SINGAPORE DENTAL JOURNAL

www.worldscientific.com/worldscinet/sdj

Sum Chee Peng

Singapore Dental Association

World Scientific

Singapore Dental Journal, Vol. 39 (2019) 1–9

DOI: 10.1142/S2214607519300015

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Mini-dental implants for definitive prosthesis retention — A synopsis of the current evidence

Ben Wang*, Ho Kok Sen, Neo Tee Khin, Ansgar C. Cheng

Specialist Dental Group, Mount Elizabeth Medical Centre, 3 Mount Elizabeth #08-03, 228510, Singapore

Keywords:
Dental implant
mini-dental implant
prosthesis retention

A B S T R A C T

Background: This narrative review provides an evidence-based overview of the comparison between mini-dental implants (MDI) and conventional dental implants for definitive prosthesis retention. In addition, recommendations are made on whether the use of reduced diameter dental implants is more appropriate.
Method: A literature review was conducted via electronic search addressing the following topics: (1) osseointegration, (2) peri-implant soft tissue characteristics, (3) biomechanics, (4) implant survival and (5) implant success.
Conclusion: The procedure for dental implant prosthetic rehabilitation should preferentially include conventional dental implants (i.e. $>$ 3 mm fixture diameter). Small (3–3.25 mm) and narrow (3.3–3.5 mm) dental implants should primarily be used in non-load-bearing regions. MDI ($<$ 3 mm) should be considered to retain definitive prosthesis, only for reasons of anatomy or patient-centred preferences and as a last resort. If MDI are to be used, patients should be made aware of the lack of long-term, high-quality evidence as a part of the informed consent process and that most of the prospective data available pertain to MDI retaining complete dentures.

Introduction

The modern endosseous dental implant is a common replacement option for missing teeth.[1] Decades of clinical research with long-term follow-ups have shown that even after 10 years or more of functional loading, they continue to exhibit a high survival rate.[1–3] Dental implant treatment is however not without risks nor complications.[1,2] Dental implant treatment is generally not only longer, more invasive and more expensive but the incidence of both biological and technical complications are also greater than tooth-supported prosthesis.[1,2] Increasing patient expectations for cheaper, faster, more aesthetic and less invasive dental implant treatment have also led to a shift of current research interests to implant design features, surgical techniques, biomaterials, and so on to better achieve these demands. Smaller dental implant fixture diameters are one such design feature that may help to simplify the treatment process.

*Corresponding author: Ben Wang, Specialist Dental Group, Mount Elizabeth Medical Centre, 3 Mount Elizabeth #08-03, 228510, Singapore, E-mail: drwang@specialistdentalgroup.com

Whilst there is no universal consensus, conventional endosseous dental implants including those deemed "small" and narrow" are generally regarded as those with a diameter of 3 mm or more.[4,5] They generally come as a two-piece design, consisting of a fixture with an internal connection for a separate screw-retained abutment.[4] They were initially placed with a flap procedure in mature alveolar bone to treat edentulism.[6] Human histological studies on titanium dental implants placed without augmentation have shown that the transition from primary to secondary stability occurs within 4–8 weeks depending on factors such as implant surface characteristics.[7] A structural and functional connection between ordered living bone and the surface of a titanium dental implant deemed to be satisfactory to bear load occurs between 8 and 12 weeks of healing.[8] The dental implant is then exposed, either provisionally or permanently loaded.

Mini-dental implants (MDI) are generally regarded as those with a diameter of less than 3 mm.[5] Typically, they come as a solid one-piece screw design with a coronal abutment attachment.[4] The first cohort of literature on MDI for prosthesis retention dates to the 1990s when they were initially used as provisional implants to sustain immediately loaded prosthesis during the osseointegration phase of conventional dental implants.[9] During this period, clinicians commonly found that these MDI osseointegrated quite well and were extremely difficult to remove.[10,11] These early clinical findings led to an ongoing interest in their application for use in modern implant dentistry and as orthodontic temporary anchorage devices.[12,13] MDI have distinct advantages over conventional dental implants in terms of versatility. They are less invasive to place, require less surgical time and are cheaper. They are also particularly suitable for the narrow atrophic alveolar ridge to avoid augmentation, where there is a lack of intra-occlusal spacing or close root proximity. These advantages were recognised by national bodies such as the United States Food and Drugs Administration that has provided clearance to various forms of titanium MDI for dental use.[14]

Despite such significant advantages over conventional dental implants, to date, MDI by comparison remain less frequently used in restorative dentistry.[5] Until now, the last narrative review on MDI for prosthesis retention was published in 2011.[15] This current review aims to summarise and provide a balanced overview of the topic by critically evaluating the latest evidence base.

Materials and Methods

Search strategy and data extraction

An electronic search was conducted for the addressed topics. The PubMed database of the US National Library of Medicine and the Excerpta Medica database (Embase) maintained by Elsevier were searched for relevant articles (i.e. experimental studies on animals and humans, observational studies, randomised/controlled trials, systematic reviews/meta-analyses and consensus reports). Data from identified and relevant publications were extracted and, if indicated, presented as evidence tables. Overall findings were summarised in a narrative manner.

Discussion

Osseointegration

Several studies with long-term follow-ups have demonstrated that conventional titanium dental implants of varying surface characteristics can be osseointegrated in the human alveolus as demonstrated by histology and histomorphometric analysis.[16–19] The bone to implant contact (BIC) range identified from this heterogeneous group of studies varies substantially from $<10\%$ to 100% mainly because of differences in methodology of histological processing, implant characteristics, loading time and duration of osseointegration.[20] After 5 years of loading, the BIC of a conventional titanium dental implant in the human alveolus can be expected to be in the region of 75% or more.[16]

The existing literature base provides less information on the osseointegration of MDI. Of the various studies available, most are short-term animal studies of MDI used for orthodontic anchorage.[21–23] A recent animal study that compared titanium MDI with conventional titanium dental implants found both to offer similar osseointegration potential in the animal model.[24] Currently, there is only one human histological study with histomorphometry of MDI placed in the posterior mandible for prosthesis retention, which was immediately loaded. Histomorphometric analysis at 12 weeks revealed a BIC range of 69.8%–86.3%.[25]

Peri-implant soft tissue barrier

Our current understanding of the peri-implant soft tissue barrier is mainly based on animal experimentation.[20,26,27] No studies specifically investigating the peri-implant soft tissue barrier around MDI were identified. A mature soft tissue attachment to an exposed transmucosal dental implant is typically established 6–8 weeks following surgery.[26,27] This soft tissue attachment is comparable to those around natural teeth and consists of an epithelial and supracrestal connective tissue barrier with a mean biological width in the region of 2.93–4 mm.[28,29] The nature of this attachment however differs from that of the attachment around natural teeth.[20] The peri-implant mucosa, for example, has higher collagen to fibroblast ratio and a greater proportion of collagen fibres running parallel to the implant surface.[20] It may also vary depending on factors such as but not limited to the implant angle, depth of placement, surface

material and topography.[29,30] It appears that the peri-implant soft tissue barrier is not as resilient to periodontal inflammation as those around natural teeth. Several experimental gingivitis models have shown even mild marginal inflammation around a dental implant to be associated with deeper probe penetration in comparison to teeth.[31,32] This susceptibility is also reflected in recent systematic reviews of the frequency of peri-implant diseases at the patient level which is estimated in the region of 43%–63.4% for peri-implant mucositis and 18.8%–22% for peri-implantitis.[33–35]

Factors found to be associated with a greater risk of developing peri-implant diseases include but are not limited to a history of periodontitis, smoking, an increased number of implants placed, high plaque index, lack of supportive therapy, retained cement, uncleansable suprastructures, absence of keratinised tissue, clinician experience and the implant type or brand.[36–40] It is important to note that not all of these factors are equally well studied nor have the same quality of evidence supporting them. A recent review from the 2017 World Workshop found only strong evidence for the increased risk of peri-implantitis in patients who have a history of chronic periodontitis, poor plaque control skills and lack of maintenance care.[41] Irrespective of the choice of dental implant used, when these potential risk factors/indicators are not accounted for in the dental implant treatment planning process, catastrophic failure may ensue (Fig. 1).

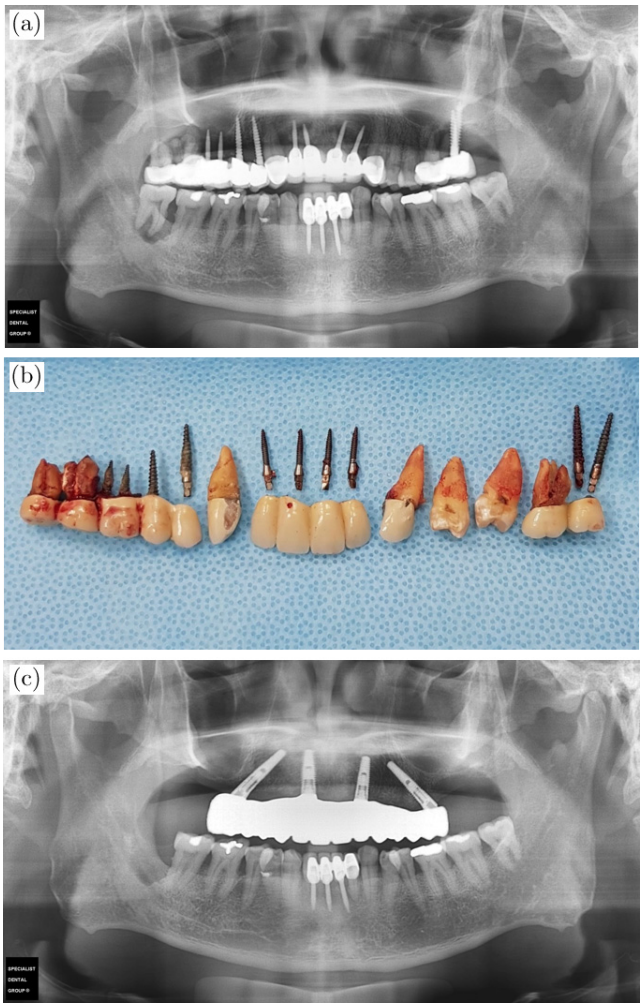


Fig. 1. Maxillary arch MDI failure in a male patient approximately 5 years following placement. (a) Dental panoramic radiograph showing generalised severe peri-implantitis and bone loss. (b) Maxillary full arch dental clearance (note the excessive splinting and use of fixtures). (c) Dental panoramic radiograph shows that the Nobel BioCare All-on-4® implant system replaces the previous 10 maxillary arch MDI.

Biomechanics

Masticatory loading places strains not only on the dental implant fixture itself but also on the implant fixture-alveolus interface.[42–44] There are fewer laboratory and clinical studies that demonstrate the clinical efficacy of dental implants of reduced diameters. Cyclic loading test data mimicking long-term masticatory function remain largely unpublished by manufacturers.[44,45] The body of evidence indicates a trend towards increasingly reduced dental implant diameters to be associated with a higher risk of fatigue failure, distortion and fracture, especially in areas of high loading.[42,44–46] Reduced diameter dental implants are also associated with an increase in crestal alveolar bone strain under load especially when also of reduced length and greater taper.[43,44] This may induce a levering effect on the dental implant fixture and predispose to marginal bone loss.[43] For example, when lateral forces were applied to MDI implants of 2.4 mm × 13 mm dimensions compared with conventional 4 mm × 13 mm Branemark implants (Nobel Biocare™) embedded in a block mixture, greater discrepancies in mobility were observed in the MDI implant fixture/block matrix interface.[47] The splinting of multiple dental implants can reduce this effect but may hinder cleansability.[48,49] Reduced diameter dental implants therefore tend to be constructed from mechanically stronger metal alloys such as titanium–zirconium or titanium–aluminium–vanadium and are recommended for placement in denser bone, in non-load bearing areas with longer length fixtures.[43,44,50,51]

Although the precise specifications are not available for many MDI, most are made from various titanium alloys and constructed as a solid one-piece screw with a coronal abutment attachment.[15] The absence of a hollow internal connection to some extent makes up for their reduced dimensions by strengthening load resistance. The advantages of this design include fewer implant components,

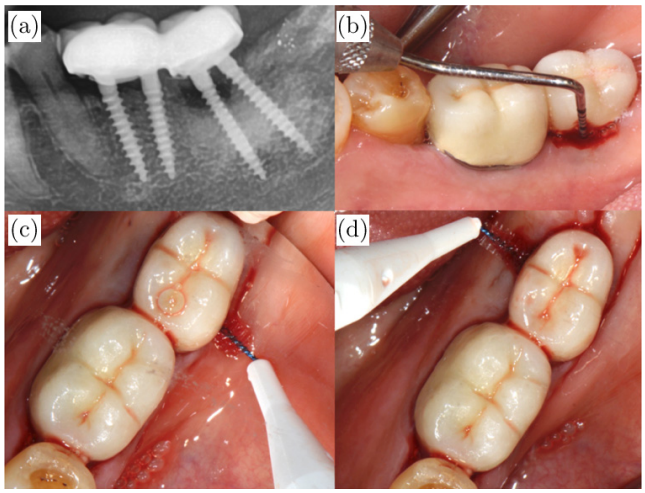


Fig. 2. Four MDI were used to replace 2 molars in the left mandibular arch in 2016. The patient was referred in April 2018, with the complaint of mobility, drifting of his upper teeth, bleeding gums and difficulty in cleaning the LL6 and LL7 implants. A diagnosis of localised severe periodontitis, pathological tooth migration and moderate/severe peri-implantitis was made. (a) Periapical radiograph showing bone loss to the mesial MDI of the LL7. (b) Probing depth of 9 mm with pus and bleeding. (c/d) A small inter-dental brush of 0.4 mm diameter was insertable but only to certain niches and with an awkward angle of insertion. The patient struggled with self-performed oral hygiene around the LL6 and LL7.

cheaper costs and the absence of a fixture-abutment micro gap. Moreover, MDI are less able to customise their emergence profile and can usually only sustain cement-retained restorations. Another drawback with this design is that MDI are used to replace teeth of a much larger cervical diameter. To attain the necessary support and retention of the overlying prosthesis and prevent mechanical failure, multiple MDI are often used to replace a large premolar or molar unit (Figs. 1 and 2). This aspect makes their overlying suprastructures much harder to maintain for the patient due to excessive undercuts and difficulty of cleaning between two or more MDI placed in near proximity.

Implant survival

Survival is a loose assessment criterion assessing only if the dental implant is still present in the mouth without consideration of its overall health. For example, a dental implant with mobility, pus and peri-implant bone loss, which require multiple interventional treatments, would still be regarded as having "survived." Most systematic reviews that assess the survival rate of dental implants for prosthesis retention do not differentiate between implant diameter in their inclusion criteria.[1–3,52,53] After assessing included studies of at least controlled clinical trials or those of higher quality, most dental implants employed were found to be of the conventional two-piece type. These systematic reviews of dental implants retaining various prosthesis types have a high mean cumulative survival rate in the 95% region after 5 years and 85%–95% region after 10 years or more of functional loading.[1–3,53] Of the few systematic reviews that do differentiate between dental implant fixture diameters for prosthesis retention, studies on MDI were only available for single, short span non-load-bearing and edentulous regions.[4,5,54,55] Prospective studies with at least 1 year follow-up reporting on the survival rate of MDI for definitive prosthetic treatment were available only for complete dentures and are presented in Table 1. The overall quality of evidence of these studies was low with a high risk of bias, lack of clear reporting, short follow-ups and small sample sizes. Within limitations of the evidence available, it appears that MDI retaining a range of prosthesis have a cumulative survival rate in the region of 80%–100% after a mean of around 3-years follow-up.[4,5,54–62]

Implant success

Success is a strict assessment based on one or more specific criteria not only to determine whether the dental implant is still present in the mouth but also to determine its health. Success is deemed to be a much more important indicator of the efficacy of dental implant treatment than survival. Measuring dental implant success however is a more tedious, resource consuming process and the current body of evidence for dental implant success is less than that of survival. Success rates can also vary greatly in the literature due to the heterogeneity of case definitions used.[63–67] The most historically popular being the Albrektsson criteria.[63] The health of dental implants can be broadly divided into technical complications (e.g. screw loosening, fixture fracture, ceramic chipping, etc.) or biological complications (e.g. peri-implant disease, unaesthetic soft tissue recession, neural sensory loss, etc.). Despite the high long-term survival rates of conventional dental implants in the oral cavity, it is estimated that only around 60% or more of dental implants are free from complications within a 5-year period, when a strict success case definition is applied.[1] Currently, there are only a limited number of studies that reported on the success rate of MDI. Prospective studies with at least 1-year follow-up that reported on the success rate of MDI for definitive prosthetic treatment are presented in Table 2 and were again available only for complete dentures. These limited number of studies indicate MDI retaining complete dentures to have a success rate in the range of 78.2%–95.9% over 1–3 years of follow-up.[58,59,62,68]

Table 1
Survival rate of MDI.

Study name	Type of study and follow-up	Study sample	Type of implant/prosthesis/ loading/site	Findings
Morneburg and Pröschel[56]	Prospective Follow-up of 3.3–8.3 years (mean 6 years)	67 patients 134 MDI	2.5 mm × 9–15 mm Komet MDI Complete denture on non-splinted MDI abutments Delayed loading Anterior mandible	95.5% cumulative survival rate 6/134 MDI failed (4 MDI failures in the first year)
Jofre *et al.*[49]	Randomised clinical trial Follow-up of 2 years for all patients Group 1 ($n = 23$) MDI insertion with surgical guide Group 2 ($n = 22$) MDI insertion without surgical guide	45 patients 90 MDI	1.8 mm × 15 mm Sendax IMTEC™ MDI Complete denture on non-splinted MDI abutments Immediate loading Anterior mandible	94.4% cumulative survival rate 5/90 MDI failed over 2 years
Elsyad *et al.*[58]	Prospective Follow-up of 3 years for 26 patients (2 drop-outs)	28 patients 112 MDI	1.8 mm × 12–18 mm Sendax IMTEC™ MDI Complete denture on non-splinted MDI abutments Immediate loading Anterior mandible	96.2% survival rate 4/104 MDI failed over 3 years ($n = 26$)
Preoteasa *et al.*[59]	Prospective Follow-up of 3 years for all patients	23 patients 110 MDI	1.8/2.1/2.4 mm × 10–18 mm IMTEC/3M ESPE™ MDI Complete denture on non-splinted MDI abutments Immediate loading Anterior mandible and maxilla	92.7% survival rate 8/110 MDI failed over 3 years
Maryod *et al.*[60]	Randomised clinical trial Follow-up of 3 years for 30 patients (6 drop-outs) Group 1 ($n = 18$) Four MDI supporting complete denture with immediate loading Group 2 ($n = 18$) Four MDI supporting complete denture with early loading	36 patients 144 MDI	1.8 mm × 15 mm 3M ESPE™ MDI Complete denture on non-splinted MDI abutments Immediate loading or early loading Anterior mandible	94.2% cumulative survival rate 7/120 MDI failed over 3 years ($n = 30$)
de Souza *et al.*[61]	Randomised clinical trial Follow-up of 1 year for all patients Group 1 ($n = 38$) Four MDI supporting complete denture Group 2 ($n = 42$) Two MDI supporting complete denture Group 3 ($n = 40$) Two conventional implants supporting complete denture	120 patients 316 implants (236 MDI)	2.0 mm × 10 mm, Mini-Drive-Lock™ MDI 4.0 mm × 10 mm, Morse-Lock Straight, Intra-Lock International Inc. Complete denture on non-splinted abutments Delayed loading Anterior mandible	89.5% survival rate for four MDI (group 1) over 1 year (16/152 MDI failed) 82.1% survival rate for two MDI (group 2) over 1 year (15/84 MDI failed)

Table 1 (*Continued*)

Study name	Type of study and follow-up	Study sample	Type of implant/prosthesis/ loading/site	Findings
Zygogiannis *et al.*[62]	Randomised clinical trial Follow-up of 1 year for 49 patients (1 drop-out) Group 1 ($n = 25$) Four MDI retaining complete denture Group 2a ($n = 14$) Two conventional implants retaining complete denture with immediate loading Group 2b ($n = 10$) Two conventional implants retaining complete denture with delayed loading	50 patients 150 implants (100 MDI)	1.8–2.4 mm × 10–18 mm 3M ESPE™ MDI 3.3/4.1 mm × 10/12 mm Straumann SLActive™ or Standard Plus implants Complete denture on non-splinted MDI abutments or splinted conventional implants Immediate or delayed loading Anterior mandible	98% survival rate for four MDI (group 1) over 1 year (2/100 MDI failed)

Table 2
Success rate of MDI.

