have similarly found significantly raised levels of MDA and reduced levels of catalase and SOD in patients of COPD when compared to healthy controls.^[18,19] However, very few studies have evaluated role of metals in COPD. We found significantly higher levels of iron (as a marker of oxidative stress) and low copper in COPD patients as compared to controls. The part played by copper in oxidant-antioxidant mechanism is controversial. Some studies have labeled it as an oxidant and demonstrated higher copper levels in COPD patients.^[20] Other studies have highlighted role of copper as an integral part of copper-zinc SOD system, and hence, as an antioxidant.^[21] In the present study, copper levels were hand in glove with antioxidant enzymes catalase and SOD and inversely correlated with MDA and iron. In a nutshell, copper behaved similar to conventional antioxidants in our study.

Gender and smoking had discriminating effects on oxidative and antioxidant imbalance. In our study, males had higher serum level of all biomarkers of oxidative stress (MDA and serum iron) compared to females. The level of antioxidant enzymes was depleted in females when compared to males. Very few studies have elucidated gender differences in levels of oxidative markers. Our study would be first of its kind to show signal of gender differences of oxidative markers. The higher prevalence of smoking and greater external exposure would be key factors for this difference. Role of sex hormones may have some role. Smoking patients with COPD in our study had higher levels of oxidative stress markers and diminished levels of antioxidant enzymes when compared to nonsmokers. The results are not surprising as cigarette smoke is the prime generator of oxidative free radicals.^[22] However, nonsmoking COPD patient do continue to have oxidative stress from other sources such as respiratory infections, inflammation, dust, and air pollution. Depletion of naturally occurring antioxidants also plays a major role in perpetuation of oxidative stress.

With increasing grades of GOLD class for COPD severity, the levels of MDA and iron were progressively increased.

Table 3: Comparison of markers between male and female among the chronic obstructive pulmonary disease subjects

Markers	Gender		P ^a
	Male	Female	
MDA (nmol MDA/ml)	5.59±1.86	4.05±1.77	0.0001*
Catalase (U/ml)	0.10±0.11	0.21±0.13	0.0001*
SOD (U/ml)	8.28±5.92	17.63±8.36	0.0001*
Iron (µg/dl)	184.39±79.34	123.90±88.87	0.0001*
Copper (µg/dl)	60.63±61.08	71.70±18.76	0.23

*Significant. MDA: Malondialdehyde, SOD: Superoxide dismutase

Table 4: Correlation of biomarkers with forced expiratory volume 1 s and forced vital capacity among chronic obstructive pulmonary disease subjects

Markers	Correlation coefficient, P		
	FEV ₁	FVC	FEV ₁ /FVC ratio
MDA (nmolMDA/ml)	-0.19, 0.01*	-0.21, 0.004*	0.07, 0.32
Catalase (U/ml)	-0.10, 0.15	-0.06, 0.39	-0.07, 0.34
SOD (U/ml)	-0.07, 0.34	-0.01, 0.86	-0.05, 0.44
Iron (µg/dl)	0.09, 0.21	0.04, 0.57	0.03, 0.62
Copper (µg/dl)	0.01, 0.91	-0.003, 0.97	-0.03, 0.66

*Significant. FEV₁: Forced expiratory volume 1 s, FVC: Forced vital capacity, MDA: Malondialdehyde, SOD: Superoxide dismutase

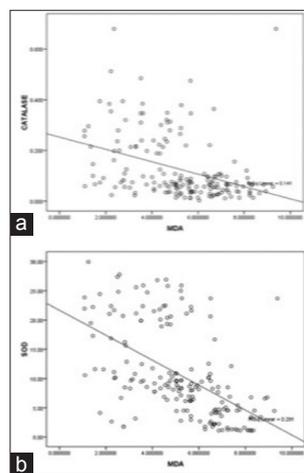


Figure 2: Scatter diagram showing negative linear correlation of malondialdehyde with catalase (a) and superoxide dismutase (b), respectively

Similarly, catalase and SOD were depleted significantly with advancing GOLD stages. Copper levels followed similar trend but failed to show significance.