Study name	Type of study/study sample/ follow-up	Type of implant/site/ prosthesis	Success case definition	Findings
Elsyad *et al.*[58]	Prospective 28 patients 112 MDI Follow-up of 3 years for 26 patients (2 drop-outs)	1.8 mm × 12–18 mm Sendax IMTEC™ MDI Complete denture on non-splinted MDI abutments Immediate loading Anterior mandible	Albrektsson *et al.*[63]	92.3% success rate 8/104 MDI ($n = 26$) were unsuccessful over 3 years
Šćepanović *et al.*[68]	Prospective 30 patients 123 MDI Follow-up of 1 year for all patients	1.8 mm × 13 mm 3M ESPE™ MDI Complete denture on non-splinted MDI abutments Immediate loading Anterior mandible	Buser *et al.*[65]	95.9% success rate 5/123 MDI were unsuccessful over 1 year
Preoteasa *et al.*[59]	Prospective 23 patients 110 MDI Follow-up of 3 years for all patients	1.8/2.1/2.4 mm × 10–18 mm IMTEC/3M ESPE™ MDI Complete denture on non-splinted MDI abutments Immediate loading Anterior mandible and maxilla	Misch *et al.*[66]	78.2% success rate 24/110 MDI were unsuccessful over 3 years
Zygogiannis *et al.*[62]	Randomised clinical trial 50 patients 150 implants (100 MDI) Follow-up of 1 year for 49 patients (1 drop-out) Group 1 ($n = 25$) Four MDI retaining complete denture Group 2a ($n = 14$)	1.8–2.4 mm × 10–18 mm 3M ESPE™ MDI 3.3/4.1 mm × 10/12 mm Straumann SLActive™ or Standard Plus implants Complete denture on non-splinted MDI abutments or splinted conventional implants Immediate or delayed loading	Albrektsson and Zarb[67]	91% success rate for four MDI retaining complete dentures (group 1) (9/100 MDI were unsuccessful over 1 year)

Table 2 (*Continued*)

Study name	Type of study/study sample/ follow-up	Type of implant/site/ prosthesis	Success case definition	Findings
	Two conventional implants retaining complete denture with immediate loading Group 2b ($n = 10$) Two conventional implants retaining complete denture with delayed loading	Anterior mandible		

Conclusion

The overall body of evidence for the efficacy of conventional dental implants for prosthesis retention exceeds more than that of MDI not only in terms of quantity and quality, but also in terms of the diversity of research question investigated. There is currently some evidence for MDI used to retain overdentures and in single, short span non-load-bearing areas; however, this evidence base is generally of low quality and at high risk of bias. There is little long-term data on the survival or success rate of MDI for prosthesis retention. Prospective data identified in this review were available only for MDI retaining complete dentures.

On the basis of the findings from this narrative review, the following recommendations are made:

- The procedure for dental implant prosthetic rehabilitation should preferentially include conventional dental implants (i.e. $>$ 3 mm fixture diameter).
- Small (3–3.25 mm) and narrow (3.3–3.5 mm) dental implants should primarily be used in non-load-bearing regions.
- Only for reasons of anatomy or patient-centred preferences and as a last resort should MDI ($<$3 mm) be considered to retain definitive prosthesis.
- If MDI are to be used, patients should be made aware of the lack of long-term, high-quality evidence as a part of the informed consent process and that most of the prospective data available pertain to MDI retaining complete dentures.

Acknowledgements

The authors have not received any institutional, private, or corporate financial support for the study reported herein. In addition, the authors do not have a financial interest in the companies that manufacture the products in this study.

References

[1] Pjetursson BE, Brägger U, Lang NP, Zwahlen M. Comparison of survival and complication rates of tooth-supported fixed dental prostheses (FDPs) and implant-supported FDPs and single crowns (SCs). *Clin Oral Implants Res* 2007;**18**:97–113.

[2] Jung E, Zembic R, Pjetursson A, Zwahlen BE, Zwahlen M, Thoma DS. Systematic review of the survival rate and the incidence of biological, technical, and aesthetic complications of single crowns on implants reported in longitudinal studies with a mean follow-up of 5 years. *Clin Oral Implants Res* 2012;**23**:2–21.

[3] Moraschini V, Poubel LA, Ferreira VF, dos Santos Porto Barboza E. Evaluation of survival and success rates of dental implants reported in longitudinal studies with a follow-up period of at least 10 years: A systematic review. *Int J Oral Maxillofac Surg* 2015;**44**(3):377–88.

[4] Bidra AS, Almas K. Mini implants for definitive prosthodontic treatment: A systematic review. *J Prosthet Dent* 2013;**109**(3):156–64.

[5] Klein MO, Schiegnitz E, Al-Nawas B. Systematic review on success of narrow-diameter dental implants. *Int J Oral Maxillofac Implants* 2014;**29**:43–54.

[6] Brånemark PI, Hansson BO, Adell R, Breine U, Lindstrom J, Hallen O *et al.* Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scand J Plast Reconstr Surg Suppl* 1977;**16**:1–132.

[7] Bosshardt D, Salvi GE, Huynh-Ba G, Ivanovski S, Donos N, Lang NP. The role of bone debris in early healing adjacent to hydrophilic and hydrophobic implant surfaces in man. *Clin Oral Implants Res* 2011;**22**:357–64.

[8] Schropp L, Wenzel A, Kostopoulos L, Karring T. Bone healing and soft tissue contour changes following single-tooth extraction: A clinical and radiographic 12-month prospective study. *Int J Periodontics Restorative Dent* 2003;**23**(4):313–23.

[9] Barber HD, Seckinger RJ. The role of the small-diameter dental implant: A preliminary report on the Miniplant system. *Compendium* 1994;**15**:1390–2.

[10] Sendax VI. Mini-implants as adjuncts for transitional prostheses. *Dent Implantol Update* 1996;**7**:12–5.

[11] Balkin BE, Steflik DE, Naval F. Mini–dental implant insertion with the auto-advance technique for ongoing applications. *J Oral Implantol* 2001;**27**(1):32–7.

[12] Adell R, Lekholm U, Rockler B, Brånemark PI. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *Int J Surg* 1981;**10**(6):387–416.

[13] Roberts WE, Marshall KJ, Mozsary PG. Rigid endosseous implant utilized as anchorage to protract molars and close an atrophic extraction site. *Angle Orthod* 1990;**60**:135–52.

[14] United States Food and Drug Administration. Pre-market notification; Indication for use statement of mini dental implants. 2003. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf3/K031106.pdf (accessed 1 April 2018).

[15] Flanagan D, Mascolo A. The mini dental implant in fixed and removable prosthetics: A review. *J Oral Implantol* 2011;**37**:123–32.

[16] Piattelli A, Scarano A, Piattelli M. Histologic observations on 230 retrieved dental implants: 8 years' experience (1989–1996). *J Periodontol* 1998;**69**:178–84.

[17] Wilson TG, Schenk R, Buser D, Cochran D. Implants placed in immediate extraction sites: A report of histologic and histometric analyses of human biopsies. *Int J Oral Maxillofac Implants* 1998;**13**:333–41.

[18] Ivanoff CJ, Hallgren C, Widmark G, Sennerby L, Wennerberg A. Histologic evaluation of the bone integration of TiO_2 blasted and polished titanium microimplants in humans. *Clin Oral Implants Res* 2001;**12**:128–34.

[19] Grassi S, Piattelli A, Ferrari DS, Figueiredo LC, Feres M, Iezzi G *et al.* Histologic evaluation of human bone integration on polished and sandblasted acid-etched titanium surfaces in type IV bone. *J Oral Implantol* 2007;**33**:8–12.

[20] Salvi GE, Bosshardt DD, Lang NP, Abrahamsson I, Berglundh T, Lindhe J *et al.* Temporal sequence of hard and soft tissue healing around titanium dental implants. *Periodontol 2000* 2015;**68**(1):135–52.

[21] Ohmae M, Saito S, Morohashi T, Seki K, Qu H, Kanomi R *et al.* A clinical and histological evaluation of titanium mini-implants as anchors for orthodontic intrusion in the beagle dog. *Am J Orthod Dentofacial Orthop* 2001;**119**(5):489–97.

[22] Serra G, Morais LS, Elias CN, Meyers MA, Andrade L, Muller CA *et al.* Sequential bone healing of immediately loaded mini-implants: Histomorphometric and fluorescence analysis. *Am J Orthod Dentofacial Orthop* 2010;**137**:80–90.

[23] Yadav S, Upadhyay M, Roberts WE. Biomechanical and histomorphometric properties of four different mini-implant surfaces. *Eur J Orthod* 2015;**37**(6):627–35.

[24] Dhaliwal JS, Albuquerque RF, Murshed M, Feine JS. Osseointegration of standard and mini dental implants: A histomorphometric comparison. *Int J Implant Dent* 2017;**3**(1):15.

[25] Di Lorio D, Sinjari B, Cupaiolo R, Caputi S, Murmura G. Histomorphometry of 2 immediately loaded mini implants retrieved from human mandible after 3 months: A light and scanning electron microscopy report. *J Oral Implantol* 2013;**39**:280–6.

[26] Berglundh T, Abrahamsson I, Lang NP, Lindhe J. De novo alveolar bone formation adjacent to endosseous implants. *Clin Oral Implants Res* 2003;**14**:251–62.

[27] Abrahamsson I, Berglundh T, Linder E, Lang NP, Lindhe J. Early bone formation adjacent to rough and polished endosseous implant surfaces. An experimental study in the dog. *Clin Oral Implants Res* 2004;**15**:381–92.

[28] Cochran DL, Hermann JS, Schenk RK, Higginbottom FL, Buser D. Biologic width around titanium implants. *A histometric analysis of the implanto-gingival junction around unloaded and loaded non-submerged implants in the canine mandible. J Periodontol* 1997;**68**(2):186–97.

[29] Glauser R, Schüpbach P, Gottlow J, Hämmerle CH. Periimplant soft tissue barrier at experimental one-piece mini-implants with different surface topography in humans: A light-microscopic overview and histometric analysis. *Clin Implant Dent Relat Res* 2005;**7**(s1):44–51.

[30] Nisapakultorn K, Suphanantachat S, Silkosessak O, Rattanamongkolgul S. Factors affecting soft tissue level around anterior maxillary single-tooth implants. *Clin Oral Implants Res* 2010;**21**(6):662–70.

[31] Lang NP, Wetzel AC, Stich H, Caffesse RG. Histologic probe penetration in healthy and inflamed peri-implant tissues. *Clin Oral Implants Res* 1994;**5**(4):191–201.

[32] Schou S, Holmstrup P, Stoltze K, Hjørting-Hansen E, Fiehn NE, Skovgaard LT. Probing around implants and teeth with healthy or inflamed peri-implant mucosa/gingiva. *Clin Oral Implants Res* 2002;**13**(2):113–26.

[33] Atieh MA, Alsabeeha NH, Faggion Jr CM, Duncan WJ. The frequency of peri-implant diseases: A systematic review and meta-analysis. *J Periodontol* 2013;**84**(11):1586–98.

[34] Derks J, Tomasi C. Peri-implant health and disease. A systematic review of current epidemiology. *J Clin Periodontol* 2015;**42**(16):158–71.

[35] Lee CT, Huang YW, Zhu L, Weltman R. Prevalences of peri-implantitis and peri-implant mucositis: Systematic review and meta-analysis. *J Dent* 2017;**62**:1–12.

[36] Serino G, Ström C. Peri-implantitis in partially edentulous patients: Association with inadequate plaque control. *Clin Oral Implants Res* 2009;**20**(2):169–74.

[37] Costa FO, Takenaka-Martinez S, Cota LOM, Ferreira SD, Silva GLM, Costa JE. Peri-implant disease in subjects with and without preventive maintenance: A 5-year follow-up. *J Clin Periodontol* 2012;**39**(2):173–181.

[38] Moraschini V, dos Santos Porto Barboza E. Success of dental implants in smokers and non-smokers: A systematic review and meta-analysis. *Int J Oral Maxillofac Surg* 2016;**45**(2):205–15.

[39] Derks J, Schaller D, Håkansson J, Wennström JL, Tomasi C, Berglundh T. Effectiveness of implant therapy analyzed in a Swedish population: Prevalence of peri-implantitis. *J Dent Res* 2016;**95**(1):43–9.

[40] Staubli N, Walter C, Schmidt JC, Weiger R, Zitzmann NU. Excess cement and the risk of peri-implant disease — a systematic review. *Clin Oral Implants Res* 2016;**28**(10):1278–90.

[41] Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. *J Clin Periodontol* 2018;**89**(1):267–90.

[42] Zinsli B, Sägesser T, Mericske E, Mericske-Stern R. Clinical evaluation of small-diameter ITI implants: A prospective study. *Int J Oral Maxillofac Implants* 2004;**19**(1):92–9.

[43] Petrie CS, Williams JL. Comparative evaluation of implant designs: Influence of diameter, length, and taper on strains in the alveolar crest. *Clin Oral Implants Res* 2005;**16**(4):486–94.

[44] Hasan I, Bourauel C, Mundt T, Stark H, Heinemann F. Biomechanics and load resistance of small-diameter and mini dental implants: A review of literature. *Biomed Tech (Berl)* 2014;**59**(1):1–5.

[45] Allum SR, Tomlinson RA, Joshi R. The impact of loads on standard diameter, small diameter and mini implants: A comparative laboratory study. *Clin Oral Implants Res* 2008;**19**(6):553–9.

[46] Shemtov-Yona K, Rittel D, Machtei EE, Levin L. Effect of dental implant diameter on fatigue performance. *Part II: Failure analysis. Clin Implant Dent Relat Res* 2014;**16**(2):178–84.

[47] Ertugrul HZ, Pipko DJ. Measuring mobility of 2 dental implant fixtures of different configurations: An *in vitro* study. *Implant Dent* 2006;**15**(3):290–7.

[48] Bergkvist G, Simonsson K, Rydberg K, Johansson F, Dérand, T. A finite element analysis of stress distribution in bone tissue surrounding uncoupled or splinted dental implants. *Clin Implant Dent Relat Res* 2008;**10**(1):40–6.

[49] Jofre J, Cendoya P, Munoz P. Effect of splinting mini-implants on marginal bone loss: A biomechanical model and clinical randomized study with mandibular overdentures. *Int J Oral Maxillofac Implants* 2010;**25**:1137–44.

[50] Romeo E, Lops D, Amorfini L, Chiapasco M, Ghisolfi M, Vogel G. Clinical and radiographic evaluation of small-diameter (3.3 mm) implants followed for 1–7 years: A longitudinal study. *Clin Oral Implants Res* 2006;**17**(2):139–48.

[51] Sohrabi K, Mushantat A, Esfandiari S, Feine J. How successful are small-diameter implants? A literature review. *Clin Oral Implants Res* 2012;**23**(5):515–25.

[52] Papaspyridakos P, Mokti M, Chen CJ, Benic GI, Gallucci GO, Chronopoulos V. Implant and prosthodontic survival rates with implant fixed complete dental prostheses in the edentulous mandible after at least 5 years: A systematic review. *Clin Implant Dent Relat Res* 2014;**16**(5):705–17.

[53] Srinivasan M, Meyer S, Mombelli A, Müller F. Dental implants in the elderly population: A systematic review and meta-analysis. *Clin Oral Implants Res* 2017;**28**(8):920–30.

[54] Ortega-Oller I, Suárez F, Galindo-Moreno P, Torrecillas-Martínez L, Monje A, Catena A *et al.* The influence of implant diameter on its survival: A meta-analysis based on prospective clinical trials. *J Periodontol* 2014;**85**(4):569–80.

[55] Lemos CAA, Verri FR, de Souza Batista VE, Júnior JFS, Mello CC, Pellizzer EP. Complete overdentures retained by mini implants: A systematic review. *J Dent* 2017;**57**:4–13.

[56] Morneburg TR, Pröschel PA. Success rates of micro-implants in edentulous patients with residual ridge resorption. *Int J Oral Maxillofac Implants* 2008;**23**(2):270–6.

[57] Jofré J, Conrady Y, Carrasco C. Survival of splinted mini-implants after contamination with stainless steel. *Int J Oral Maxillofac Implants* 2010;**25**(2):351–6.

[58] Elsyad MA, Gebreel AA, Fouad MM, Elshoukouki AH. The clinical and radiographic outcome of immediately loaded mini implants supporting a mandibular overdenture. A 3-year prospective study. *J Oral Rehabil* 2011;**38**(11):827–34.

[59] Preoteasa E, Imre M, Preoteasa, T. A 3-year follow-up study of overdentures retained by mini–dental implants. *Int J Oral Maxillofac Implants* 2014;**29**(5):1170–6.

[60] Maryod WH, Ali SM, Shawky AF. Immediate versus early loading of mini-implants supporting mandibular overdentures: A preliminary 3-year clinical outcome report. *Int J Prosthodont* 2014;**27**(6):553–60.

[61] de Souza RF, Ribeiro AB, Della Vecchia MP, Costa L, Cunha TR, Reis AC *et al.* Mini vs. standard implants for mandibular overdentures: A randomized trial. *J Dent Res* 2015;**94**(10):1376–84.

[62] Zygogiannis K, Aartman IH, Parsa A, Tahmaseb A, Wismeijer D. Implant mandibular overdentures retained by immediately loaded implants: A 1-year randomized trial comparing the clinical and radiographic outcomes between mini dental implants and standard-sized implants. *Int J Oral Maxillofac Implants* 2017;**32**(6):197–205.

[63] Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: A review and proposed criteria of success. *Int J Oral Maxillofac Implants* 1986;**1**:11–25.

[64] Papaspyridakos P, Chen CJ, Singh M, Weber HP, Gallucci GO. Success criteria in implant dentistry: A systematic review. *J Dent Res* 2012;**91**(3):242–8.

[65] Buser D, Mericske-Stern R, Bernard JP, Behneke A, Behneke N, Hirt HP *et al.* Long-term evaluation of non-submerged ITI implants. Part 1:8-year life table analysis of a prospective multi-center study with 2359 implants. *Clin Oral Implants Res* 1997;**8**(3):161–72.

[66] Misch CE, Perel ML, Wang HL, Sammartino G, Galindo-Moreno P, Trisi P *et al.* Implant success, survival, and failure: The International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference. *Implant Dent* 2008;**17**(1):5–15.

[67] Albrektsson T, Zarb GA. Determinants of correct clinical reporting. *Int J Prosthodont* 1998;**11**(5):517–21.

[68] Šćepanović M, Calvo-Guirado JL, Marković A, Delgado-Ruiz R, Todorović A, Miličić B *et al.* A 1-year prospective cohort study on mandibular overdentures retained by mini dental implants. *Eur J Oral Implantol* 2012;**5**(4):367–79.

Singapore Dental Journal, Vol. 39 (2019) 11–19

DOI: 10.1142/S2214607519500019

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Nitrous oxide inhalation sedation in dentistry: An overview of its applications and safety profile

Ruixiang Yee*, Danny Wong†, Pui Ling Chay*, Vivian Yung Yee Wong‡, Chai Kiat Chng§, Marie Therese Hosey¶

*Dental Service, KK Women's and Children's Hospital, Singapore

†National Institute of Academic Anaesthesia Health Services Research Centre, Royal College of Anaesthetists, UK

‡National Healthcare Group Polyclinics, Singapore

§Cleft and Craniofacial Dentistry Unit, KK Women's and Children's Hospital, Singapore

¶Centre of Oral, Clinical and Translational Science, Faculty of Dentistry, Oral & Craniofacial Sciences, King's College, London

Keywords:
Nitrous oxide
Inhalation sedation
Dental sedation
Safety

A B S T R A C T

Nitrous oxide in oxygen (N_2O/O_2) inhalation sedation is used less commonly by Singapore dentists than their counterparts in the United Kingdom and the United States. Using this technique, trained dentists often perform the dual roles of a sedationist and an operating dentist. This paper describes the mechanism of action of N_2O and highlights the modern gas delivery system commonly used in dentistry. The built-in safety features of this unique system helps to ensure that patient-specific therapeutic dosages are effectively and safely administered by dentists. Existing evidence for adverse events and the safety profile of the N_2O/O_2 inhalation sedation is discussed. Finally, recommendations of equipment, training and techniques for safe N_2O/O_2 inhalation sedation are provided.

Introduction

According to international guidelines, titrated nitrous oxide in oxygen (N_2O/O_2) is considered a safe and effective dental sedation technique, and recommended as a first-line option especially for children.[1–8] Unlike pre-mixed medical gas mixtures of 50:50 N_2O:O_2, for example Entonox® (widely used in maternity wards), dentists commonly use modern mixer machines to titrate and deliver a patient-specific therapeutic mixture of N_2O/O_2, according to individual patient

Corresponding author: Ruixiang Yee, Dental Service, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, E-mail: ruixiang85@yahoo.com.sg.

responses. These machines are designed with features to facilitate easy and safe use of N_2O/O_2 by dentists who serve as both the sedationist and operator.[9] With careful patient selection, N_2O/O_2 sedation can be successful in at least 90% of patients.[15] Despite a long international history of safe use, safety concerns still persist in countries where N_2O/O_2 sedation is less commonly practised. The present paper aims to provide an overview of: (1) the pharmacological properties of N_2O and (2) the indications, technique, staffing and equipment required for safe and effective N_2O/O_2 dental sedation. The pharmacological basis and scientific evidence for safety concerns are also discussed in this review, with a focus on outpatient dentistry.

Mechanism of action

N_2O is a mildly sweet-smelling and colourless gas that is non-irritant to tissues, with a minimal alveolar concentration of 105. Emmanouil and Quock (2007) proposed respective mechanisms of actions for its analgesic, anxiolytic and anaesthetic effects, but emphasised that these mechanisms are yet to be fully understood. Its anxiolytic effect is believed to be from agonism at benzodiazepine binding sites on the $GABA_A$ receptor and a potentiation of a signalling pathway that involves nitric oxide synthase, soluble guanylyl cyclase and cGMP-dependent protein kinase. Its analgesic effect arises from the release of endogenous opioid peptides in the central nervous system and subsequent inhibition of pain pathways via opioid receptors.[10] For its anaesthetic effect, N_2O acts as an antagonist on the N-Methyl-D-aspartate receptor, a glutamate binding, non-selective ion channel that is involved in synaptic plasticity and memory formation.[11]

During administration, N_2O is rapidly taken up from the lung alveoli into the blood. As N_2O has low blood solubility, it quickly diffuses out of blood down the concentration gradient into tissues including the central nervous system, resulting in a rapid onset (a few minutes). The reverse process also occurs rapidly, with N_2O excreted from lungs quickly at the cessation of its inhalation.

Effectiveness

N_2O/O_2 sedation is recommended for dental sedation due to its wide safety margins and minimal effect on cardiovascular and respiratory function.[12,13] It is also particularly helpful in preventing and managing dental anxiety in children. Almost one-fifth of Singaporean children aged 10–14 years have been found to have dental anxiety and fear;[14] N_2O/O_2 sedation can therefore be a particularly useful behavioural management tool for paediatric dentists. In a 1-year prospective study, 93% of 312 paediatric patients (4.1–16.0 years old) were successfully treated; almost three-quarters had 30:70 N_2O/O_2 mixture for up to 40 min. Most were treated for dental extractions, with $> 40\%$ being permanent teeth extractions. However, failure of treatment under sedation seems to be associated with lower operator experience, highlighting the importance of staff training.[15]

General anaesthesia (GA) may sometimes be the only viable option for managing anxious paediatric dental patients. However, children undergoing GA may suffer from induction distress and associated post-operative morbidities, including feeling sick and poor sleep, with some symptoms lasting for a week.[16] In a matched pair study, 83.4% of 256 children aged 3–16 years originally referred for dental extraction under GA were successfully treated under inhalation sedation instead of GA. Furthermore, inhalation sedation was found to be cheaper than GA and had a higher parental satisfaction.[17] Likewise, when compared with buccal (transmucosal) midazolam (0.5 mg/min to maximum 5 mg) or intravenous midazolam in 10–16-year olds (0.2 mg/kg) for orthodontic extractions, 30:70 N_2O/O_2 sedation was found to be as effective as midazolam, but required lesser time to reach the desired level of sedation and to recover.[18,19]

Adult studies are rarer, but international guidelines have also recommended N_2O/O_2 sedation to be the first-line basic sedation technique for adults.[4,6] In an equivalence study, N_2O (at concentrations below 40%) and sevoflurane (at concentrations below 0.3%) in anxious adults between 18 and 62 years old undergoing dental restorations, were found to be similar in efficacy.[20]

N_2O/O_2 sedation can be a more pleasant and cost-effective alternative to GA, and as effective as other forms of sedation, when delivered by trained staff in the appropriate patient and in the appropriate setting.

Indications and contraindications

Patient selection is crucial for the safe and effective use of N_2O/O_2 sedation. Its indications and contraindications are summarised in Table 1.

N_2O/O_2 sedation technique in dentistry

In outpatient dentistry, N_2O is delivered with O_2 via a purpose-made mixer system that allows easy titration of gas concentrations. The titrated gases may be inhaled through the patient's nose using a specialised nasal hood (Fig. 1), allowing unobstructed oral access for dental treatment. Nasal hoods are available in different sizes to fit patients of different ages and sizes; some are pre-scented to help increase acceptability in children.

The "Singapore Guidelines On Safe Sedation Practice for Non-Anaesthesiologists in Medical Clinics"[21] state that "non-anaesthesiologists shall limit their sedation techniques to achieve a level of minimal or moderate sedation" only.

Table 1
Indications and contra-indications of N_2O/O_2 inhalation sedation.[2,3]

Indications	Contraindications
• American Society of Anaesthesiologists Physical Grade (ASA) I and II • Mature enough to cooperate and understand • Mild-to-moderate dental anxiety • Unpleasant procedures including dental extractions and management of acute dental trauma • Management of certain medically compromised patients where dental stress could trigger exacerbation, e.g. asthma, epilepsy, etc. • Needle phobia • Gag reflex • Other sedation methods contraindicated • Alternative to GA	• Children who are not able or too young to cooperate or understand • Inability to breathe nasally with mouth open due to acute/chronic nasal obstruction, common cold or tonsillitis • Chronic obstructive pulmonary diseases • Nasal or facial deformity • Nasal hood phobia • First trimester of pregnancy • Bleomycin (sulphate) chemotherapy • Myasthenia gravis and multiple sclerosis • Severe psychological disorders or drug-related dependencies • Methylenetetrahydrofolate reductase deficiency • Cobalamin deficiency • Otitis media and pneumothorax

Fig. 1. Nasal hood permits oral access for dental procedures. The use of a dental rubber dam (not shown in picture) is recommended to reduce atmospheric pollution.

"Minimal to moderate sedation" is defined by the American Society of Anaesthesiologists[22] (Table 2) and is consistent with providing anxiolysis and some analgesia, while allowing the patient to remain responsive and maintain airway reflexes.[23]

Patients are initially administered 100% O_2 (0% N_2O), with N_2O concentrations incrementally increased (with simultaneous reduction in O_2 concentrations) until a desired level of sedation is achieved — often at 30–50% N_2O, after which the dental procedure is performed. At such N_2O concentrations, the analgesic effect is minimal and local infiltration of local anaesthesia is still required for painful procedures. At the end of procedure, 100% O_2 is administered for 3–5 min to flush N_2O out from the system and to prevent diffusion hypoxia. Careful titration tailors N_2O administration to individual responses, and allows the regulation of the depth of sedation, thereby reducing the risk of over-sedation.

N_2O/O_2 sedation is a complement to, but not a replacement of, basic non-pharmacological behaviour management techniques.[24] These include tell-show-do, distraction, semi-hypnotic suggestions, and relaxation techniques to help anxious patients to relax, thereby keeping the required

Table 2
Continuum of sedation and definition of GA and levels of sedation, adapted from the American Society of Anaesthesiologists.[22]

	Minimal sedation (Anxiolysis)	Moderate sedation/analgesia ("Conscious sedation")	Deep sedation/analgesia	GA
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

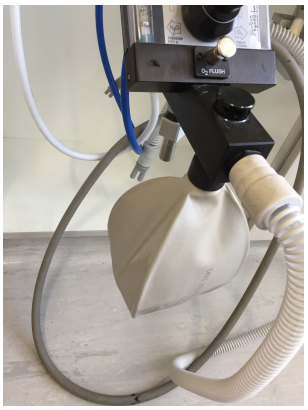
Fig. 2. (a) Mobile dental inhalation sedation machine. (b) Wall-mounted inhalation sedation machine. (c) Analogue mixer flowmeter. (d) Digital mixer flowmeter.

level of N_2O to a minimum while increasing the likelihood of treatment success. For instance, children may be asked to imagine themselves at a beach while breathing in N_2O with long, deep and controlled breaths. They are more susceptible to these semi-hypnotic suggestions under the effect of N_2O.

In-built safety features of dedicated dental mixer machines

Dental N_2O/O_2 mixer machines can be mobile stand-alone units with gas cylinders or wall-mounted with a central gas supply (Figs. 2(a) and 2(b)). They can also have analogue or digital interfaces (Figs. 2(c) and 2(d)). Modern

(a)



(b)

Fig. 3. Safety features of the Matrx MDM® N_2O/O_2 Mixer machine for dental sedation. (a) Colour coding of tubings and (b) oxygen flush button and reservoir bag.

units are designed with the following safety features incorporated[25,26] (Fig. 3):

- N_2O and O_2 cylinders/tanks are colour-coded (commonly blue for N_2O, black with a white collar for O_2 in Singapore/UK).
- Tubing is often colour-coded and matches the colours used on the cylinders (commonly blue for N_2O and white/black for O_2, though this may not always be the case).
- Unique pin-index system for each tubing/fixture pair ensures correct fitting of tubing to corresponding fixture.
- Mixer dial ensures that a minimum of 30% O_2 is delivered (and a maximum of 70% N_2O), to prevent the delivery of a hypoxic gas mixture.
- O_2 flush button allows 100% O_2 to be delivered quickly and immediately during an emergency.
- Reservoir bag allows respiration rate monitoring.
- Oxygen fail-safe valve ensures that N_2O supply is automatically turned off when the O_2 supply runs out, ensuring that 100% N_2O is never delivered.

- Air intake valve allows in-flow of atmospheric gases, should either N_2O or O_2 runs out.
- Many nasal hoods have a built-in scavenger system connected to a dental suction/scavenger unit to actively remove excess gases. (It is usually recommended that the windows are also kept open to allow some passive scavenging.)

All equipment should be checked daily for defects prior to use and maintained regularly according to manufacturers' recommendations. Incorrect equipment usage and defects can lead to adverse outcomes even with in-built safety features.[26]

Other equipment

Clinics should make provision for access for emergency service and patient transfer,[4] and be equipped to manage any adverse outcomes or emergencies, including oxygen supply and self-inflating bag for artificial ventilation.[27]

Pre-sedation assessment, fasting, monitoring and discharge

Pre-sedation assessment of patients' medical history, anxiety level, dental needs and indications is important. International guidelines recommend that pre-sedation fasting is not required for N_2O/O_2 inhalation sedation; only a light meal two hours prior sedation is advised.[2,4,6] The American Academy of Paediatric Dentistry, Australian Dental Association and the Intercollegiate Advisory Committee on Sedation in Dentistry (UK) 2015 report all recommend that clinical patient monitoring is required during N_2O/O_2 sedation. This includes observing the patient's level of consciousness, responsiveness to verbal commands and physical stimulation, mucosa/skin colour and breathing rhythm/rate.[2,4,6] Anecdotally, some clinicians prefer to have additional pulse oximetry monitoring. It is important to refer to the local hospital/practices policies regarding fasting and monitoring requirements.

After administration of 100% O_2 for a few minutes, the patient should continue to be monitored, and discharge should only be considered when pre-sedation level of consciousness is regained with stable vital signs. A responsible adult escort should be present for children.

Documentation

Contemporary documentation and records should be kept at all stages. The European Academy of Paediatric Dentistry's (EAPD) "Guidelines on Sedation in Paediatric Dentistry 2005" provide a recommended list of items to be included in documentation.[3] The present paper adapted these guidelines into a sedation checklist for systematic documentation, which could be easily adopted into routine clinical practice as follows:

Pre-sedation assessment

- Medical history, medications and allergies;
- Dental needs and anxiety level;
- Previous dental history and treatment;
- Previous history of sedation and GA with any adverse events;
- Indication for the use of N_2O/O_2 sedation and alternatives;
- Written information leaflet given to patient.

During and after sedation

- Dose (level and flow rate of N_2O:O_2) and if any other sedative drugs given;
- Time of start and end of sedation, duration of 100% administration at recovery and time of discharge;
- Sedation level;
- Patient's acceptance of sedation and treatment, for example Frankl Behaviour Scale;
- Any adverse events/complications and management, for example nausea and vomiting;
- Dose and type of LA administered;
- Dental treatment performed;
- Post-sedation assessment and written post-operative instructions given to patient.

Staff training and accreditation

The safety of any drug or equipment largely depends on the person using it and how he/she uses it. The "Singapore Guidelines on Safe Sedation Practice for Non-Anaesthesiologists in Medical Clinics" state that a sedationist must undergo formal training as part of a relevant specialist or postgraduate programme, to be equipped with both knowledge and skills for delivering safe sedation and ability to rescue patients from unplanned deep sedation. For minimal sedation with less than 50% N_2O in O_2, all staff involved in the procedure must also be at least competent with basic resuscitation skills including Basic Cardiac Life Support or its equivalent.[21] This is consistent with the guidelines of the American Academy of Paediatric Dentistry.[2] In addition, continuing professional education is also strongly recommended.

However, it would be useful to have a sedation guideline specific for dental nitrous sedation with dentists as sedationists because the equipment and setup in a dental clinic might be slightly different from that in medical clinics. For instance, the EU directive by the Council of European Dentists (CED) provides training standards for the use of

N_2O inhalation sedation in dentistry. The CED recommends that a training programme should include a two-day theoretical course covering didactic knowledge on "anxiety and behaviour management strategies, technical aspects of different sedation units, chemical, physiological and biological aspects of N_2O, emergency management and basic life support." In addition, the CED also advised that practical training should be conducted via "role-playing" and supervised cases. The trainee should be able to provide evidence of "five assessments, five observations, and five treated cases" before being accredited.[28]

A review of the safety profile of nitrous oxide

In this section, we address the safety profile of N_2O with evidence from the literature and discuss steps to mitigate against potential concerns/adverse effects during routine use.

Potential concerns/adverse effects in patients

- Nausea and Vomiting

The most common side effect is nausea and vomiting; this is infrequent (0.5% of patients)[29] and occurs mostly when appropriate titration techniques are not practised.[30]

- Diffusion Hypoxia and Pressure Volume Effect

N_2O is less soluble than O_2 in blood; thus, when it washes out of the patient, its rapid diffusion into alveoli reduces the alveolar oxygen concentration and may result in "diffusion hypoxia." This occurs when high N_2O concentrations are used, that are not commonly administered during dental sedation, and is also rare due to the co-administration of oxygen. Furthermore, it can be prevented by administering 100% O_2 for 3–5 min at recovery while N_2O washes out of the circulation.[9]

N_2O enters a gas-filled body space faster than nitrogen can escape from the space, for example an inflamed tympanic cavity. This results in an increase of the gas volume/pressure in the space. This in turn can lead to adverse consequences, for example rupture of the tympanic membrane. It is therefore contraindicated in patients with otitis media and pneumothorax.[31]

- Hypoxia

Modern dental N_2O/O_2 delivery machines obligate a minimum of 30% O_2 to be delivered, a level that is higher than atmospheric O_2 levels. For another layer of precaution, they incorporate the pin-index system to ensure fixing of tubing to correct the N_2O/O_2 gas outlets (Fig. 2). However, misconnection of supposedly fail-safe machines can still occur. For example, pins of pin-index system can dislodge and result in hypoxia of patient, when N_2O is wrongly delivered to the O_2 gas outlet instead of the N_2O gas outlet.[32] Therefore, frequent equipment checks are essential.

- Loss of Protective Reflexes

Roberts and Wignall (1982) placed radio-opaque dye on the tongues of children undergoing dental restorations, with and without inhalation sedation. Post-operative medical radiographs revealed the absence of dye in the larynx and chest in the patients that had received inhalation sedation. This means that the dye was not aspirated during inhalation sedation and allayed concerns of N_2O-induced laryngeal reflex depression.[33] Laryngospasm, desaturation, apnoea and seizures have been reported in isolated reports of the use of high levels of N_2O (in the range of 50%–70%) for medical procedures mostly in children aged 3 years.[34] Although a causative relationship cannot be established between these serious adverse events and the use of N_2O, such high dosages in young children are not recommended for use by dentists because patients can transit to deeper planes of sedation with a potential loss of protective reflexes and consciousness.

- Systemic Effects and Its Use in the Medically Compromised Patients

Unlike most drugs that are excreted by the liver/kidney, N_2O is eliminated by lungs without metabolism. Hence, it can be used safely in patients with chronic liver or kidney disease.[9]

Typical dental sedation units deliver < 0.5 MAC and have minimal respiratory and cardiac effects.[31] Roberts *et al.* (1982) studied the effects of N_2O (mean 47%) on children undergoing dental treatment. All of the reported changes in blood pressure, pulse rate and respiratory rate were within physiologic ranges.[35]

N_2O/O_2 inhalation sedation has been suggested as an alternative to GA to manage selected medically compromised patients. The high oxygen tension, anxiolytic and mild analgesic properties are invaluable in patients with cardiac conditions, sickle cell disease and severe asthma. Notwithstanding, it is advisable that only ASA I and II patients should receive N_2O/O_2 sedation outside hospital settings.[23]

- Bone Marrow Suppression

N_2O inactivates vitamin B_{12} by oxidation.[36] It also reacts with Cob[I]alamin to produce free radicals that chemically change enzyme methionine synthase. Both pathways impair the functioning of methionine synthase and affect purine nucleotide formation, and consequently influence DNA synthesis in the bone marrow. This forms a biochemical basis for N_2O-related complications, for example megaloblastic anaemia.[37,38] Megaloblastic anaemia has been reported in surgical patients who are exposed to 70% N_2O for 4–36 h,[39] and 50% N_2O for up to 24 h, respectively.[40] However, prolonged use of higher concentrations of N_2O is

Table 3
Other reported health problems with chronic occupational exposure to N_2O.[42]

Health problems	Increase in incidence	
	Male dentists	Female dental assistants
Liver disease	1.7 ×	1.6 ×
Kidney disease	1.2 ×	1.7 ×
Neurological disease	1.9 ×	2.8 ×

irrelevant to dental sedation where patients are exposed to short-term N_2O of low concentrations.

- Hallucination

Patients' sexual hallucinations have been reported in previous case reports. Dentists risk sexual abuse allegations and hence should be chaperoned by a dental assistant at all times.[41]

Occupational safety

Chronic staff exposure to N_2O has been associated with various adverse effects, including the risk of spontaneous abortion, bone marrow suppression, liver disease, kidney disease and neurological disease. However, the evidence for these effects is conflicting and weak, and mostly from retrospective studies that are prone to bias, or studies with small sample sizes.

Reproductive risk has been reported, but the evidence is equivocal. A survey by Cohen *et al.* (1980) reported that heavily exposed ($>$ 8 hours/week) male dentists' spouses and female assistants were 1.5 and 2.3 times more likely to have spontaneous abortion respectively, than non-exposed controls.[42] In another survey, Rowland *et al.* (1992) found reduced fertility in female dental assistants with exposure of $\geq$ 5 hours/week.[43] In contrast, spontaneous abortion and congenital malformations were not observed in a survey of nurses exposed to anaesthetic gases, including N_2O and halothane gases.[44] Moreover, these aforementioned surveys were retrospective and prone to recall/respondent bias. Hence, the Health Services Advisory Committee of the Health and Safety Commission concluded that insufficient human evidence exists to prove reproductive risks.[45] Nevertheless, Paterson and Tahmassebi (2003) advised that staff who are expecting or attempting to conceive to avoid N_2O exposure.[23]

Bone marrow suppression from chronic exposure has also been reported. Sweeney *et al.* (1985) performed bone marrow aspiration examinations and deoxyuridine suppression tests (to measure Vitamin-B12-dependent DNA synthesis) in a small sample of 21 dentists, and compared these baseline results with the results after N_2O exposure sampled over a period of 3–11 weeks. Of 21 dentists investigated, only two reported bone marrow changes (megaloblastic and white blood cells changes); the majority had no abnormalities detected. Moreover, there were no definite neurological problems in all subjects.

Cohen *et al.* (1980)[42] also reported other health problems (Table 3). The limitations of the survey study have been discussed earlier. A number of steps can be taken to mitigate against the occupational risks of prolonged exposure to N_2O. The United Kingdom recommends occupational exposure levels of $<$100 ppm over an 8-hour time-weighted average reference period.[45] Regular ambient N_2O checks are important to ensure that the scavenging system is effective and well-maintained.[38,46] With effective scavenging, it is generally accepted that risks of occupational exposure are rendered insignificant.[31] In Singapore, the long-term Permissible Exposure Level (maximum time-weighted average concentration of N_2O to which an individual may be exposed over an 8-hour working day and a 40-hour work week) is 50 ppm.[47]

Environmental pollution

N_2O is found in nature and altogether accounts for approximately 5% of greenhouse effect; but only 0.35%–2% of this is estimated to be from medical/dental use.[2]

N_2O abuse

A survey reported recreational use of N_2O in approximately 20% of 524 dental/medical students. However, dental students do not have a higher incidence of abuse than medical students, despite their greater access to N_2O.[48] In any case, systems should be in place to ensure monitored and controlled access to N_2O.