The elevated oxidative stress biomarkers in stable COPD patients (those attending outpatient department) indicate its predominant role in pathogenesis and not a second fiddle to exacerbations or infections. Surprisingly, the presence of cough indicated high-oxidative stress and diminished antioxidants.

The levels of MDA correlated positively with number of pack years and increasing age. MDA levels had also negative correlation with FEV₁ and FVC. The levels of MDA had negative correlation with catalase, SOD, copper. Catalase levels had also negative correlation with iron and positive correlation with SOD and copper.

Our study and various studies^[23,24] mentioned clearly prove the point that MDA is the marker which has consistently shown correlation with lung functions, namely, FEV₁ and hence disease severity.

The understanding of COPD has undergone a paradigm shift in recent years. It is now considered rather a systemic disease associated with extrapulmonary manifestations such as cardiovascular disease, diabetes, obstructive sleep apnea, and metabolic syndrome.^[25] Even subclinical atherosclerosis is common in COPD patients contributing to overall COPD morbidity.^[26] Oxidative stress can be the only plausible common pathogenetic link between COPD and other systemic manifestations.

COPD is a chronic disease without any disease modifying therapy till date. Oxidative stress is potential mechanism which can be altered to halt its progression. A biomarker-based (preferably MDA) study can be utilized to assess the efficacy of novel antioxidant or other agents in modifying the course of this disease.

The primary limitations of the study include smaller sample size and lesser number of healthy volunteers compared to diseased subjects. Lack of follow-up of these patients over time to see the temporal trends of these biomarkers values is also one.

CONCLUSION

Oxidative stress markers (MDA and iron) are significantly elevated in North Indian patients of COPD, whereas antioxidant (catalase, SOD, and copper) levels are depleted. Male and smoking COPD patients demonstrate this disparity further. Of these markers, MDA levels correlate with decline in lung functions (FEV₁ and FVC).

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Conflicts of interest

There are no conflicts of interest.

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Surgery for Graves' Disease

Kul Ranjan Singh and Anand Kumar Mishra

Abstract

Graves' Disease (GD) is the commonest cause of hyperthyroidism followed by toxic nodular goitre. Patients presenting as goitre with clinical features of hyperthyroidism are to be carefully evaluated with biochemically with thyroid stimulating hormone (TSH), free thyroxine (fT4) and radionuclide scan (Technitium-99/ Iodine-123). Those with GD also have raised thyroid receptor stimulating antibody levels. Patients are simultaneously evaluated for eye disease and managed accordingly. Initial treatment is rendering patient euthyroid using anti thyroid drugs (ATD) and if remission does not occur either continue medical therapy or proceed for definitive therapy by radioactive iodine ablation (RAI) or surgery. In last decades there is ample literature preferring surgery as preferred definitive therapy. Surgery in thyroid disease has become safer with development of many intra-operative adjuncts but it should be performed by high volume thyroid surgeon. The procedure of choice is near total or total thyroidectomy as it avoids recurrences. Patients who are not eligible or willing for surgery can be managed with RAI.

Keywords: hyperthyroidism, Graves' Disease, thyroidectomy, radioactive iodine

1. Introduction

Graves' Disease (GD) is the commonest cause of hyperthyroidism world over representing more than 50% of hyperthyroid patients [1]. A woman is 7–10 times more likely to be affected by it [2]. The incidence of autoimmune thyroid diseases like GD and Hashimoto's thyroiditis is on the rise in tropical countries probably due to environmental immunological factors [3]. GD has systemic manifestations. Eyes are involved to variable extent in more than half the patients. Treatment aims to restore to the thyroid hormones to normal levels along with achieving remission and care of ophthalmological manifestations. Anti-thyroid drugs (ATD), Radioactive Iodine (RAI) and surgery are the current modalities of treatment [1]. They have their unique indications, advantages, disadvantages and complications. ATD are the usual first line of treatment. Relapsing patients or GD with certain co existing conditions may require a definitive treatment. RAI or surgery are indicated in such patients. The choice of definitive therapy depends on the patient and treating physician. Patients involvement in decision making has been associated with increased patients satisfaction [4, 5].

2. Epidemiology and pathogenesis

The peak incidence of GD is observed between 30 to 50 years of age. Annual reported incidence of GD is 50 and of ophthalmopathy is 16 per 100000 population.

Orbital imaging if performed in all patients of GD will reveal changes of ophthalmopathy in upto 70% of patients. Approximately 3% of women and 0.5% of men during their life time can develop GD [6].

GD is an organ specific auto immune disease caused by thyroid stimulating hormone receptor (TSHR) circulating stimulating auto antibodies. The TSHR stimulating antibody binds to leucine rich extracellular domain of TSHR on surface of thyrocytes and orbital fibroblasts and IGF1 receptors. After binding it increases production of intracellular cyclic AMP causing thyrocyte growth and increased thyroid hormone production.

3. Diagnosis

Measurement of Free T4/Free T3 and TSH is the initial diagnostic test. In overt hyperthyroidism FT4 and FT3 are elevated but in milder hyperthyroidism FT4 may be normal with only FT3 elevation. TSH R antibody is sensitive (97%) and specific (98%) tool for accurate diagnosis of GD [7]. High resolution ultrasound reveals diffuse goiter and hypoechogenicity. Diagnosis is confirmed by thyroid scintigraphy by Tc⁹⁹ pertechnatate or I¹²³ scintigraphy. Scintigraphy is definitely needed for diagnosis.

4. Treatment options

Anti-thyroid drugs (ATD) are used in the initial management of GD with aim to achieve euthyroidism. Once patient is euthyroid it should be maintained to achieve remission. About half of the patients go into remission after 18 to 24 months of treatment with ATD. Patients without remission and recurrent disease (30–40% in the first 12 months and approximately 50–60% in long term) require definitive therapy. Definitive therapy is either surgical or medical ablation of all thyrocytes. The options are radioactive iodine (RIA) or thyroidectomy. After ablative therapy thyroid hormone replacement is provided to control hypothyroidism. There are reports of use of long term ATD to achieve remission. Choice between RIA and thyroidectomy are influenced by physician, patient, institutional and geographical beliefs and practice patterns. The most “effective” therapy for both physician’s and patient perspective will be which will provide rapid euthyroidism and prevent recurrences.

Early and rapid euthyroidism is desirable in all GD patients as it decreases mortality and halts eye disease progression. In a retrospective cohort study of 4189 GD patients regardless of the method of treatment, low TSH at 1 year following GD diagnosis was associated with a 55% increase in cardiovascular mortality (atrial fibrillation, heart failure, pulmonary hypertension, angina pectoris, and stroke) [8]. Lillevang et al. in a cohort study of 235,547 individual investigated association between hyperthyroidism and mortality in both treated and untreated groups and concluded that decreased TSH increases mortality in both groups and with every duration of 6 months of suppressed TSH was associated with 11–13% increase in total mortality [9]. Dale et al. found that even transient hypothyroidism during treatment was associated with greater weight-gain during medical treatment in 162 consecutive hyperthyroid patients [10]. Even consensus statement of the European Group on Graves’ orbitopathy (EUGOGO) recommends avoidance of hypothyroidism as it can cause exacerbation of thyroid eye disease [11].

Thyroidectomy is the only modality of treatment which can provide both rapid euthyroidism and prevent recurrence. There are reports of RAI worsening GD ophthalmopathy [12, 13]. In a systematic review of literature between 2001 and 2011 which included retrospective and prospective studies (14,245 patients) on the

comparison of RAI and surgery as best definitive treatment for GD, reported surgery to be 3.44 times more likely to be successful than RAI ($P < .001$). And total thyroidectomy (TT) was 95.45 times more successful than RAI ($P < .001$) and concluded thyroidectomy as the most successful modality for the management of GD [14].