Conclusion

N_2O/O_2 sedation is an invaluable pharmacological behavioural management technique safely administered for many years internationally, providing significant clinical benefits. Sound knowledge of its mechanism of action, indications/contraindications, and techniques of delivery promote its safety and effectiveness. The evidence for adverse effects are largely limited to retrospective surveys or studies with small samples, and such risks can often be effectively mitigated through appropriate steps. With competent training, dental teams can provide N_2O/O_2 inhalation sedation safely and effectively.

Acknowledgements

The authors thank Dr Ng JJ for providing the photo of her son as a model for the use of the nasal hood.

References

[1] Academy of Medical Royal Colleges. Safe sedation practice for healthcare procedures: standards and guidance. 2013. Available from: https://www.rcoa.ac.uk/system/files/PUB-SafeSedPrac2013.pdf (accessed 8 March 2018).

[2] American Academy of Paediatric Dentistry. Guideline on use of nitrous oxide for pediatric dental patients. 2013. Available from: http://www.aapd.org/media/Policies_Guidelines/G_Nitrous.pdf (accessed 8 March 2018).

[3] Dentistry EAoP. EAPD guidelines on sedation in paediatric dentistry. 2005. Available from: https://www.eapd.eu/uploads/5CF03741_file.pdf (accessed 28 February 2018).

[4] Intercollegiate Advisory Committee on Sedation in Dentistry. Standards for conscious sedation in the provision of dental care and accreditation: report of the Intercollegiate Advisory Committee for Sedation in Dentistry (IACSD). 2015. Available from: https://www.rcseng.ac.uk/dental-faculties/fds/publications-guidelines/standards-for-conscious-sedation-in-the-provision-of-dental-care-and-accreditation/ (accessed 8 March 2018).

[5] National Institute for Health and Clinical Excellence (NICE). Sedation for diagnostic and therapeutic procedures in children and young people. 2010. Available from: https://www.nice.org.uk/guidance/cg112/evidence/cg112-sedation-in-children-and-young-people-full-guideline3 (accessed 8 March 2018).

[6] Scottish Dental Clinical Effectiveness Programme. Conscious sedation in dentistry. Scottish Dental Clinical Effectiveness Programme (SDCEP) dental clinical guidance, Third Edition. 2017. Available from: http://www.sdcep.org.uk/wp-content/uploads/2017/07/SDCEP-Conscious-Sedation-Guidance.pdf (accessed 8 March 2018).

[7] EU Directive. The use of nitrous oxide inhalation sedation in dentistry. Community of European Dentists European Directive. 2015. Available from: https://www.omd.pt/noticias/2012/06/201205cedsedacaoconsciente.pdf (accessed 8 March 2018).

[8] British Society of Paediatric Dentistry. UK National Clinical Guidelines in Paediatric Dentistry. Managing anxious children: the use of conscious sedation in paediatric dentistry. 2002. Available from: https://www.rcseng.ac.uk/-/media/files/rcs/fds/publications/paed_sedation.pdf?la=en (accessed 8 March 2018).

[9] Craig D, Skelly M. *Practical Conscious Sedation: Quintessence*. London: Quintessence Publishing, 2004.

[10] Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. *Anesth Prog* 2007;**541**:9–18.

[11] Brown SM, Sneyd JR. Nitrous oxide in modern anaesthetic practice. *BJA Educ* 2016;**163**:87–91.

[12] Hosey MT. UK national clinical guidelines in paediatric dentistry. *Managing anxious children: the use of conscious sedation in paediatric dentistry. Int J Paediatr Dent* 2002;**125**:359–72.

[13] Intercollegiate Advisory Committee for Sedation in Dentistry. Standards for conscious sedation in the provision of dental care. 2015. Available from: http://www.dstg.co.uk/wp-content/uploads/2015/04/Linked-IACSD-2015.pdf (accessed 1 December 2016).

[14] Chellappah NK, Vignehsa H, Milgrom P, Lam LG. Prevalence of dental anxiety and fear in children in Singapore. *Community Dent Oral Epidemiol* 1990;**185**:269–71.

[15] Foley J. A prospective study of the use of nitrous oxide inhalation sedation for dental treatment in anxious children. *Eur J Paediatr Dent* 2005;**6**:121–128.

[16] Hosey MT, Macpherson LM, Adair P, Tochel C, Burnside G, Pine C. Dental anxiety, distress at induction and postoperative morbidity in children undergoing tooth extraction using general anaesthesia. *Br Dent J* 2006;**2001**:39–43; discussion 27; quiz 50.

[17] Blain KM, Hill FJ. The use of inhalation sedation and local anaesthesia as an alternative to general anaesthesia for dental extractions in children. *Br Dent J* 1998;**18412**:608–11.

[18] Wilson KE, Girdler NM, Welbury RR. Randomized, controlled, cross-over clinical trial comparing intravenous midazolam sedation with nitrous oxide sedation in children undergoing dental extractions. *Br J Anaesth* 2003;**916**:850–6.

[19] Wilson KE, Welbury RR, Girdler NM. Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children. A randomized, cross-over, clinical trial. *Acta Anaesthesiol Scand* 2007;**518**:1062–7.

[20] Allen M, Thompson S. An equivalence study comparing nitrous oxide and oxygen with low-dose sevoflurane and oxygen as inhalation sedation agents in dentistry for adults. *Br Dent J* 2014;**2179**:E18.

[21] Singapore Academy of Medicine. Guidelines on safe sedation practice for non-anaesthesiologists in medical clinics. 2014. Available from: https://www.google.com.sg/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwi7gbLL99HQAhWMK48KHQenClkQFggbMAA&url=https%3A%2F%2Felis.moh.gov.sg%2Felis%2FpublishInfo.do%3Ftask%3Ddownload%26pkId%3D174&usg=AFQjCNGNwo8fOJ8k_5SBIO_8PhZTJ0depQ (accessed 1 December 2016).

[22] American Society of Anaesthesiologists. Continuum of depth of sedation: definition of general anaesthesia and levels of sedation/analgesia. 2009. Available from: http://www.asahq.org/~/media/sites/asahq/files/public/resources/standards-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedation-analgesia.pdf (accessed 1 December 2016).

[23] Paterson SA, Tahmassebi JF. Paediatric dentistry in the new millennium: 3. Use of inhalation sedation in paediatric dentistry. *Dent Update* 2003;**307**:350–6, 358.

[24] Campbell C, Soldani F, Busuttil-Naudi A, Chadwick B. UK National Clinical Guidelines in Paediatric Dentistry: update of non-pharmacological behaviour management guideline. 2011. Available from: http://www.bspd.co.uk/LinkClick.aspx?fileticket=LXYpX7ih7_k%3d&tabid=62 (accessed 27 November 2013).

[25] Wilson KE. Overview of paediatric dental sedation: 2. Nitrous oxide/oxygen inhalation sedation. *Dent Update* 2013;**4010**:822–4, 826–9.

[26] Donaldson M, Donaldson D, Quarnstrom FC. Nitrous oxide–oxygen administration: when safety features no longer are safe. *J Am Dent Assoc.* 2012;**1432**:134–43.

[27] Australian Dental Association. Policy statement 6.17 — conscious sedation in dentistry [Including the ADA recommended guidelines for conscious sedation in dentistry and guidelines for the administration of nitrous oxide inhalation sedation in dentistry]. 2017. Available from: https://www.ada.org.au/Dental-Professionals/Policies/Dental-Practice/6-17-Conscious-Sedation-in-Dentistry/ADAPolicies_6-17_ConsciousSedationinDentistry_V1 (accessed 23 May 2018).

[28] Council of European Dentists (CED). The use of nitrous oxide inhalation sedation in dentistry. 2012. Available from: http://www.eoo.gr/files/pdfs/enimerosi/ced_annual_report_2012.pdf (accessed 17 October 2018).

[29] Kupietzky A, Tal E, Shapira J, Ram D. Fasting state and episodes of vomiting in children receiving nitrous oxide for dental treatment. *Pediatr Dent* 2008;**305**:414–9.

[30] Malamed SF, Clark MS. Nitrous oxide-oxygen: a new look at a very old technique. *J Calif Dent Assoc* 2003;**315**:397–403.

[31] Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. *Anesth Prog* 2008;**554**:124–31.

[32] Duncan GH, Moore P. Nitrous oxide and the dental patient: a review of adverse reactions. *J Am Dent Assoc* 1984;**1082**:213–9.
[33] Roberts GJ, Wignall BK. Efficacy of the larygneal reflex during oxygen–nitrous oxide sedation (relative analgesia). *Br J Anaesth* 1982;**5412**:1277–81.
[34] Chi SI. Complications caused by nitrous oxide in dental sedation. *J Dent Anesth Pain Med* 2018;**182**:71–8.
[35] Roberts GJ, Gibson A, Porter J, de Zoysa S. Physiological changes during relative analgesia — a clinical study. *J Dent* 1982;**101**:55–64.
[36] Fleming P, Walker PO, Priest JR. Bleomycin therapy: a contraindication to the use of nitrous oxide-oxygen psychosedation in the dental office. *Pediatr Dent* 1988;**104**:345–6.
[37] Banks RGS, Henderson RJ, Pratt JM. Reactions of gases in solution. Part III. Some reactions of nitrous oxide with transition-metal complexes. *J Chem Soc A* 1968;**0**:2886–9.
[38] Yagiela JA. Health hazards and nitrous oxide: a time for reappraisal. *Anesth Prog* 1991;**381**:1–11.
[39] Skacel PO, Hewlett AM, Lewis JD, Lumb M, Nunn JF, Chanarin I. Studies on the haemopoietic toxicity of nitrous oxide in man. *Br J Haematol* 1983;**532**:189–200.
[40] Amess JAL, Rees GM, Burman JF, Nancekievill DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. *Lancet* 1978;**3128085**:339–42.
[41] Balasubramaniam B, Park GR. Sexual hallucinations during and after sedation and anaesthesia. *Anaesthesia* 2003;**586**:549–53.
[42] Cohen EN, Gift HC, Brown BW, Greenfield W, Wu ML, Jones TW *et al.*, Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *J Am Dent Assoc* 1980;**1011**:21–31.
[43] Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992;**32714**:993–7.
[44] Hemminki K, Kyyrönen P, Lindbohm ML. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. *J Epidemiol Community Health* 1985;**392**:141–7.
[45] Health Services Advisory Committee of the Health and Safety Commission. Anaesthetic agents: Controlling exposure under COSHH. 1995.
[46] Gilchrist F, Whitters CJ, Cairns AM, Simpson M, Hosey MT. Exposure to nitrous oxide in a paediatric dental unit. *Int J Paediatr Dent* 2007;**172**:116–22.
[47] Workplace Safety and Health Act. Chapter 354A S. Workplace safety and health (general provisions) regulations. 2014. Available from: https://sso.agc.gov.sg/SL/WSHA2006-RG1?Timeline=On (accessed 20 April 2018).
[48] Rosenberg H, Orkin FK, Springstead J. Abuse of nitrous oxide. *Anesth Analg* 1979;**582**:104–6.

Singapore Dental Journal, Vol. 39 (2019) 21–31

DOI: 10.1142/S2214607519500020

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Effect of scaling and root planing on level of immunoglobulin E and immunoglobulin G_4 in children with gingivitis and house-dust mite allergy: A pilot randomised controlled trial

Sindy Cornelia Nelwan[*,‖], Ricardo Adrian Nugraha[†], Anang Endaryanto[‡], Frisma Dewi[*], Prawati Nuraini[*], Udijanto Tedjosasongko[*], Daniel Haryono Utomo[§], on behalf of Indonesian Association of Pediatric Dentistry[¶]

[*]*Department of Pediatric Dentistry, Universitas Airlangga, Surabaya, 60135, Indonesia*

[†]*Department of Medicine, Universitas Airlangga, Surabaya, 60135, Indonesia*

[‡]*Department of Child Health, Universitas Airlangga, Surabaya, 60135, Indonesia*

[§]*Department of Orthodontics, Universitas Airlangga, Surabaya, 60135, Indonesia*

Keywords:
Dental scaling
Gingivitis
House-dust mite
Immunoglobulin E
Root planing

A B S T R A C T

Background and Objective: There is a pressing need for developing innovative strategies to prevent allergic diseases among children. As house-dust mite (HDM) allergy is often seen in children with gingivitis, strategies should be derived from a conceptual framework of allergen elimination and pathogen eradication; one such strategy is dental scaling and root planing (SRP) to remove dental plaque and periodontal pathogens. The study aimed to evaluate the beneficial effects of comprehensive 6-months dental SRP to reduce the level of immunoglobulin E (IgE) and immunoglobulin G_4 (IgG_4) in children with gingivitis and HDM allergy. IgE and IgG_4, whose production is controlled mainly by Th-2 cells and B cells, are proven biomarkers for atopic inflammatory responses.

Methods: The present study conducted a non-blinded randomised controlled trial with superiority design. A total of 10 subjects (age range 6–16 years) with gingivitis and positive skin-prick test to HDM from Pediatric Allergy Outpatient Clinic, Dr. Soetomo General Hospital were enrolled in the present study. Of the 10 subjects, only five received dental SRP. We further evaluated total serum IgE and IgG_4 level before and 6 months after treatment.

Results and Discussion: Subjects in the standard treatment group showed a slight decrease in the IgE level ($p = 0.019$) but no change in the IgG_4 level ($p = 0.839$), while subjects in the intervention group showed a significant decrease in IgE ($p < 0.001$) and IgG_4 levels ($p = 0.001$).

[‖]Corresponding author: Sindy Cornelia Nelwan, Department of Pediatric Dentistry, Universitas Airlangga, Surabaya, 60135, Indonesia, E-mail: sindy-c-n@fkg.unair.ac.id.

[¶]List of members of the Indonesian Association of Pediatric Dentistry is provided in the Acknowledgements section.

Conclusion: The study results suggest that 6-month comprehensive dental scaling combined with root planing may help to reduce IgE and IgG_4 levels in children with gingivitis and HDM allergy. Furthermore, untreated or undertreated gingivitis is often associated with worsening allergic manifestation and thus should be avoided.
Trial Registration: ISRCTN31416107, retrospectively registered on 17 April 2018.

Background

Indonesia has a major issue with house dust mites (HDMs) compared to other countries, because HDMs generally thrive in warm-temperate and humid climate, particularly in some urban and rural areas of Indonesia.[1] HDM allergy is very common among children and adults living in Indonesia.[2] In the general population, 1 in 20 preschool children and 1 in 5 school-going children show positive results when tested for HDM allergy, though not all have symptoms.[3]

HDM, remains the most common major perennial allergen source.[4] It is one of the most common allergens, of size 0.1–0.5 mm, and lives in pillows, mattresses, blankets, carpets and other soft materials.[4] They are actually harmless, as they neither bite nor transmit disease. However, for children with predisposition to allergies, HDM droppings contain approximately 14 fully identified proteins such as cysteine, protease and chymotrypsin, which have the potential to induce atopic inflammatory responses.[5] Sensitisation to HDM is an important trigger of asthmatic exacerbations and allergic diseases in children.[6] According to the World Health Organization, approximately 70% of asthma and hay fever are caused by HDM worldwide.[7] As HDM is mostly found in homes in Indonesia, the exposure to this allergen is inevitable.[7]

Despite the proven record of specific allergen immunotherapy (SIT) in managing HDM allergy in the developed countries, it is still only a control measure that requires a very strict and expensive medical procedure for longer period of time to enhance desensitisation effect and sustained clinical remission.[8,9] The present study aimed to develop an alternative strategy to induce faster desensitisation effect and to improve biomolecular markers of atopy in children with HDM allergy.

Atopic disorders in children share a common pathogenesis, being mediated by immunoglobulin E (IgE).[10] Atopic inflammatory responses are reflected by the production of IgE and IgG_4, which are controlled mainly by B cells and Th-2 cells.[11] Not only IgE but also IgG_4 are manifested as high-frequency type I hypersensitivity.[12] Allergens of different sources are characterised by their tendency to induce IgE and IgG_4 antibodies to induce host inflammatory response.[12] An IgE serological concentration cutoff value of >900 ng/mL and plasma IgG_4 titer >135 mg/dL or serological IgG_4/IgG >8% >8% cutoff value of IgG4 were used as standard for triggering allergies.[13,14]

Some versions of the hygiene hypothesis proposed that gut microbiota has been found to contribute to systemic immune effects.[15] These gut microbiotas influence immune maturation during childhood and are involved in protecting children from developing allergies early in life.[16] Unlike gut microbiota, periodontal bacteria have not been subjected to allergy research. However, recent studies have revealed that the periodontal pathogen *Porphyromonas gingivalis* (Pg) adversely affects the host immune response and affects even remote tissue sites.[17] The colonisation of gingival bacteria, either acute or chronic in nature, is nearly universal among children and adults.[18] Some components of *Pg* antigens (e.g. lipopolysaccharide [LPS]) may enhance atopic inflammatory responses, whereas gut microbiota consistently inhibits atopic inflammatory responses.[19] Interactions between bacterial antigens and local B cells lead to the production of antibodies within the periodontal tissues, which is essential for bacterial phagocytosis, and the interactions of bacterial antigens with peripheral dendritic cells lead to the production of systemic antibodies, such as IgE and IgG_4.[20] Proinflammatory cytokines are also released, thus leading to an imbalance between Th-1 and Th-2 cytokines and resulting in a chronic state of systemic inflammation.[21] Therefore, dysbiotic oral microbiota ecologies even in children may create permissive conditions for Th-2 cell patterns involved in IgE-mediated allergy.[22–24]

It was evidenced from an animal model that oral infection due to *Pg* in rats was a risk factor for the development of allergies.[25] While this was an interesting finding for future research in the management of allergies, further clinical studies are needed to verify this finding. According to our knowledge, one of the most potent periodontal bacteria affecting the oral cavity is *Pg*, which is a major cause of gingivitis and gingival inflammation.[26] The LPS of this bacterium may disrupt inflammatory responses.[27] As such, targeting this periodontal pathogen and its LPS by dental scaling and root planing (SRP) as a potential tool to control allergies has recently garnered much attention and interest from numerous research studies in our dental laboratory. Moreover, a minimum 6-month comprehensive dental SRP is needed to prevent recurrent infection with this periodontal pathogen.[28]

Aims and hypotheses

The main aim of this current study was to evaluate the beneficial effects of a comprehensive 6-month dental SRP and investigate whether dental plaque and calculus removal can improve IgE and IgG_4 biomarkers of atopy as mentioned above in subjects with HDM allergy at Pediatric Allergy Outpatient Clinic, Dr. Soetomo General Hospital, Surabaya. The specific aim and hypotheses are as follows:

Specific aim 1: To evaluate the total change in the IgE level following a comprehensive 6-month dental SRP.
Hypothesis 1: A comprehensive 6-month dental SRP reduces the IgE level.
Specific aim 2: To evaluate the total change in the IgG_4 level following a comprehensive 6-month dental SRP.
Hypothesis 2: A comprehensive 6-month dental SRP reduces the IgG_4 level.

Ethics statement

The study was approved by the Institutional Review Boards of Universitas Airlangga – Dr. Soetomo General Hospital Ethics Committee for Health Research (20/Panke. KKE/I). The study was performed according to the guidelines of Good Clinical Practice standards and the declaration of Helsinki. The results of this study will be disseminated through peer-reviewed publications within 1-year after completion.

Methods

Study design

This pilot study is an investigator-initiated, randomised, non-blinded, placebo-controlled clinical study conducted to assess the beneficial effects of dental SRP in children with gingivitis and HDM allergy. This clinical trial included two groups of pre-test and post-test superiority-group designs, consisting of a 6-month standard allergic treatment run-in period and a comprehensive 6-month dental SRP. The experimental procedure included enrolling subjects for this study, conducting pre-tests, doing randomisation and allocation, engaging in a comprehensive 6-month dental SRP or just standard allergic treatment, and conducting post-tests. This trial was registered with the ISRCTN Clinical Trials Registry (registration no. ISRCTN31416107, available at http://www.isrctn.com/ISRCTN31416107).

Study setting

The trial was conducted at the Faculty of Dental Medicine of Universitas Airlangga (UNAIR)'s Oral and Dental Laboratory. The experimental study was performed from January to December 2017 at Pediatric Allergy Outpatient Clinic, Dr. Soetomo General Hospital, and data analysis was performed at the Institute of Tropical Diseases of Universitas Airlangga.

Sample size estimation

The sample size is based on a substantially significant change in IgE level observed in the group. Korn *et al.*[29] stated that ELISA can be used to assay free IgE in a concentration range of 1–2,000 IU/mL from peripheral blood samples with a substantially significant change in IgE level due to immunomodulating therapy with 0.5 IU/mL, and the expected standard deviation (SD) of IgE concentration is assumed to be 0.01 IU/mL.[29]

For clinical superiority design with a dichotomous variable, the formula for calculating the size (N) is[30]:

$$N = 2x\left(\frac{z_{1-\alpha} + z_{1-\beta}}{d-\delta}\right)^2 xpx(1-p)$$

The parameters were assumed as follows: mean change of IgE in intervention group = 10 pg/mL; mean change of IgE in control group = 0 pg/mL; $\alpha = 0.05$; $\beta = 0.20$; $\delta = 10$ IU/mL; $s = 7$; $s^2 = 49$. The value of N was calculated to be 7.71. This estimate required eight patients, four in each group, to obtain 80% statistical power with 5% significance level for independent samples and paired t-tests. Because this study was a pilot study, a minimum of 10 subjects were enrolled to compensate for an estimate of 20% dropouts.

Recruitment

Subjects were enrolled by direct invitation and pamphlets from Pediatric Allergy Outpatient Clinic, Dr. Soetomo General Hospital with minimum eligibility criteria, so that the intervention can be tested in "real-world" clinical settings.

Participants

After sampling, 22 subjects were selected from this hospital. They were pre-screened from January 31, 2017 to February 28, 2017. Based on the inclusion and exclusion criteria mentioned in Table 1, 12 subjects were eligible for the study, of which, 10 parents agreed and 2 parents declined to participate in the study. After consenting, enrolling in the study, and completing baseline questionnaires, 10 selected subjects were randomised into two parallel groups, intervention and control.

Randomisation and allocation

Subjects were randomised (1:1) into intervention and control groups, using a computer-generated allocation

Table 1
Eligibility criteria for clinical study and participants.

Inclusion criteria	Exclusion criteria
• Children aged 6–16 years of any gender and ethnic • Have been diagnosed with HDM allergies by positive skin-prick test • Have been diagnosed with gingivitis by $\geq$2 plaque index according to Silness-Löe criteria • Have high baseline IgE titer (>90 pg/mL), suggesting a positive childhood allergic potency • Understand and able to cooperate with the study protocol • Subjects' parents can voluntarily, sign written consent in accordance with our institutional policies	• Taking any antihistamines or steroid within 1 month, which commonly interfere with results of skin-prick test • received any immunotherapy before treatment • received dental scaling and root planing within 6 months before treatment • The presence of low-grade fever due to infections rather than gingivitis • Recent blood disorders or congenital abnormalities • Any medical conditions that may be harmful to be involved in this study

sequence. The allocation sequence was generated by a statistician who had no involvement in the recruitment and intervention delivery. The study protocol has been explained completely to the parents of the subjects, who were instructed not to allow the subject to use neither antibiotic nor other dental treatment within the study period. Data collection was performed at baseline and follow-up for both groups. As this study was a non-blinded study, subjects' parents, principal investigator and entire research team were allowed to know about treatments being given to each subject. Following randomisation, subjects were informed by telephone in which group they are allocated to (see flow chart in Fig. 1).

Materials

The following materials were used: skin-prick test kit with 16 commercial test solutions and fresh material (inc. HDM); dental mirror; dental instrument kit; periodontal probe; dental ultrasonic scaler (vibrates in the ultrasonic range of 20–30 kHz); syringe (3 mL, Terumo) with needle; BD Vacutainer® (EDTA tubes, 3 mL); high-speed refrigerated micro centrifuge (MX-307, Tomy); microbiological safety cabinet; deep freezer to maintain temperature at -80°C (or -112°F); the monoclonal antibody against IgE and IgG_4 (R&D System Europe Ltd., Abingdon, UK) used according to the manufacturer's instructions; human IgE and IgG ELISA kit (GWB-2E2ECD) containing chromogenic substrate (12 mL of 3,3′,5,5′-tetramethylbenzidine, TMB), diluent buffers, and washing buffer.

Intervention

The intervention group received a three-component intervention for 6 months: dental scaling, root planing, and standard allergic treatments (glucocorticoid and/or 2nd generation antihistamines). The control group received only standard allergic treatments (glucocorticoid and/or 2nd generation antihistamines). Dental scaling is a procedure involving the removal of dental plaque and calculus from the oral cavity. Root planing is a procedure involving the removal of dental plaque and calculus on the root surface inside the periodontal pocket. Dental SRP was performed based on the procedure described by Tonetti and colleagues, using ultrasonic dental scaler following the administration of local anaesthesia.[31] The intervention was performed by registered dental professionals over three visits; baseline, 3 months and 6 months post-baseline. The comprehensive dental SRP was successfully evaluated by visual inspection using optimum illumination using a dental mirror with air spray to keep the mirror clean. The surfaces of teeth were examined using a periodontal probe, through which the entire surface of both the supra-gingival and subgingival teeth can be ensured to be smooth and clean.

Outcomes

The primary outcome was the total change in the level of IgE, defined as the difference in the level of IgE changes from baseline to the end of the intervention between the intervention and control groups. Secondary outcomes include the total change in the level of IgG_4, defined as the difference in the level of IgG_4 from baseline to termination of the intervention, in children with gingivitis and allergies to HDM.

Assessment and data collection

Subjects were followed up for 6 months after treatment. During follow-up, all subjects were advised to visit the outpatient clinic every month. Data were collected prior to treatment and 6 months after treatment by collecting blood sample for measuring total serum IgE and IgG_4. The total serum IgE and IgG_4 were assessed by using direct-sandwich ELISA (R&D System Europe Ltd., Abingdon, UK), following the manufacturer's instructions. Briefly, the total serum IgE

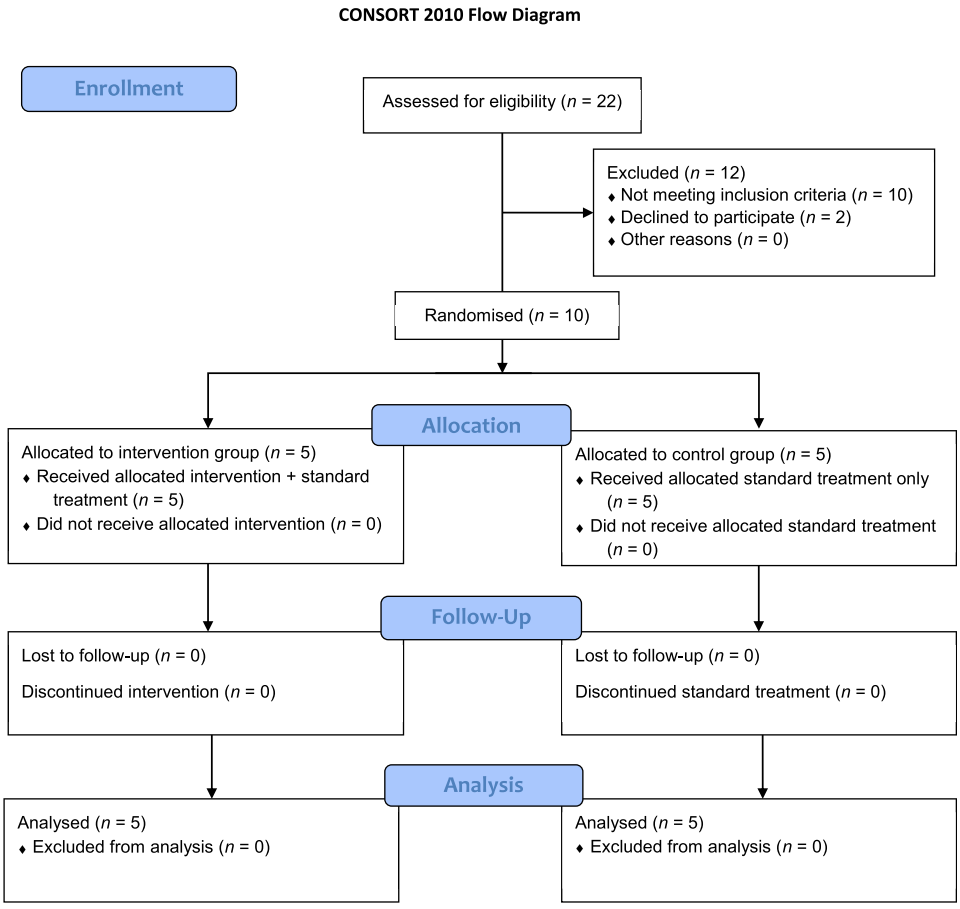


Fig. 1. Flow chart of participants in the study.

was detected by phosphate-buffered saline (pH 7.4) in 1:200 dilutions, transferred to pre-coated plates and added the supplied conjugate. However, total serum IgG_4 were detected using matched monoclonal antibody pairs against IgG_4, followed by additions of 0.1% bovine serum albumin as blocking solution and incubation buffer, diluted plasma sample (1:100,000) or standards, and conjugate, with washing between the steps. Total serum IgE and IgG_4 ELISA solutions were prepared with the supplied TMB substrate and stop solutions. The total serum IgE and IgG_4 concentrations were determined using assay-specific 7-point calibration curves generated following the manufacturer-supplied standard. A value of 0.01 pg/mL was assigned for concentrations below the limit of detection. All measurements were performed in duplicates and values were averaged for analysis.

Adverse event reporting

Data on adverse events were collected at treatment and follow-up visits. Adverse events such as pain, low-grade fever, and headache during SRP, or pain and hematoma during venesection, were recorded by technicians. The participants and their parents were also instructed to report any adverse events. The trial was also compliant with a UK regulation with a real-time serious adverse event reporting process to identify serious adverse reaction and suspected unexpected serious adverse reaction that could suspend/stop the trial if warranted. However, no adverse event was reported by 10 subjects during treatment and follow-up periods.

End of the trial

The trial was ended when the last patient had their last data collected.

Statistical analysis

The results of the study were reported in accordance with CONSORT guidelines.[32] Statistical analysis was performed using SPSS software version 17.0 (IBM Corp.,

Chicago, USA). The assumption of the normality for the complete data was assessed by the one-sample Kolmogorov–Smirnov test. Statistical analyses were also performed by paired *t*-test and independent samples *t*-test. The results are presented as mean ± SD. Paired *t*-test was used to compare the total change in IgE and IgG_4 levels in the intervention group before and after treatment. Independent samples *t*-test was used to compare the differences in IgE and IgG_4 levels between the intervention group and the control group. The significant differences were based on two-tailed tests with a *p*-value of less than 0.05.

Results

Baseline characteristics investigations

At baseline, parents reported their allergic histories, parent and children's racial and ethnic backgrounds, number of families/caregivers living in their home, their children's insurance status (private, public or none), and the highest level of parental education. Children's gender, body weight, date of birth (to calculate age), date of allergy diagnosis (to calculate the duration of allergy) and date of gingivitis diagnosis (to calculate the duration of gingivitis) were extracted from their medical records (Table 2).

Table 2
Baseline characteristics of clinical trial participants.

Characteristic	Intervention ($n = 5$)	Control ($n = 5$)	*p* Value
Age (year, mean)	10.2 ± 3.9	9.8 ± 2.4	0.270
Gender			
Male	2	2	
Female	3	3	0.738
Body weight (kg, mean)	27.8 ± 5.2	27.8 ± 4.5	0.761
Ethnic			
Java	4	4	0.778
Madura	1	1	
Others	0	0	
People living in home (*n*, mean)	4.6 ± 1.5	5.4 ± 1.7	0.776
Parents education			
Unschooled	1	2	0.717
Elementary school	2	1	
High school	2	2	
College/University	0	0	
Insurance status			
Public	5	5	N/A
Private	0	0	
None	0	0	
Self-reported allergic histories			
Asthma	4	5	0.292
Eczema	1	0	
Hay fever	0	0	
Food allergies	0	0	
Asymptomatic allergies	0	0	
Duration of allergies (year, mean)	2.0 ± 1.4	2.1 ± 0.7	0.072
Gingival index according to Silness-Löe plaque score			
0–0.9	0	0	0.490
1.0–1.9	0	0	
2.0–2.9	2	1	
3.0–3.9	3	4	
Duration of gingivitis (year, mean)	2.3 ± 1.0	2.4 ± 1.1	0.829
Baseline lipopolysaccharide of *Porphyromonas gingivalis* (μg)	8.03 ± 0.99	9.49 ± 1.12	0.061
Baseline IgE (pg/mL)	99.84 ± 2.16	139.42 ± 1.49	<0.001
Baseline IgG_4 (ng/mL)	28.62 ± 3.88	38.66 ± 1.85	0.001

Table 3
Comparison of pre-test and post-test total serum IgE and IgG_4 levels between two groups.

	Pre-test (T1)		Post-test (T2)		Difference (T2–T1)		
Variable groups	Mean	SD	Mean	SD	Mean	SD	*t*-Test
Immunoglobulin E					Effect size: 6.413		
Intervention group	99.84	2.16	80.03	1.65	−19.81	0.96	46.087***
Control group	139.42	1.49	138.48	1.45	−0.94	0.56	7.858*
Immunoglobulin G_4					Effect size: 4.898		
Intervention group	28.62	3.88	18.05	2.38	−10.57	3.00	3.780**
Control group	38.66	1.85	38.75	1.87	0.09	1.01	−0.217

Notes: Two tailed test results: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Differences in the total serum of immunoglobulin E (IgE) and immunoglobulin G (IgG_4) at baseline and 6 months after treatment

Table 3 presents the mean changes in IgE and IgG_4 levels between baseline and 6 months after treatment. In the intervention group (both SIT and scaling and polishing at 6 months), there was a significant decrease in both the total serum of IgE ($p < 0.001$) and total serum of IgG_4 ($p = 0.001$) compared to baseline. On the other hand, the control group (SIT only) also showed a significant decrease in the total serum of IgE ($p = 0.019$) but failed to achieve a significant decrease in the total serum of IgG_4 ($p = 0.839$) compared to baseline (Table 3).

Differences in the total change in immunoglobulin E (IgE) level between two groups

After 6 months, the total serum of IgE in the intervention group decreased by 19.81 ± 0.96 pg/mL, while it decreased by 0.94 ± 0.56 pg/mL in the control group. An independent *t*-test shows a significant difference in the total change in IgE between the two groups ($p < 0.001$) (Fig. 2).

Differences in the total change in immunoglobulin G_4 (IgG_4) level between two groups

After 6 months, the total serum of IgG_4 in the intervention group decreased by 10.57 ± 3.00 ng/mL, while it increased by 0.09 ± 1.01 ng/mL in the control group. All subjects in the intervention group showed a decrease in the total change in IgG_4 levels. However, in the control group, only two subjects showed a decrease in IgG_4 level, whereas the remaining three subjects showed an increase in the IgG_4 level. An independent samples *t*-test shows a significant difference in the total change in IgG_4 level between the two groups ($p < 0.001$) (Fig. 3).

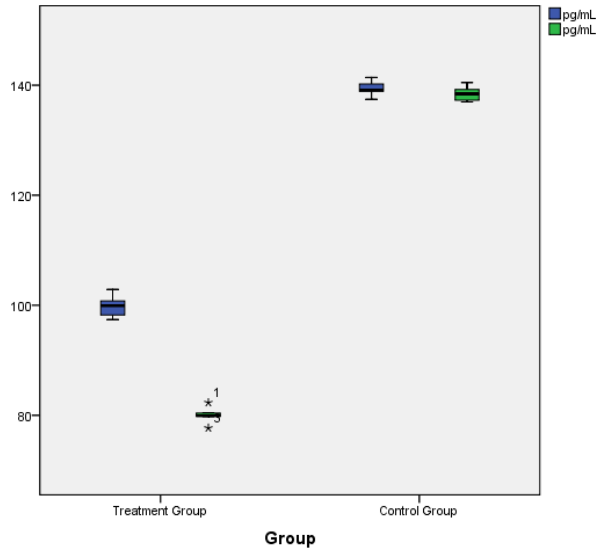


Fig. 2. Level of immunoglobulin E (IgE) between two groups before and after treatment.

Discussion

This study was conducted to evaluate the beneficial effects of a comprehensive 6-month dental SRP to improve biomolecular markers of atopy. The results showed that, in the intervention group, a comprehensive 6-month dental SRP along with SIT showed more marked improvement in the biomolecular markers of atopy than the control group. This finding supports compelling evidence that comprehensive 6-month dental SRP is inversely related to the level of IgE and IgG_4 in children with gingivitis and HDM allergies.

As gingival inflammation may induce elevated atopic inflammatory mediators and dental plaque appears to form more rapidly in children aged 8–12 years, many studies have begun to scrutinise the effect of periodontal pathogen

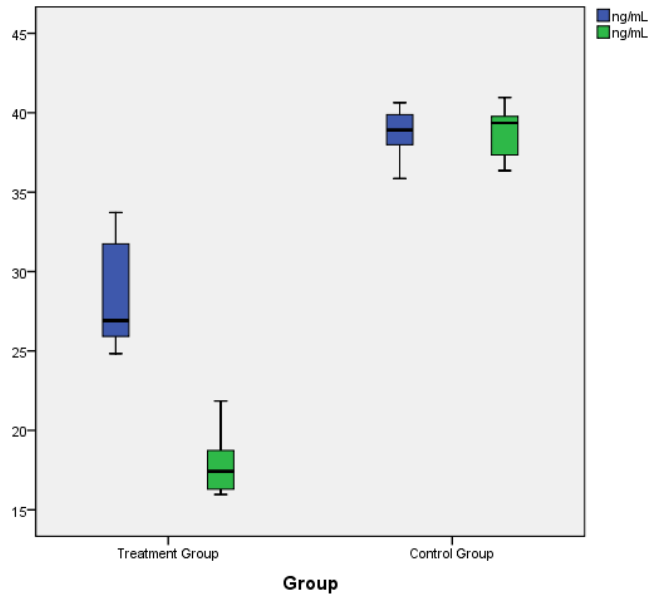


Fig. 3. Level of immunoglobulin G_4 (IgG_4) between two groups before and after treatment.

infections and gingival inflammation on the appearance of allergies in children aged 8–12 years.[33–35] Children with HDM allergies have more dental plaque and calculus and tend to have more severe gingivitis.[36] A previous study by Cortelli *et al.* have shown that children with gingivitis have significantly higher levels of systemic LPS levels than gingival healthy individuals.[37] The main purpose of dental SRP is to restore healthy gingivae by completely removing dental plaque, calculus and toxic substances such as LPS that trigger gingival inflammation, from the tooth surface.[38] This strategy may cause a drastic reduction in the number of subgingival microorganisms as well as a change in the composition of the plaque from one with more gram-negative anaerobic bacteria (*Pg*) to one with more gram-positive facultative bacteria (*Streptococcus salivarius, Streptococcus gordonii, Streptococcus mutans, Streptococcus sanguinis* and some *Lactobacillus* species). Therefore, this leads to less exposure to LPS, which is mainly produced by gram-negative bacteria.[39]

Kalash *et al.* observed a significant decrease in systemic LPS among each subsequent time point following dental SRP, where initially the serum LPS level appeared to slightly decrease at 3 months and slightly rebound at 6 months, but reached to a significant reduction at 12 months.[40] To our knowledge, for clinical purpose, the American Dental Association advises periodical visit for SRP every 6–12 months due to the nature of periodontal pathogen formation and rebound of systemic LPS at 6 months. On the other hand, for research purpose, a comprehensive 6-month dental SRP is enough to maintain the level of local or systemic LPS and to prevent rebound.[41]

Interactions between allergens, periodontal bacteria and pro-inflammatory cytokines have been previously reported.[42] Lipopolysaccharide of *Pg* is a gram-negative endotoxin, which is ubiquitous in the environment and can therefore exacerbate allergic responses.[43] At very low concentration, LPS may induce atopic inflammatory responses by Th-1 shifting into Th-2, which is more potent to stimulate antibodies production.[44] Lipopolysaccharide binds to toll-like receptor 4 (TLR4) and highly enhances the response of TLR4-transfected cells. Thus, damage due to LPS extends beyond the exhaustion of host innate immunity.[45] Previous studies demonstrated the pathogenic role of *Pg* dental biofilm to stimulate LPS-driven inflammatory responses,[46] and therefore, lack of dental plaque and calculus in supra-gingival surface, sub-gingival surface and human epithelial cell rests of Malassez accounted for the lack of response to LPS to induce sensitisation of atopic inflammatory responses.[47,48] Moreover, given the unique LPS-induced atopic inflammatory responses, we can control atopic inflammatory responses by removing dental biofilm. This reduces the subject body's load of LPS-triggered mast cells derived from periodontal inflammation.[49,50]

Following dental SRP, there is also evidence of increasing certain *Lactobacilli* populations, which are beneficial for controlling atopic inflammatory pathway.[51] It is widely accepted that *Lactobacilli* in the oral cavity may determine the population of *Lactobacilli* in the gut.[52] Therefore, an increase in the amount of *Lactobacilli* species can result in the induction of IgA antibodies and $CD4^+$ T regulatory cells (producing IL-10 and IFN-γ).[53] Due to its beneficial role in inhibiting IL-4 and IL-5 secretion, *Lactobacilli* markedly suppress total and antigen-specific IgE, and thus may control atopic inflammatory pathways.[54]

Considering the above findings, it is believed that the combination of decreasing systemic LPS of *Pg* and increasing of *Lactobacilli* species following dental SRP may regulate atopic inflammatory responses system, particularly for children with HDM allergies. Finally, controlling microbiota in the gut and the oral cavity plays an important role in the attenuation of IgE sensitisation induced by dust allergens.