5. Thyroidectomy

Thyroidectomy has been performed for GD since 19th century. However, the earlier years were fraught with significant morbidity and mortality. Introduction of RAI resulted in a rapid decline in popularity of thyroidectomy for GD. Improvements in medical management and refinements in surgical techniques along with knowledge of long term effects of RAI has renewed interests in surgery and it is re gaining the lost grounds [15–17].

6. Indications for surgery

Surgery is the treatment of choice in those with compressive symptoms attributable to goiter, large goiters, presence/suspicion of co-existing malignancy, GD with non-malignant nodule with no/reduced uptake of RAI which is large in size, co-existing parathyroid pathology. Those lactating, pregnant or desirous of pregnancy within next 6 months and presence of significant active ophthalmopathy are advised surgery [5, 18–20]. Pediatric patients failing ATD are more likely to undergo thyroidectomy compared to RAI [21]. Intolerance/non-compliance to ATD, patient preference is an indication in themselves for surgery as treatment of choice.

Indications of thyroidectomy in GD patients include following (6C's):

1. ATD Contraindicated: Difficulty with adequate hormonal control on medications, or Intolerance, or recurrence after ATD treatment
2. RAI Contraindicated: pregnant and nursing women, Large goiter with or without compressive symptoms (dysphagia, dysphonia, dyspnoea), Relatively low uptake of RAI, associated thyroid nodule with confirmed or suspected thyroid malignancy,
3. Coexisting moderate-to-severe active Graves' orbitopathy
4. Associated Coexisting disease: periodic paralysis
5. Other Conditions: Young or pediatric patients, women planning a pregnancy within 6 months, refusal or lack of facilities for RAI, individual preference for surgery
6. Cigarette Smokers (increased risk of exacerbation of eye disease after definitive treatment with radioactive iodine).

7. Advantages of surgery

Surgery is considered the most effective treatment for GD. It results in prompt control of hyperthyroidism. Co-existing thyroid nodules a subset of which may be harboring malignancy are treated concurrently by surgery [22]. Surgery is said to have

the best ophthalmological outcome in ophthalmopathy compared to ATD and RAI although these observations are based on expert opinion or non-randomized clinical trials [23–27]. Recurrence has been seen both after ATD and RAI with the former having a significantly higher recurrence rate. Though the recurrence rates after RAI and surgery are not significantly different, multiple doses of RAI may be required for cure in a given patient [23]. In a meta-analysis involving 1402 patients across 5 continents, surgery had the lowest recurrence rates even though a sub total thyroidectomy was the procedure performed in those with available surgical records [27]. More over surgery avoids the long-term systemic side effects of ATD and radiation exposure of RAI. Though a matter of debate, patients having chosen surgery as a definitive treatment are likely to be more satisfied compared to RAI [5, 28]. Patients preference should always be taken into consideration. Patients are likely to browse the internet for more information. However, the both reliability and comprehension of available information is occasionally questionable [29]. Hence, the treating physician should make available to the patient pertinent information so that patient can make an un biased decision which will further improve compliance and satisfaction to treatment.

8. Geographic variability in preferred treatment options

There are wide variations in the preferred first line treatment for GD. The choice is culmination of patient and physician preference along with disease status. In the US, RAI is likely to be the primary therapy though its popularity is decreasing. ATD are preferred in Latin America, Europe and Japan [30, 31]. Popularity of ATD has also surpassed RAI in New Zealand [32]. Once again ATD are the favored first line treatment in middle east and north African regions. Also, the physician practices were found to be that between European and American preferences, probably attributed to their training and affiliations [33].