Limitations

In this study, the sample size was small. A total of 10 children with gingivitis and HDM allergies participated, with only five subjects per group. Baseline serum IgE and IgG_4 levels between intervention group and control group were significantly different ($p < 0.001$ and $p = 0.001$, respectively), implying that difference in baseline IgE and IgG_4 levels may influence the results of this trial as a confounding factor. The samples used in this study were limited to the result acquired by using this study design and sampling method. Therefore, the result could not be

extrapolated to the manifestation of allergic diseases and children matching the criteria of exclusion. Based on the principles of ethics, this study respects the parent's free will to choose the regular schedule for dental SRP within 6-months duration of treatment. Thus, the intervention was determined by the parents' choices. Therefore, it is impossible to exclude the effect of different schedules in the intervention group to participate in the intervention plan on the intervention results. Future recommendations include the profile of cytokines and number of colony-forming units of periodontal bacteria in the gum to correlate the stability of the achieved results could be considered and larger sample size with longer duration of treatment and strict regular schedule could be considered for significant results.

Conclusion

Based on the study results and discussion, it can be inferred that reduction in IgE and IgG_4 levels in children with gingivitis may be attributed to direct or indirect effects of dental SRP. Within the limitations of this study, it can be concluded that dental SRP can improve biomolecular markers of atopy in children with gingivitis and HDM allergies. Furthermore promising results from this pilot study may lead to the next phase of clinical trials to refine and further evaluate the beneficial effects of dental SRP intervention in children with gingivitis and HDM allergies. The data collected in this pilot study comprise essential preliminary data to seek funding for conducting a larger, fully powered randomised controlled trial.

List of Abbreviations

CD4	cluster differentiation 4
CONSORT	Consolidated Standards of Reporting Trials
ELISA	enzyme-linked immunosorbent assay
IFN-γ	γ-interferon
IL	interleukin
HDM	house dust mite
IgE	immunoglobulin E
IgG_4	immunoglobulin G_4
ISRCTN	International Standard Randomised Controlled Trial Number
LPS	lipopolysaccharide
ng/mL	nanogram per millilitres
pg/mL	pictogram per millilitres
Pg	*Porphyromonas gingivalis*
SIT	specific immunotherapy
SRP	scaling and root planing
Th-0	naïve T-cell
Th-1	helper T-cell type 1
Th-2	helper T-cell type 2
TLR-4	toll-like receptor 4
TMB	3,3′,5,5′-tetramethylbenzidine

Declarations

Ethics approval and consent to participate

Institutional Review Boards of Universitas Airlangga – Dr. Soetomo General Hospital's Ethics Committee for Health Research reviewed and approved the study (ethics approval number 20/Panke.KKE/I). Informed consent was validated by the Dr. Soetomo General Hospital Ethics Committee for Health Research. All parents provided written informed consent to participate and were allowed to withdraw at any time.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated and/or analysed during the study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Faculty of Dental Medicine of Universitas Airlangga. This funding source had no role in the design of this study, its execution, analyses, interpretation of the data or decision to submitting results.

Authors' Contributions

S.C.N. is the principal investigator of this work. Conception and design: F.D. and S.C.N; acquisition of data: S.C.N., A.E., R.A.N., and F.D.; analysis and interpretation of data: R.A.N. and F.D.; drafting of the manuscript: R.A.N. and M.T.; critical revision: P.N. and U.T.; statistical analysis: F.D. and D.H.U.; supervision and genera advice for the study: A.E., P.N., and U.T. Guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors read and approved the final manuscript.

Acknowledgements

This research is funded by a Research Project Grant from the Faculty of Dental Medicine of Universitas Airlangga.

We would like to thank and appreciate the significant contributions of members of the Indonesian Association of Pediatric Dentistry (IDGAI) Surabaya branch: Seno Pradopo, Soegeng Wahluyo, Els Sunarsih, Teguh Wibowo, Satiti Kuntari, Tania Saskianti, Betadion Sinaredi, Mega Moeharyono, Ardianti Maartrina and Dimas Prasetianto, who performed dental SRP for our subjects. We would like to acknowledge the contribution of Dr. Soetomo General Hospital, including Harsono (director of the hospital) and Zahrah Hikmah (head of Pediatric Allergy Outpatient Clinic) who allowed this study carried out. We also would like to acknowledge Darmawan Setijanto from College of Dentistry for his precious advice and corrections of the manuscript. Finally, parents and their children who participated in this trial also need to be acknowledged for their significant contributions.

References

[1] Rengganis I, Susanto AJ. Pollen serum specific IgE sensitization in respiratory allergic patients in Jakarta, *Indonesia Acta Med Indones* 2017;**49**(3):243–8.

[2] Hamid F, Wiria AE, Wammes LJ, Kaisar MM, Djuardi Y, Versteeg SA *et al.* Risk factors associated with the development of atopic sensitization in Indonesia. *PLoS One* 2013;**8**(6):e67064.

[3] Ha EK, Na MS, Lee S, Baek H, Lee SJ, Sheen YH *et al.* Prevalence and clinical characteristics of local allergic rhinitis in children sensitized to house dust mites. *Int Arch Allergy Immunol* 2017;**174** (3–4):183–9.

[4] Thomas WR. Blueprint for the house dust mite. *Int Arch Allergy Immunol* 2018;**175**(3):121–5.

[5] Erban T, Harant K, Hubert J. Detailed two-dimensional gel proteomic mapping of the feces of the house dust mite *Dermatophagoides pteronyssinus* and comparison with *D. farinae*: Reduced trypsin protease content in *D. pteronyssinus* and different isoforms. *J Proteomics* 2017;**162**:11–9.

[6] Kidon MI, Chiang WC, Liew WK, Lim SH, See Y, Goh A. Sensitization to dust mites in children with allergic rhinitis in Singapore: Does it matter if you scratch while you sneeze? *Clin Exp Allergy* 2005;**35**:434–40.

[7] Ciprandi G, Puccinelli P, Incorvaia C, Passalacqua G. Italian Cometa Study Group. The relevance of house dust mites allergy in clinical practice: The epidemiological impact on allergen immunotherapy. *Immunotherapy* 2017;**9**(15):1219–24.

[8] Biagtan M, Viswanathan R, Bush RK. Immunotherapy for house dust mite sensitivity: Where are the knowledge gaps? *Curr Allergy Asthma Rep* 2014;**14**(12):482. Review.

[9] Kaplan WA, Ashigbie PG, Brooks MI, Wirtz VJ. Comparison of medicines management strategies in insurance schemes in middle-income countries: Four case studies. *J Pharm Policy Pract* 2017;**10**:17.

[10] Rasheed Z, Zedan K, Saif GB, Salama RH, Salem T, Ahmed AA *et al.* Markers of atopic dermatitis, allergic rhinitis and bronchial asthma in pediatric patients: Correlation with filaggrin, eosinophil major basic protein and immunoglobulin E. *Clin Mol Allergy* 2018;**16**:23.

[11] Dullaers M, De Bruyne R, Ramadani F, Gould HJ, Gevaert P, Lambrecht BN. The who, where, and when of IgE in allergic airway disease. *J Allergy Clin Immunol* 2012;**129**:635–45.

[12] Aalberse RC, Platts-Mills TA, Rispens T. The developmental history of IgE and IgG4 antibodies in relation to atopy, eosinophilic esophagitis, and the modified TH2 response. *Curr Allergy Asthma Rep* 2016;**16** (6):45.

[13] Gwynn CM, Smith JM, Leon GL, Stanworth DR. IgE and IgG4 subclass in atopic families. *Clin Allergy* 1979;**9**(2):119–23.

[14] Masaki Y, Kurose N, Yamamoto M, Takahashi H, Saeki T, Azumi A *et al.* Cutoff values of serum IgG4 and histopathological IgG4$^+$ plasma cells for diagnosis of patients with IgG4-related disease. *Int J Rheumatol* 2012;**2012**:580814.

[15] Petursdottir DH, Nordlander S, Qazi KR, Carvalho-Queiroz C, Ahmed Osman O, Hell E *et al.* Early-life human microbiota associated with childhood allergy promotes the T helper 17 axis in mice. *Front Immunol* 2017;**8**:1699. eCollection 2017.

[16] Chen Q, Ren Y, Lu J, Bartlett M, Chen L, Zhang Y *et al.* A novel prebiotic blend product prevents irritable bowel syndrome in mice by improving gut microbiota and modulating immune response. *Nutrients* 2017;**9**(12):1341.

[17] Hajishengallis G. Periodontitis: From microbial immune subversion to systemic inflammation. *Nat Rev Immunol* 2015;**15**(1):30–44.

[18] Al-Ghutaimel H, Riba H, Al-Kahtani S, Al-Duhaimi S. Common periodontal diseases of children and adolescents. *Int J Dent* 2014;**2014**:850674.

[19] Card JW, Carey MA, Voltz JW, Bradbury JA, Ferguson CD, Cohen EA *et al.* Modulation of allergic airway inflammation by the oral pathogen *Porphyromonas gingivalis*. *Infect Immun* 2010;**78**(6):2488–96.

[20] Arbes SJ, Sever ML, Cohen EA, Zeldin DC. Oral pathogens and allergic disease: Results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2006;**118**(5):1169–75.

[21] Haake SK, Nisengard RJ, Newman MG, Miyasaki KT. Microbial interactions with the host in periodontal diseases. In: Newman MG, Takei HH, Carranza FA. Carranza's Clinical Periodontology. Philadelphia: WB Saunders Co, 2002:132–52.

[22] Hajishengallis G. The inflammophilic character of the periodontitis-associated microbiota. *Mol Oral Microbiol* 2014;**29**(6):248–57.

[23] Okrój M, Potempa J. Complement activation as a helping hand for inflammophilic pathogens and cancer. *Front Immunol* 2019;**9**:3125.

[24] Moutsopoulos NM, Kling HM, Angelov N, Jin W, Palmer RJ, Nares S *et al. Porphyromonas gingivalis* promotes Th17 inducing pathways in chronic periodontitis. *J Autoimmun* 2012;**39**:294–303.

[25] Nelwan SC, Endaryanto A, Harjanto JM, Pradopo S, Prawati N. Shifting immune response and cytokine profiles after *Porphyromonas gingivalis* lipopolysacaride exposure. *J Int Dent Med Res* 2017: **10**(1):95–99.

[26] Ni J, Chen L, Zhong S, Chai Q, Zhang L, Wang D *et al.* Influence of periodontitis and scaling and root planing on insulin resistance and hepatic CD36 in obese rats. *J Periodontol* 2018;**89**:476–85.

[27] Nelwan SC, Nugraha RA, Endaryanto A, Retno I. Modulating toll-like receptor-mediated inflammatory responses following exposure of whole cell and lipopolysaccharide component from *Porphyromonas gingivalis* in wistar rat models. *Eur J Dent* 2017;**11**(4):422–6.

[28] Eivazi M, Falahi N, Eivazi N, Eivazi MA, Raygani AV, Rezaei F. The effect of scaling and root planing on salivary TNF-α and IL-1α concentrations in patients with chronic periodontitis. *Open Dent J* 2017;**11**:573–80.

[29] Korn S, Haasler I, Fliedner F, Becher G, Strohner P, Staatz A *et al.* Monitoring free serum IgE in severe asthma patients treated with omalizumab. *Resp Med* 2012;**106**(11):1494–500.

[30] Zhong B. How to calculate sample size in randomized controlled trial? *J Thorac Dis* 2009;**1**(1):51–4.

[31] Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M *et al.* Treatment of periodontitis and endothelial function. *N Engl J Med* 2007;**356**:911–20.

[32] CONSORT statement. Available from: (http://consort-statement.org) (accessed 18 April 2018).

[33] Giannobile WV, Beikler T, Kinney JS, Ramseier CA, Morelli T, Wong DT. Saliva as a diagnostic tool for periodontal disease: Current state and future directions. *Periodontol* 2000 2009;**50**:52–64.

[34] Umrania VV, Deepika PCR, Kulkarni M. Evaluation of dietary supplementation of omega-3 polyunsaturated fatty acids as an adjunct to scaling and root planing on salivary interleukin-1β levels in patients with chronic periodontitis: A clinico-immunological study. *J Indian Soc Periodontol* 2017;**21**(5):386–90.

[35] Arbes SJ, Matsui EC. Can oral pathogens influence allergic disease? *J Allergy Clin Immunol* 2011;**127**:1119–27.

[36] Koch G, Poulsen S. Pediatric Dentistry: A Clinical Approach, 2nd edition. New York: Willey-Blackwell, 2009:316–9.

[37] Cortelli SC, Aquino DR, Cortelli JR, Raslan SA, Roman-Torres CVG, Balejo RDP *et al.* Periodontal pathogens and clinical periodontal status of school children: A cross-sectional study. *Oral Hyg Health* 2014;**2**:2.

[38] Jacob SP, Nath S, Zade RM. Effect of periodontal therapy on circulating levels of endotoxin in women with periodontitis: A pilot clinical trial. *Indian J Dent Res* 2012;**23**(6):714–8.

[39] Al Yahfoufi Z. Prevalence of periodontal destruction and putative periodontal pathogens in the same Lebanese family. *J Contemp Dent Pract* 2017;**18**(10):970–6.

[40] Kalash D, Vovk A, Huang H, Aukhil I, Wallet SM, Shaddox LM. Influence of periodontal therapy on systemic lipopolysaccharides in children with localized aggressive periodontitis. *Pediatr Dent* 2015;**37**(5):35–40.

[41] Newman MG, Carranza FA. Clinical Periodontology, 11th edition. Philadelphia: Saunders, 2012.

[42] Kim SW, Han DH, Lee SJ, Lee CH, Rhee CS. Bronchial hyperresponsiveness in pediatric rhinitis patients: The difference between allergic and nonallergic rhinitis. *Am J Rhinol Allergy* 2013;**27**:e63–8.

[43] Kumari A, Dash D, Singh R. Lipopolysaccharide (LPS) exposure differently affects allergic asthma exacerbations and its amelioration by intranasal curcumin in mice. *Cytokine* 2015;**76**(2):334–342.

[44] Sato N, Kinbara M, Kuroishi T, Kimura K, Iwakura Y, Ohtsu H *et al.* Lipopolysaccharide promotes and augments metal allergies in mice, dependent on innate immunity and histidine decarboxylase. *Clin Exp Allergy* 2007;**37**(5):743–51.

[45] Jiang K, Guo S, Zhang T, Yang Y, Zhao G, Shaukat A *et al.* Down-regulation of TLR4 by miR-181a provides negative feedback regulation to lipopolysaccharide-induced inflammation. *Front Pharmacol* 2018;**9**:142.

[46] Okeke EB, Okwor I, Uzonna JE. Regulatory T cells restrain $CD4^+$ T cells from causing unregulated immune activation and hypersensitivity to lipopolysaccharide challenge. *J Immunol* 2014;**193**(2):655–62.

[47] Diomede F, Thangavelu SR, Merciaro I, D'Orazio M, Bramanti P, Mazzon E *et al.* Porphyromonas gingivalis lipopolysaccharide stimulation in human periodontal ligament stem cells: Role of epigenetic modifications to the inflammation. *Eur J Histochem* 2017;**61**(3):2826.

[48] Elkaim R, Bugueno-Valdebenito IM, Benkirane-Jessel N, Tenenbaum H. *Porphyromonasgingivalis* and its lipopolysaccharide differently modulate epidermal growth factor-dependent signaling in human gingival epithelial cells. *J Oral Microbiol* 2017;**9**(1):1334503.

[49] Karta MR, Gavala ML, Curran CS, Wickert LE, Keely PJ, Gern JE *et al.* LPS modulates rhinovirus-induced chemokine secretion in monocytes and macrophages. *Am J Respir Cell Mol Biol* 2014;**51**(1):125–34.

[50] Huang W, Morales JL, Gozivoda VP, August A. Non-receptor tyrosine kinases ITK and BTK negatively regulate mast cell pro-inflammatory responses to lipopolysaccharide. *J Allergy Clin Immunol* 2016;**137**(4):1197–205.

[51] Inglin RC, Stevens MJ, Meile L, Lacroix C, Meile L. High-throughput screening assays for antibacterial and antifungal activities of *Lactobacillus* species. *J Microbiol Methods* 2015;**114**:26–9.

[52] Canani RB, Costanzo MD, Pezzella V, Cosenza L, Granata V, Terrin G *et al.* The potential therapeutic efficacy of *Lactobacillus* GG in children with food allergies. *Pharmaceuticals (Basel)* 2012;**5**(6):655–64.

[53] Gourbeyre P, Denery S, Bodinier M. Probiotics, prebiotics, and synbiotics: Impact on the gut immune system and allergic reactions. *J Leukoc Biol* 2011;**89**:685–95.

[54] Shida K, Makino K, Morishita A, Takamizawa K, Hachimura S, Ametani A *et al. Lactobacillus* casei inhibits antigen-induced IgE secretion through regulation of cytokine production in murine splenocyte cultures. *Int Arch Allergy Immunol* 1998;**115**(4):278–87.

Singapore Dental Journal, Vol. 39 (2019) 33–40

DOI: 10.1142/S2214607519500032

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Platelet-rich fibrin in combination with decalcified freeze-dried bone allograft for the management of mandibular degree II furcation defect: A randomised controlled clinical trial

Ashish Agarwal*, R. G. Shiva Manjunath, Priyamwada Sethi, G. Shiva Shankar

Department of Periodontology and Implantology, Institute of Dental Sciences, Bareilly, Uttar Pradesh, India

Keywords:
Bone graft
chronic periodontitis
furcation defects
flap surgery

A B S T R A C T

Background: Treatment of furcation involvement of molars with periodontal disease remains challenging and unpredictable. Platelet-rich fibrin (PRF) has received the attention of researchers due to its pleiotropic properties essential for periodontal wound healing. The osteoinductive property of demineralized freeze-dried bone allograft (DFDBA) has been successfully used in periodontal regeneration.
Aim: The present study aimed to explore the effectiveness of PRF alone and with DFDBA in the treatment of mandibular degree II furcation defects in subjects with chronic periodontitis.
Material and Methods: Patients treated were from the Department of Periodontology and Implantology, Institute of Dental Sciences, Bareilly. A total of 60 mandibular molars were treated with either open flap debridement (OFD) alone, PRF + OFD combination or OFD + PRF + DFDBA combination. The soft and hard tissue parameters such as vertical probing depth (VPD), vertical clinical attachment level (VCAL), gingival marginal level (GML), horizontal probing depth (HPD), vertical bone fill (VBF), horizontal bone fill (HBF) and furcation width (FW) were determined at baseline and 9 months postoperatively. A paired *t*-test was conducted to assess the statistical significance between time period within each group for clinical and radiographic parameters. ANOVA and *post-hoc* Tukey's tests were also conducted for intergroup comparison of soft and hard tissue parameters. Statistical significance was set at $p < 0.05$.
Results and Discussion: After 9 months, all treatment groups showed significant ($p < 0.001$) improvement in soft and hard tissue parameters, except GML in all the three groups and HBF and FW in the OFD group as compared to baseline. The mean VBF change was highest in the OFD + PRF + DFDBA group (1.90 + 0.45) mm, followed by that in the PRF + OFD and OFD groups (1.60 + 0.88 and 0.45 + 0.51 mm, respectively).
Conclusions: It was shown that both PRF + OFD and PRF + DFDBA + OFD combinations were significantly advantageous for the management of mandibular degree II furcation defects. However, the PRF + DFDBA + OFD combination has significantly greater benefits than PRF + OFD combination in terms of VBF.

*Corresponding author: Ashish Agarwal, Department of Periodontology and Implantology, Institute of Dental Sciences, Bareilly, Uttar Pradesh, India, Email: drashish.aag@gmail.com

Introduction

Molar furcation involvement (FI) is one of the most common dentoalveolar sequelae of periodontal disease. Among periodontal defects, FI represents a challenging scenario due to the difficulty of achieving a predictable improvement regardless of the type of periodontal therapy.[1] The poor response of this defect may be related to local factors such as the complex anatomy and position of furcation entrances that negatively interfere with daily hygiene and professional debridement by clinicians.[2] Various regenerative modalities have been investigated for the management of intrabony periodontal defects, for example, bone grafts (BGs) and substitutes, guided tissue regeneration (GTR), growth factors (GFs), enamel matrix derivatives and combined approaches.[3,4]

Polypeptide growth factors (PGFs) revealed a potential application in wound healing by promoting periodontal regeneration via cell proliferation, angiogenesis, chemotaxis and differentiation.[5] The use of autologous blood concentrates (ABCs) is a safe and convenient approach to deliver high concentrations of PGFs to periodontal surgical wounds.[6] Among ABCs, platelet-rich fibrin (PRF) belongs to a group of second-generation blood autologous preparations that was originally described by Choukroun *et al.*[6] The PRF preparation process creates a gel-like matrix that contains a high concentration of non-activated, functional, intact platelets, embedded within a fibrin matrix, that release a relatively constant concentration of growth factors.[7,8] Some recent studies have also demonstrated the beneficial aspect of PRF in periodontal regeneration.[9,10]

Clinical research studies have reported the improvements in clinical attachment and bone level by applying demineralised freeze-dried bone allograft (DFDBA) in human intraosseous lesions,[11,12] while histological evidence of new attachment formation achieved by the use of DFDBA was also present.[13]

The aim of the present study was, therefore, to clinically evaluate the outcome of the adjunctive use of DFDBA with PRF as compared to the PRF alone in the treatment of human mandibular degree II furcation defects.

Material and Methods

A total of sixty mandibular molars from 46 non-smoking patients (26 females and 20 males, aged between 30 and 65 years, mean age was 48 ± 15 years) with moderate-to-severe chronic periodontitis (According to AAP 1999 classification)[14] with buccal degree II furcation defect[15,16] were enrolled for the study at the outpatient Department of Periodontics, Institute of Dental Sciences, Bareilly, India. The study was designed as a randomised, parallel, controlled clinical trial for the comparison of periodontal outcomes using open flap debridement (OFD) alone, PRF with OFD and PRF with DFDBA and OFD in the treatment of mandibular degree II FI defects.

The inclusion criterion for the study was the presence of buccal degree II furcation defects (Hamp *et al.*)[16] in endodontically vital, asymptomatic mandibular molars with probing depth (PD) of ≥ 5 mm and horizontal PD of ≥ 3 mm after phase I therapy (scaling and root planing). The exclusion criteria for the study were the presence of any systemic disease, hypersensitivity to any medication, patients under any medication, pregnancy or lactation, smokers, previously treated for periodontal issues, and mobility of tooth $\geq$ Grade II.[15]

The study protocol, risks, benefits and procedures were explained, and written informed consent was obtained from every patient. The study was approved by the ethical committee of Institute of Dental Sciences, Bareilly, India, and all the examinations, treatment and procedures of this study followed the guidelines of Declaration of Helsinki of 1975, as revised in 2008.

Initial therapy

Initial therapy consisted of detailing instructions regarding proper oral hygiene measures followed by full mouth scaling and root planing using hand and ultrasonic instruments under local anaesthesia. Eight weeks following phase I therapy, a periodontal re-evaluation was performed to confirm the suitability of the sites for this periodontal surgical study. The selected sites were equally divided randomly (computer-generated tables) into the control group sites and test group sites; control group sites treated with OFD, whereas the test group sites were treated with OFD with autologous PRF or PRF with DFDBA. One operator (AA) performed all the surgeries, whereas another operator (RGSM) performed all the clinical and radiographic measurements without knowledge of the groups.

Presurgical clinical measurements

Clinical parameters related to the treated teeth included Plaque index (PI),[17] Gingival index (GI),[18] vertical probing depth (VPD), vertical clinical attachment level (VCAL), gingival margin position (GMP) and horizontal probing depth (HPD) into the furcation defect, which was measured as a single reading at the mid-facial furcation entrance site. Soft tissue measurements were performed using customised acrylic stents with a single mid-facial groove to ensure a reproducible placement of the University of North Carolina no. 15 (UNC-15, Hu-Friedy, Chicago, IL, USA) periodontal probe and Nabers probe for furcation to the nearest millimetre. These measurements were obtained just before the surgery and after 9 months of the postoperative period by re-entry procedure.

Hard tissue (intra-surgical) parameters

Measurements of the vertical and horizontal component of the furcation were performed after surgical flap access and complete debridement using a UNC-15 periodontal probe and a fissured acrylic template. The following measurements were recorded (the details of measurement are presented in Fig. 1). Fornix to base of the defect (FBD): the distance from the furcation fornix to the base of the defect at the mid-facial aspect of the teeth; vertical bone fill (VBF) in the apico-coronal direction within the furcation was calculated by subtracting the 9-month FBD from baseline FBD. Horizontal furcation depth (HFD): the horizontal distance between the deepest probed region of defects and the rubber stop contacting the root convexity, where the probe is perpendicular to the long axis of tooth in the horizontal direction. Horizontal bone fill (HBF) in the facio-lingual direction was calculated by subtracting the 9-month HFD from baseline HFD. Furcation width (FW): the mesio-distal width of the furcation entrance measured with the probe positioned at the level of alveolar crest (Fig. 1).

PRF preparation

The PRF was produced according to the protocol developed by Choukroun *et al.*[6] On the day of surgery, 10 mL of blood was drawn from each patient by venipuncture of the antecubital vein. Blood was collected in a sterile glass test tube without any anti-coagulant. The test tube was immediately centrifuged using a refrigerated centrifugal machine at 400 × *g* for 12 min. Differential densities, separate blood components to three basic fractions: a base of red blood cells at the bottom, acellular plasma on the surface and finally a PRF clot between the two. The middle layer (PRF) was removed and placed in a sterile dappen dish. This clot was either minced into small pieces and mixed with graft material or pressed between two sterile compresses to form a membrane.

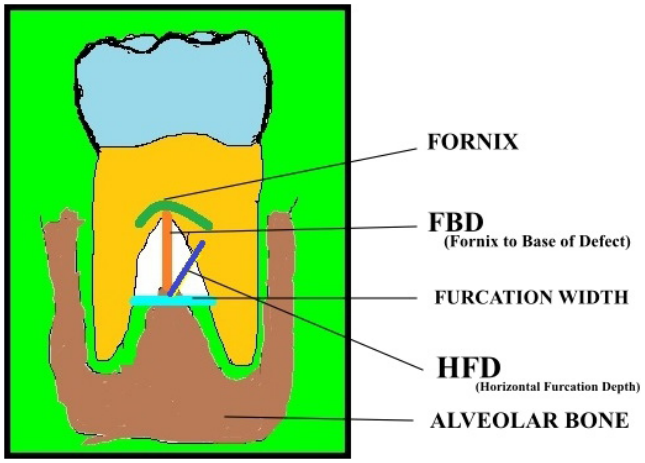


Fig. 1. Measurement details of the study.

Surgical procedure

Following the administration of local anaesthesia, buccal and lingual sulcular incisions were made and the mucoperiosteal flaps were reflected. A thorough debridement of the defect was performed with manual and power-driven scalers. No osseous recontouring was carried out. The defect was filled by PRF and also covered by PRF membrane.

For the PRF + DFDBA group, both materials were mixed in a proportion of 1:1 (v/v), filled into the furcation and covered with a PRF membrane. An interrupted suturing technique was used for repositioning the flaps with 3-0 non-absorbable black silk surgical suture (Figs. 2–4 show test group images; Figs. 5 and 6 show control group images). Periodontal dressing was used for covering the surgical site. Amoxicillin (500 mg) and ibuprofen (800 mg) were prescribed thrice daily for 7 days along with 0.2% chlorhexidine digluconate mouth rinses twice daily for 2 weeks.[19]

Postoperative follow-up care

Periodontal dressing and sutures were removed 2 weeks postoperatively. Surgical wounds were gently cleansed

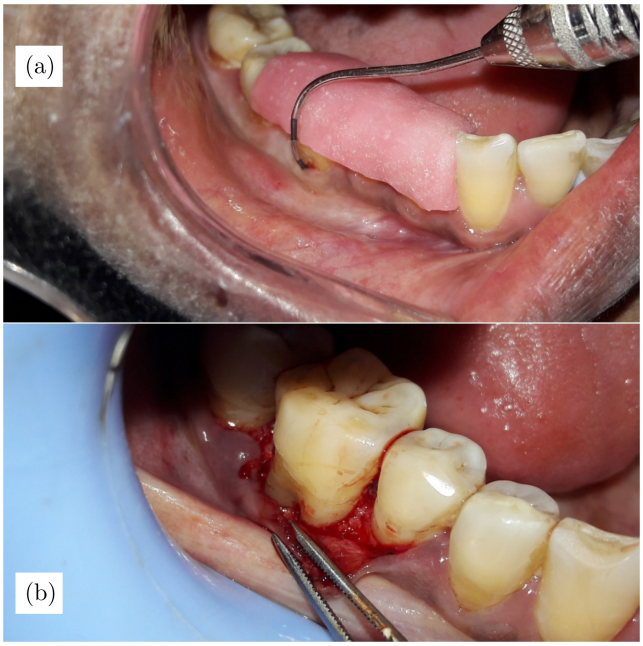


Fig. 2. (a) Pre-operative image with probing. (b) Image after flap reflection and debridement.

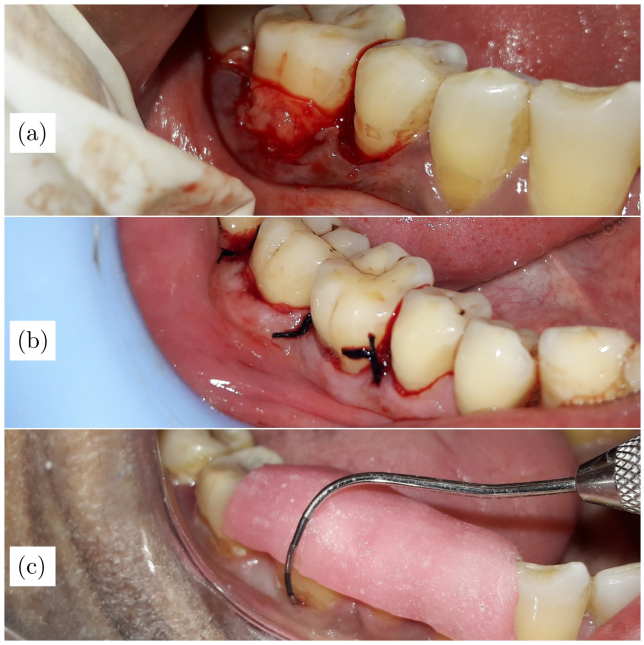


Fig. 3. (a) After PRF and DFDBA allograft placement. (b) After suturing. (c) 9 months post-operative with probing.

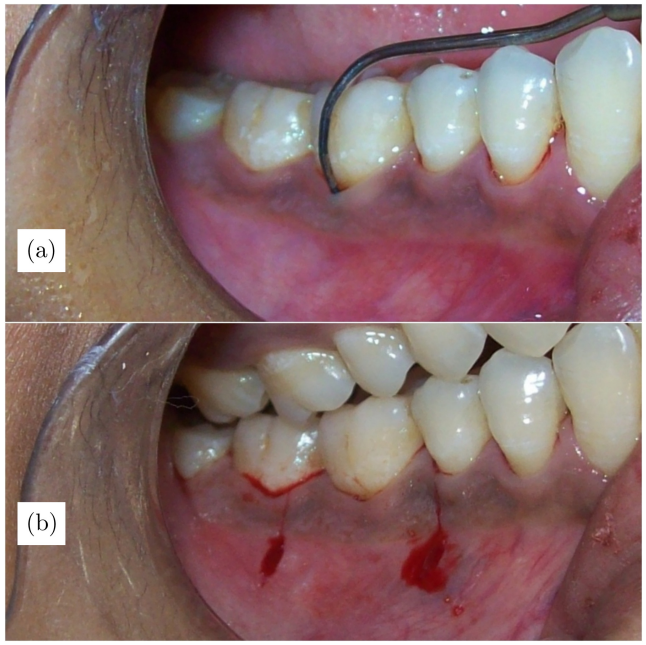


Fig. 5. (a) Pre-operative image and (b) after incision image of the control group.

with 0.12% of chlorhexidine (chlorhexidine digluconate) (PerioGard®), and patients were instructed for gentle brushing with a soft toothbrush. Patients were instructed for maintaining proper oral hygiene and follow-up visits were scheduled weekly up to 1 month and then at 3 and 9 months of the postoperative period. After 9 months of postoperative period, soft and hard tissue assessments were performed with previously used acrylic stents.[20]

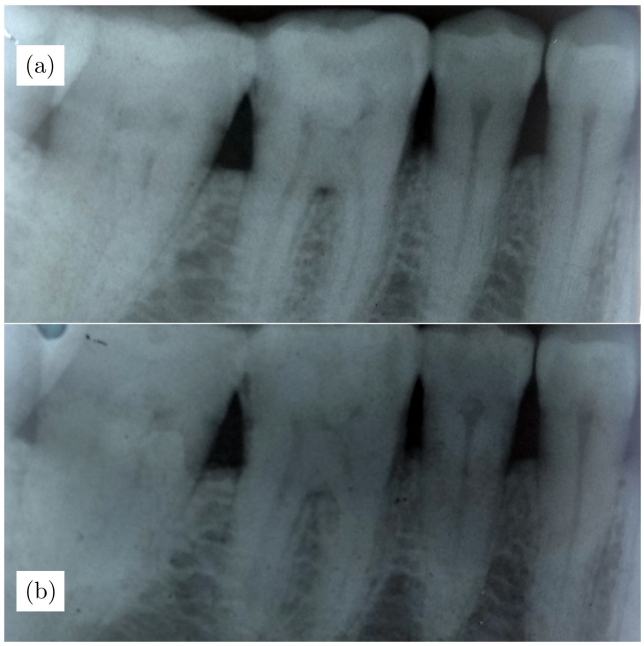


Fig. 4. (a) Pre-operative IOPA and (b) 9 months post-operative IOPA.

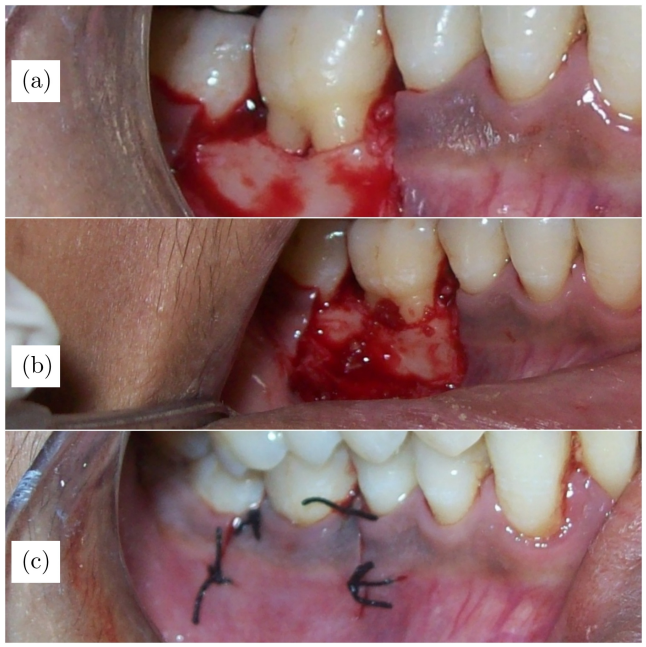


Fig. 6. (a) After reflection and debridement of the control group. (b) After PRF placement. (c) After suturing the control group.

Primary and secondary outcome measures

The primary outcome of the study was HBF and VBF. The secondary outcomes included VPD, VCAL, HPD, GMP, PI and GI.

Statistical analysis

The data were analysed using statistical software (SPSS version 10.5, SPSS, Chicago, IL, USA). Power calculations were performed before the study was initiated. To achieve 85% power and detect mean differences of the clinical parameters between groups, 20 molars in each group that contributed one facial site each were required. The results were averaged (mean ± SD) for each parameter at baseline and 9 months. The difference between each pair of measurements was calculated (at baseline and 9 months). A paired *t*-test was conducted to assess the statistical significance between time periods within each group for clinical and radiographic parameters. ANOVA and *post-hoc* Tukey's test were conducted for intergroup comparison of soft and hard tissue parameters. Statistical significance was set at $p < 0.05$.

Results

All patients completed the 9 months follow-up. During the study period, the oral hygiene level, PI and GI remained stable or improved with respect to the values detected at baseline. There was a significant ($p < 0.05$) improvement in PI and GI among the OFD + PRF + DFDBA and OFD + PRF groups, after 9 months. Between the groups, a non-significant relationship was observed between PI and GI.

The outcomes of this clinical trial suggested that all treatment groups showed significant ($p < 0.001$) improvement in soft and hard tissue parameters between baseline and 9 months of postoperative period, except for GMP, in all the three groups, and HFD and FW in the OFD group. On intergroup comparison, the OFD + PRF and OFD + PRF + DFDBA treatment groups showed significant ($p < 0.001$) improvement in terms of VPD, VCAL, VBF, and HBF than the OFD group. The OFD + PRF + DFDBA group showed more significant improvement in terms of VPD than other the two groups (Tables 1 and 2).

Table 1
Intragroup comparison of soft and hard tissue parameters (mean ± SD).

		OFD group		PRF group		PRF + DFDBA group	
Parameter	Time period	Mean ± SD	*p*-value	Mean ± SD	*p*-value	Mean ± SD	*p*-value
HPD (mm)	Baseline	5.20 ± 0.62	< 0.001**	5.30 ± 0.66	< 0.001**	5.20 ± 0.77	< 0.001**
	9 months	3.85 ± 0.77		3.50 ± 0.69		3.40 ± 0.59	
VPD (mm)	Baseline	6.10 ± 0.85	< 0.001**	6.35 ± 0.93	< 0.001**	6.30 ± 0.73	< 0.001**
	9 months	4.60 ± 0.60		2.55 ± 0.51		2.30 ± 0.47	
VCAL (mm)	Baseline	6.90 ± 0.64	< 0.001**	7.15 ± 0.67	< 0.001**	7.15 ± 0.67	< 0.001**
	9 months	5.55 ± 0.51		3.60 ± 0.99		3.25 ± 0.44	
GMP (mm)	Baseline	0.85 ± 0.87	NS	0.75 ± 0.79	NS	0.85 ± 0.93	NS
	9 months	0.95 ± 0.76		1.10 ± 0.91		0.95 ± 0.69	
FBD (mm)	Baseline	3.95 ± 0.76	0.001	3.85 ± 0.49	< 0.001**	4.00 ± 0.92	< 0.001**
	9 months	3.50 ± 0.61		2.25 ± 0.55		2.10 ± 0.79	
HFD (mm)	Baseline	5.15 ± 0.81	NS	5.50 ± 0.69	< 0.001**	5.25 ± 0.72	< 0.001**
	9 months	4.95 ± 0.76		4.10 ± 0.55		3.75 ± 0.55	
FW (mm)	Baseline	2.35 ± 0.49	NS	2.30 ± 0.47	< 0.05*	2.20 ± 0.61	< 0.05*
	9 months	2.25 ± 0.44		2.05 ± 0.39		1.85 ± 0.74	
PI	Baseline	0.62 ± 0.22	NS	0.61 ± 0.24	NS	0.59 ± 0.17	< 0.05*
	9 months	0.60 ± 0.28		0.56 ± 0.27		0.53 ± 0.14	
GI	Baseline	0.99 ± 0.28	NS	0.97 ± 0.30	< 0.05	0.95 ± 0.24	NS
	9 months	0.96 ± 0.25		0.89 ± 0.31		0.92 ± 0.30	

NS = Non-significant.
*$p < 0.05$ (significant); **$p < 0.001$ (highly significant)

Table 2
Intergroup comparison of the changes in soft and hard tissue parameters (mean ± SD) from baseline to 9 months postoperatively.

Changes (mm)	OFD	PRF	PRF + DFDBA	*p*-value	
Mean HPD change (mm)	1.35 ± 0.67	1.80 ± 0.83	1.80 ± 0.41	OFD vs. PRF	0.089[NS]
				OFD vs. PRF + DFDBA	0.089[NS]
				PRF vs. PRF + DFDBA	1.000[NS]
Mean VPD change (mm)	1.50 ± 0.76	3.80 ± 0.77	4.00 ± 0.79	OFD vs. PRF	<0.001**
				OFD vs. PRF + DFDBA	<0.001**
				PRF vs. PRF + DFDBA	0.694[NS]
Mean VCAL change (mm)	1.35 ± 0.49	3.55 ± 1.05	3.90 ± 0.72	OFD vs. PRF	<0.001**
				OFD vs. PRF + DFDBA	<0.001**
				PRF vs. PRF + DFDBA	0.256[NS]
Mean GMP change (mm)	−0.100 ± 0.97	−0.35 ± 1.13	−0.100 ± 1.11	OFD vs. PRF	0.745[NS]
				OFD vs. PRF + DFDBA	1.000[NS]
				PRF vs. PRF + DFDBA	0.745[NS]
Mean VBF change (mm)	0.45 ± 0.51	1.60 ± 0.88	1.90 ± 0.45	OFD vs. PRF	<0.001**
				OFD vs. PRF + DFDBA	<0.001**
				PRF vs. PRF + DFDBA	<0.001**
Mean HBF change (mm)	0.20 ± 0.52	1.40 ± 0.50	1.50 ± 0.76	OFD vs. PRF	<0.001**
				OFD vs. PRF + DFDBA	<0.001**
				PRF vs. PRF + DFDBA	0.665[NS]
Mean FW change (mm)	0.10 ± 0.30	0.25 ± 0.44	0.35 ± 0.49	OFD vs. PRF	0.502[NS]
				OFD vs. PRF + DFDBA	0.154[NS]
				PRF vs. PRF + DFDBA	0.734[NS]
Mean PI	0.02 ± 0.13	0.05 ± 0.13	0.06 ± 0.10	OFD vs. PRF	0.638[NS]
				OFD vs. PRF + DFDBA	0.450[NS]
				PRF vs. PRF + DFDBA	0.949[NS]
Mean GI	0.03 ± 0.08	0.08 ± 0.14	0.03 ± 0.15	OFD vs. PRF	0.417[NS]
				OFD vs. PRF + DFDBA	0.986[NS]
				PRF vs. PRF + DFDBA	0.511[NS]

*$p < 0.05$ (significant); **$p < 0.001$ (highly significant).
[NS]Non-significant.