9. Peri operative management

Imaging of thyroid is essential, and ultrasonography is useful. It aids in surgical planning and presence of nodule(s) mandates a fine needle aspiration cytology before surgery. Contrast enhanced CT scan (CECT) may be required for large goiters. Euthyroid state should be achieved in all patients before surgery [30]. This is achieved by ATD which is continued till the morning of surgery. Tachycardia if present is controlled by institution on beta blockers. The role of pre-operative Iodine solution remains controversial but the authors favor same [34]. Lugols Iodine/ collosal Iodine/SSKI is given thrice a day for 7–12 days prior to surgery. Iodine has been shown to decrease the vascularity the thyroid and makes the gland firmer. These changes aid the surgeon [35]. Guidelines suggested by various professional bodies aid in management and peri operative preparation of hyperthyroid patients of which American Thyroid Association (ATA) seems to be most commonly followed. However, a study by Siddique Akram et al. found that adherence to ATA guidelines did not impact the outcome significantly but for increased intra operative tachycardia in patient not following ATA guidelines [36]. In fact, almost 28% of the cohort remained hyperthyroid at the time of surgery but no adverse impact was noted. Pre-operative vit D deficiency may result in higher incidence of post thyroidectomy hypocalcemia [37]. Vit D and calcium may be supplemented in pre-operative period to reduce the incidence of post-surgery hypocalcemia [38, 39]. However unpublished data from authors have not shown any advantage of supplementation in reducing post TT hypocalcemia.

Surgery is best performed by a high-volume surgeon in a specialized unit for best outcome [40]. Surgical adjuncts may be utilized as per need, availability, cost constraints and surgeon preference. Meticulous surgery parathyroid vascularity is of prime importance in bettering outcomes. Parathyroid auto transplantation after inadvertent injury or excision results in increased occurrence of temporary hypocalcemia but not permanent hypocalcemia [41].

Post thyroidectomy, patients are kept under observation for development of hypocalcemia or risk of bleed. These were traditionally said to occur at a higher incidence after surgery performed for GD [41]. Hungry bone syndrome, Vitamin D deficiency, female sex are factors that have been associated with apparent higher incidence of post TT hypocalcemia in GD. However, recent studies have concluded that hypocalcemia and post thyroidectomy bleed do not occur at a significantly higher rate in GD [42]. Post TT PTH may be evaluated as per institutional protocols to predict hypocalcemia and plan early discharge. PTH gradient is said to better predict hypocalcemia than any single value. Same day safe discharge of patients is feasible for GD after surgery with no adverse outcomes [43]. ATD are discontinued and Beta blockers if prescribed are tapered gradually in the post-operative period. Thyroxine supplement is started between POD1–7 at a dose of 1.6–2.1 microgram/Kg.

10. Rapid preparation for Graves surgery

Patients are usually rendered euthyroid by ATD to reduce peri operative complications with thyroid storm being the most dreaded one. However, a subset of patients may require urgent/emergent surgery in view of significant compression, intolerance of drugs or failure of drugs. Such patients may be subjected to a rapid preparation protocol where in two or more of dexamethasone, beta blocker, sodium iodopodate, iopanoic acid, collosal/lugols Iodine, cholestyramine, iodinated radiographic contrast agent, lithium and ATD if tolerated are used for 10–12 days prior to anticipated surgery. No significantly increased morbidity has been reported after surgery in the rapidly prepared patients and this strategy is required and is feasible in a subset of patients [44–46]. The occurrence of thyroid storm is rare and biochemically hyperthyroid patients may undergo thyroidectomy safely if the surgeon and anesthetist are comfortable [47]. However, the consensus remains that the outcome is best when surgery is performed on a euthyroid patient.

11. Choice of surgical procedure

Bilateral subtotal thyroidectomy (STT), Dunhill procedure (DP), near total thyroidectomy (NTT) and total thyroidectomy (TT) are the four procedures that have been or are being performed for GD. STT, DP, NTT were the procedure of choice till 21st century due to said higher incidence of hypoparathyroidism, nerve damage or hematoma [15]. However, these have not been verified in recent large studies or meta-analysis [48]. A retrospective cohort study 8032 patients of benign thyroid disease having undergone STT or TT found no difference in temporary or permanent nerve damage and permanent hypoparathyroidism though temporary hypocalcemia was significantly higher in TT compared to STT (13.12% Vs. 2.7%) [49]. A similar trend has been seen in most other studies. TT for GD has been found to have lower rates of recurrent hyperthyroidism compared to other procedures (STT more than DP) [17, 50]. The nerve damage rates have been higher however hypocalcemia rates have been slightly higher though they do not reach statistical

significance [50]. The choice of surgical procedure did not have a difference in their effect on Graves' ophthalmopathy [17, 50]. RAI with steroid cover was found to be not inferior to surgery. The TT performed by trained surgeons at high volume center have no higher rates of these morbid complications. More and more TT are now being performed for benign diseases throughout world. Thomas WT et al. in an analysis of nationwide in patient analysis in US noted an increase in TT for benign diseases from 17.6% in 1993–1997 to 39.6 in 2003–2007 [51]. This trend is seen across the globe even in less developed regions [40, 52]. However TT may be avoided in situations where lifelong thyroxine supplements may be unreliable, more common in the lesser developed countries [3]. Never the less, 2016 ATA guidelines for Hyperthyroidism suggest that a NTT of TT should be performed for GD if surgery is being contemplated [30].

12. Disadvantages of surgery

Patients would require lifelong thyroxine replacement after thyroidectomy and compliance may be an issue in some. Also, potential risk of permanent hypoparathyroidism and recurrent laryngeal nerve damage or neck hematoma are present. However, in trained hands, their incidence is no higher than after surgery for euthyroid goiters. Vis a vis ATD and RAI, surgery is the least cost effective first line treatment of Graves' Disease [53, 54]. In recurrent GD after ATT, surgery was more cost effective than RAI or lifelong ATD to a large extent [55]. The cost implications are likely to vary across the globe depending on various factors.

13. Surgical approach to thyroid

Though conventionally, open thyroidectomy through a transverse collar incision is the standard of care, heightened cosmetic demands of patients along with refinements in surgical instruments and surgical training has resulted in significant shift favoring minimally invasive procedures. Meta-analysis of 846 cases between 1999–2011 by Zhang et al. concluded that endoscopic thyroidectomy provides better cosmetic satisfaction along with lesser blood loss at the expense of higher costs and operative time with acceptable rates of hypocalcemia and nerve compromise [56].

Robotic surgery is now a feasible option for Graves' Disease with comparable complication rates [57]. Also, larger glands can be excised via robotic technique. Retrospective analysis of 44 robotic TT via bilateral axillo-breast approach was no inferior when compared to 144 cases of open thyroidectomy in terms of recurrence, hypocalcemia and nerve damage on prolonged follow up of 35 months [58]. This is now a valid option for those concerned about cosmesis.

14. Conclusion

Etiology of hyperthyroidism has to be determined thoroughly to determine the line of management. Radioactive iodine ablation (RAI) or surgery is the main modality of treatment in GD. Anti-thyroid drug is essential to make the patient euthyroid prior to definitive therapy. Prompt discussion with patients regarding delayed outcome and retreatment in those who opt for RAI is mandatory. Surgical treatment of choice in the form of NTT or TT ought to be performed in a high-volume centre to reduce complication and recurrence. Toxic adenoma and TMNG are managed similarly to GD i.e., rendering euthyroid with ATDs, followed by

definitive therapy. Extent of surgery in toxic solitary adenoma depends on radiology, nuclear imaging after malignancy is ruled out. Newer ablative therapies like RFA, EA, LTA are considered as a substitute for definitive therapy in selective patients. Nonetheless malignancy should always be treated by surgery.

Conflict of interest

“The authors declare no conflict of interest.”

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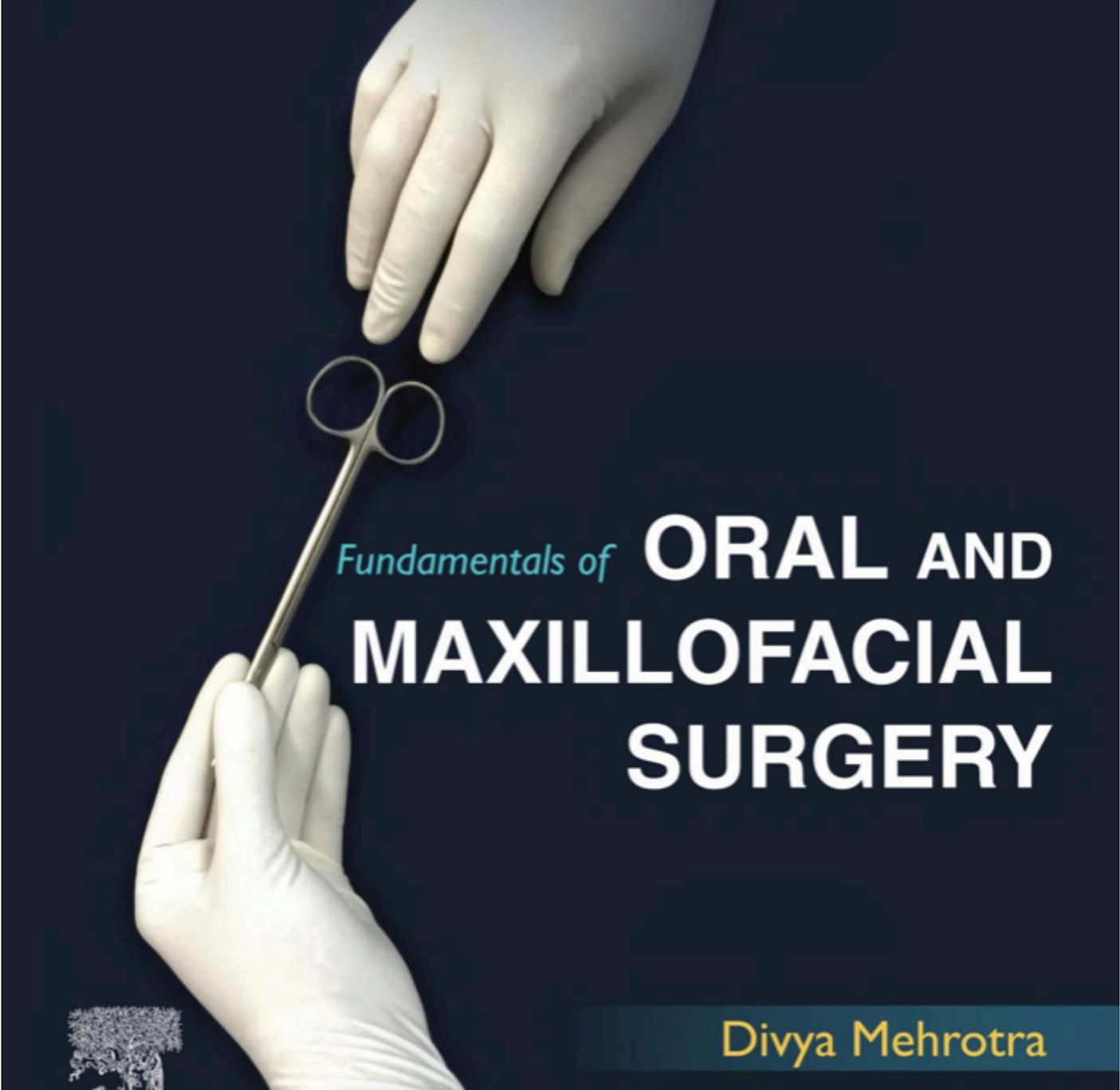
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Fundamentals of **ORAL AND
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SURGERY**

Divya Mehrotra



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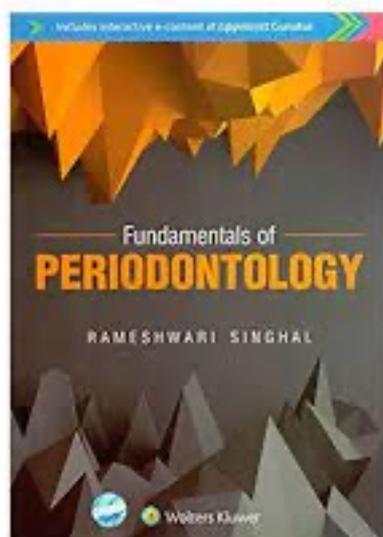
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