Discussion

The present study was designed to evaluate PRF as an adjunct to DFDBA for the management of FI in mandibular molars. All baseline parameters were recorded with non-significant differences among the groups. The uneventful healing in all the sites was in agreement with previous studies,[9–11] thus supporting the excellent properties of involved biomaterials for periodontal wound healing. The control group sites were treated with OFD alone, whereas test group sites were managed with OFD in combination with PRF or in combination with PRF and DFDBA.

Our results revealed that all the three treatment modalities are significantly effective for the treatment of mandibular degree II furcation defect after 9 months of postoperative period. Among the three groups, the OFD + PRF + DFDBA group showed significant improvement in terms of VBF compared to the other groups. The mean change in VPD, VCAL and HBF was comparable between the test groups and was significantly higher for both test groups in comparison to the control group.

The inferences of the present study are in accordance with recent trials[9,21] that showed significant improvement by OFD alone and OFD + PRF in soft and hard tissue parameters for furcation defects after 9 months of postoperative period, while, on intergroup comparison, the PRF group demonstrated significantly more improvement than the OFD alone treatment group.

The purpose of using DFDBA and PRF combination in this study was that the PRF appears to hold great promise for improving wound healing and clinical outcomes in periodontal therapy. In addition, PRF combined with osteoinductive/osteoconductive bone substitutes showed beneficial effect by providing a stable scaffold for

various growth factor of PRF, prevention of soft tissue collapse in bone defect, accelerating cellular ingrowth, revascularisation of the wound site and contribution of osteoinductive BMP.

The results of the present study are in accordance with the results of Mehta *et al.,*[22] where they compared PRF and collagen membrane with DFDBA and obtained a significant reduction in PD and improvement relative to VCAL and defect fill.

A recent study conducted by Jain *et al.*[23] showed improvements in clinical parameters where they used FDBA with and without collagen membrane, while Kanoriya *et al.*[24] used 1% alendronate, PRF and combination of both. Whereas the present study used DFDBA + PRF and PRF alone in furcation defects and achieved statistically significant improvement in clinical parameters.

Previous studies[25,26] demonstrated significant changes in clinical parameters with histological documentation of complete periodontal regeneration (new attachment apparatus, new bone, cementum and periodontal ligament) with bone allograft mixed with recombinant human platelet-derived growth factor. Nevins *et al.*[25] showed more changes in HPD (3.40 mm), GMP (−0.80 mm) but less in VCAL (3.40 mm) with growth factors + DFDBA in comparison to that observed in our study. Contradictory statement regarding the results of our study is also present that observed no additional histologic and histometric beneficial effects of autologous graft derived from extraction sockets previously treated with growth factors for the repair of mandibular class II furcation area.[27]

Lyons *et al.*[28] observed less gain in HPD (1.22 mm), VPD (1.55 mm), VCAL (0.22 mm), bone fill (1.40 mm) and FW (0.11 mm), and more furcation horizontal component (2.33 mm) for polylactic acid barrier membrane containing 4% doxycycline hyclate + DFDBA for FI. Another recent study has reported lesser improvement in VPD (0.81 mm), VCAL (0.85 mm), HPD (1.50 mm) for BG + GTR in comparison to the present study for the same treatment.[4] The results of a re-entry study determined less improvement in VPD (2.50 mm), VCAL (2.50 mm) and VBF (1.58 mm), and greater change in HPD (2.83 mm) and HFD (2.75 mm) with a porous Teflon membrane with DFDBA in furcation defects after 9 months.[29]

A superior response of PRF-associated treatment over OFD in this study was observed due to the presence of platelets, leukocytes and cytokines, and circulating stem cells incorporated in the polymerised tetramolecular structure of PRF. PRF associated with slow release of growth factors (e.g. transforming growth factor-1b, platelet-derived growth factor-AB and vascular endothelial growth factor), and glycoproteins (e.g. thrombospondin-1) during $\geq$7 days.[6–8] PRF, a biomaterial scaffold, augments the healing of surrounding architecture due to the release of cytokines, attraction and activation of fibroblasts, endothelial cells and bone-forming cells.[5,6,8] In addition to this, PRF activates alkaline phosphates that represent osteoblastic activity and active bone formation.[30]

DFDBA-related studies may show variable outcomes due to the non-standardised osteoinductivity of BG. Hence, the possible reasons for this could be insufficient amount of BMPs or inactivity of BMPs. Evidence regarding different preparation of allograft material, both from inter and intra-distributors, may have different biological activities.[31] Assuming that the processing methods are standardised at individual bone banks, the fact that there was considerable variation in bone-induction ability among the samples suggests that there is an underlying difference in the inherent capacity of the bone to promote osteogenesis, which may be correlated to donor age, previous exposure of pathology and/or drug therapy or genetic variation.[32]

Conclusion

The autologous PRF alone and with DFDBA significantly improved the periodontal outcome in the treatment of mandibular degree II furcation defects. PRF with DFDBA was significantly more beneficial in terms of VBF than PRF alone.

Acknowledgements

None.

Source of Funding

None.

Conflict of Interest

None.

References

[1] De Sanctis M, Murphy KG. The role of resective periodontal surgery in the treatment of furcation defects. *Periodontol* 2000;**22**:154–68.
[2] Newell DH. The diagnosis and treatment of molar furcation invasions. *Dent Clin North Am* 1998;**42**:301–7.
[3] Kinaia BM, Steiger J, Neely AL, Shah M, Bhola M. Treatment of class II molar furcation involvement: meta-analysis of re-entry results. *J Periodontol* 2001;**82**:413–28.
[4] Jaiswal R, Deo V. Evaluation of the effectiveness of enamel matrix derivative, bone grafts, and membrane in the treatment of mandibular class II furcation defects. *Int J Periodontics Restorative Dent* 2013;**33**:58–64.
[5] Chang YC, Zhao JH. Effects of platelet-rich fibrin on human periodontal ligament fibroblasts and application for periodontal infrabony defects. *Aust Dent J* 2011;**56**:365–71.

[6] Choukroun J, Adda F, Schoeffler C, Vervelle A. An opportunity in perio-implantology: the PRF. *Implantodontie* 2000;**42**:55–62.

[7] Davis VL, Abukabda AB, Radio NM, Witt-Enderby PA, Clafshenkel WP, Cairone JV *et al.* Platelet-rich preparations to improve healing. Part II: platelet activation and enrichment, leukocyte inclusion, and other selection criteria. *J Oral Implantol* 2014;**40**:511–21.

[8] Dohan Ehrenfest DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J *et al.* Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;**101**:37–44.

[9] Bajaj P, Pradeep AR, Agarwal E, Rao NS, Naik SB, Priyanka N *et al.* Comparative evaluation of autologous platelet-rich fibrin and platelet-rich plasma in the treatment of mandibular degree II furcation defects: a randomized controlled clinical trial. *J Periodontol Res* 2013;**48**:573–81.

[10] Pradeep AR, Pai S, Garg G, Devi P, Shetty SK. A randomized clinical trial of autologous platelet rich plasma in treatment of mandibular degree II furcation defects. *J Clin Periodontol* 2009;**36**:581–8.

[11] Agarwal A, Gupta ND. Platelet rich plasma combined with decalcified freeze dried bone allograft for the treatment of non-contained human intrabony periodontal defects: a randomized controlled split mouth study. *Int J Periodontics Restorative Dent* 2014;**34**:705–11.

[12] Hoidal MJ, Grimard BA, Mills MP, Schoolfield JD, Mellonig JT, Mealey BL. Clinical evaluation of demineralized freeze-dried bone allograft with and without enamel matrix derivative for the treatment of periodontal osseous defects in humans. *J Periodontol* 2008;**79**:2273–80.

[13] Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J *et al.* Histologic evaluation of new attachment apparatus formation in humans. Part II. *J Periodontol* 1989;**60**:675–82.

[14] American Academy of Periodontology task force report on the update to the 1999 classification of periodontal diseases and conditions. J Periodontol 2015;**86**:835–8.

[15] Lindhe J, Nyman S. The effect of plaque control and surgical pocket elimination on the establishment and maintenance of periodontal health. A longitudinal study of periodontal therapy in cases of advanced disease. *J Clin Periodontol* 1975;**2**:67–79.

[16] Hamp SE, Nyman S, Lindhe J. Periodontal treatment of multirooted teeth. Results after 5 years. *J Clin Periodontol* 1975;**2**:126–35.

[17] Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontol Scand* 1964;**22**:121–35.

[18] Loe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontol Scand* 1963;**21**:533–51.

[19] Mehta D, Deshpande N, Dave D, Modi B, Bharwani A. Platelet rich fibrin: new treatment modality in grade II furcation defects. *J Oral Dis Marker* 2016;**1**:1–5.

[20] Sharma A, Pradeep AR. Treatment of 3-wall intrabony defects in patients with chronic periodontitis with autologous platelet-rich fibrin: a randomized controlled clinical trial. *J Periodontol* 2011;**82**:1705–12.

[21] Sharma A, Pradeep AR. Autologous platelet-rich fibrin in the treatment of mandibular degree II furcation defects: a randomized clinical trial. *J Periodontol* 2011;**82**:1396–403.

[22] Mehta DB, Deshpande NC, Dandekar SA. Comparative evaluation of platelet-rich fibrin membrane and collagen membrane along with demineralized freeze-dried bone allograft in Grade II furcation defects: a randomized controlled study. *J Indian Soc Periodontol* 2018;**22**:322–7.

[23] Jain D, Deepa D. A comparative evaluation of freeze-dried bone allograft with and without bioabsorbable guided tissue regeneration membrane Healiguide® in the treatment of Grade II furcation defects: a clinical study. *J Indian Soc Periodontol* 2015;**19**:645–50.

[24] Kanoriya D, Pradeep A, Garg V, Singhal S. Mandibular degree II furcation defects treatment with platelet-rich fibrin and 1% alendronate gel combination: a randomized controlled clinical trial. *J Periodontol* 2017;**88**(3):250–8.

[25] Nevins M, Camelo M, Nevins ML, Schenk RK, Lynch SE. Periodontal regeneration in humans using recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and allogenic bone. *J Periodontol* 2003;**74**:1282–92.

[26] Camelo M, Nevitis ML, Schenk RK, Lynch SE, Nevins M. Periodontal regeneration in human class II furcations using purified recombinant human platelet-derived growth factor-BB (rhPDGF-BB) with bone allograft. *Int J Periodontics Restorative Dent* 2003;**23**:213–25.

[27] Soares FP, Hayashi F, Yorioka CW, Pannuti CM, Gioso MA, Alves de Lima LAP *et al.* Repair of class II furcation defects after a reparative tissue graft obtained from extraction socket treated with growth factors: a histologic and histometric study in dogs. *J Periodontol* 2005;**76**:1681–9.

[28] Lyons LC, Weltan RL, Antonio MJ, Trejo PM. Regeneration of degree II furcation defects with a 4% doxycycline hyclate bioabsorbable barrier. *J Periodontol* 2008;**79**:72–9.

[29] Lamb JW, Greenwell H, Drisko C, Henderson RD, Scheetz JP, Rebitski G. A comparison of porous and nonporous Teflon membrane plus demineralized freeze dried bone allograft in the treatment of class II buccal/lingual furcation defects: a clinical reentry study. *J Periodontol* 2001;**72**:1580–7.

[30] Chang IC, Tsai CH, Chang YC. Platelet-rich fibrin modulates the expression of extracellular signal-regulated protein kinase and osteoprotegerin in human osteoblasts. *J Biomed Mater Res A* 2010;**95**:327–32.

[31] Wang HL, Greenwell H, Fiorellini J, Giannobile W, Offenbacher S, Salkin L *et al.* Periodontal regeneration. *J Periodontol* 2005;**76**:1601–22.

[32] American Academy of Periodontology. Tissue banking of bone allografts used in periodontal regeneration (position paper). *J Periodontol* 2001;**72**:834–8.

Singapore Dental Journal, Vol. 39 (2019) 41–52

DOI: 10.1142/S2214607519500044

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Does facial appearance of dentofacial deformity influence the need for orthognathic surgery: The Malaysian perception

Fatin Halini Abdul Halim Chong*, Siti Nuriyah Md Salleh*, Noraini Abu Bakar†, Izzati Nabilah Ismail‡,§

*Undergraduate Dental Students, Kulliyyah of Dentistry
International Islamic University Malaysia, Kuantan, Pahang, Malaysia

†Assistant Professor, Orthodontic Department
Kulliyyah of Dentistry, International Islamic University Malaysia
Kuantan, Pahang, Malaysia

‡Assistant Professor, Oral and Maxillofacial Surgery Department
Kulliyyah of Dentistry, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

Keywords:
Dentofacial deformity
knowledge
perception
facial attractiveness
treatment need

A B S T R A C T

Aim: This study evaluates perception toward facial appearance in dentofacial deformity and the need for orthognathic surgery among the public with and without dental backgrounds.
Materials and Methods: A questionnaire consisting of 12 facial photographs of cases with dentofacial deformity or malocclusion in varying severity was used. A hundred individuals were selected to answer the questionnaire. The perception of facial appearance (FAS), treatment need score (TNS), and knowledge regarding dentofacial deformity were used for the evaluation.
Results: Significant differences were found between dental and non-dental when the respondents' knowledge in all the questionnaire items ($p < 0.05$) was assessed. However, no significant difference was found in the mean of FAS and TNS in all the presented cases (normal, borderline, severe). Pearson correlation between perceived FAS and TNS was statistically negative for severe and normal cases, whereby a decrease in FAS for severe cases showed an increase in TNS, and an increase in FAS for normal cases showed a decrease in TNS.
Conclusion: Respondents with dental background had sound knowledge of dentofacial deformity. A poorly attractive respondent with dentofacial deformity showed a greater need for orthognathic surgery.

§*Corresponding author.* Izzati Nabilah Ismail, Assistant Professor, Oral and Maxillofacial Surgery Department
Kulliyyah of Dentistry, International Islamic University Malaysia, Kuantan, Pahang, Malaysia
Tel: +6095704000 ext. 2942. Mobile: +60122099505. E-mail address: izzatiismail@iium.edu.my (I.N. Ismail)
Presented at Malaysia-International Dental Exhibition and Conference 2018 (MIDEC 2018) Malaysian Dental Association Kuala Lumpur Convention Center, 21 July 2018

Introduction

Facial attractiveness has long been a desirable physical characteristic in all societies, where facially attractive people are known to be treated better than less attractive people. It was believed that the factors and components that contribute to facial attractiveness were not arbitrary.[1,2] They are mainly contributed by the skeletal features underlying the soft tissues. The lower face is also largely influenced by the occlusal relationship of the maxillary and the mandibular dentition.[3–5] A major consequence of dentofacial deformity is malocclusion, in addition to a lack of facial attractiveness, which negatively affects the psychosocial function. Multiple studies have reported that dentofacial deformity can significantly affect patients' psychosocial function and, hence, their quality of life.[6–8]

Most patients visiting orthodontic clinics seek treatment to improve dental function and aesthetics.[9,10] The objective of orthodontic treatment is to improve facial aesthetics while establishing the ideal occlusion. Unfortunately, for non-growing patients with severe dentofacial deformity, orthognathic surgery is the only solution. Many studies have shown that the outcome of orthognathic surgery can positively benefit the patients' psychological health.[8,11,12]

An assessment of the need for orthodontic treatment should include the objective evaluation of dentofacial appearance. One of the standardized techniques that are most commonly used for assessing malocclusion for orthodontic treatment involves a rating system, which uses an index to determine dental health and the aesthetic impairment component.[13–16] However, the assessment of dentofacial attractiveness is difficult to quantify, as judgments for facial attractiveness vary greatly between individuals and cultures. While historians and artists believe that symmetry and averageness contribute to the ideal of facial beauty, the review of the literature suggests that a distinguishing facial feature, which is contributed by the occlusion and gender-specific characteristics, leads to an intuitive idea of attractive. There are numerous ways to assess dentofacial attractiveness qualitatively and quantitatively.[17] One of the pioneer standardized rating scales for aesthetics consists of 10 standard reference photographs demonstrating different levels of dental attractiveness.

In developed countries, the idea of undergoing orthognathic surgery has been widely popular among the public.[18–22] The decision to opt for orthognathic surgery in severe cases of malocclusion is highly dependent on the influence made by the referring dentist. However, in Malaysia, a limited number of cases of orthognathic surgery have been reported in the past twenty years.[23] The main reason for the refusal to undergo surgery is believed to be socio-cultural differences among Malaysians, be it laypersons or dental practitioners. The perception of defying cosmetic surgery to improve facial appearance for aesthetic purposes is believed to be strongly against moral and religious reasons. Yet, there is no report that lends credence to this reasoning. In addition, public awareness about dentofacial deformity and orthognathic surgery has never been studied in Malaysia.

Therefore, the purpose of this study is to evaluate the knowledge of dentofacial deformity and the perception of dentofacial deformity affecting facial appearance and treatment needs among Malaysians. This study also compares the knowledge and perception of individuals with dental and non-dental background about dentofacial deformity.

Materials and Methods

An approval to conduct this questionnaire-based study was obtained from the IIUM Research Ethics Committee (IREC-760). This cross-sectional study consisted of 100 respondents attending a dental polyclinic in an institution on the east coast of Malaysia. The sampling frame for the respondents included individuals attending polyclinic for dental treatments, family members accompanying the individuals, and clinical staff members in the institution. The sample size was determined using the Altman's nomogram, based on the desired statistical power of 0.95. The inclusion criteria for the respondents were 1) age of more than 18 years; 2) no apparent facial deformities, craniofacial abnormalities, or psychological problems; and 3) medically and physically capable of participating in the questionnaire. Patients undergoing orthodontic or orthognathic treatment or review were excluded from this research. The respondents were selected using convenience sampling and, then, divided into two groups according to their dental education background.

For the questionnaire design, 12 clinical cases presenting malocclusion and with or without accompanying dentofacial deformity were selected by an orthodontist, based on several criteria. Lateral cephalograms were traced for cephalometric analysis using Eastman Standard.[24] The analysis was done by two dentists and further verified by an orthodontist. Measurements for cephalometric analysis include ANB value, incisal inclination indicative of dental compensation, and the aesthetic E-line for soft tissue. These cases were, then, divided into three groups, according to the overall assessment and cephalometric values. ANB angle, incisal inclination, and asymmetry were set as the primary predictors, while soft tissue evaluation (E-line) was a secondary predictor. The division of the groups was summarized in Table 1. Their facial photodocumentations were presented to the respondents for reference (see Fig. 1). Informed consent from these twelve cases was obtained prior to the commencement of this study.

Table 1.
Summary of criteria used for division of groups based on severity of dentofacial deformity

	Normal	Borderline	Severe
ANB angle	0° to 5°	5° to 7° for Class II −1° to −3° for Class III	> 7° for Class II < −4° for Class III
Incisal inclination	Mandibular incisal 93° ± 6°	Maxillary incisal 101° to 102° for Class II skeletal base	> 100° of maxillary incisal inclination for Class II skeletal base
	Maxillary incisal 109° ± 6°	Mandibular incisal 85° to 86° for Class III skeletal base	< 83° for mandibular incisal for Class III skeletal base
Facial asymmetry	No facial asymmetry	Mild to moderate facial asymmetry	Severe facial asymmetry
Aesthetic E-line (Rickett's)	Both lips should be behind this line, with the upper lip by around 4 mm and the lower lip by around 2 mm		

The questionnaire was divided into three sections (refer to Appendix) to assess the socio-demographic background, knowledge regarding dentofacial deformity, and perception of facial attractiveness and the need for surgical treatment. Seven questionnaire items — regarding facial appearance, malocclusion, speech, mastication, social health, orthodontic treatment, and surgical treatment related to dentofacial deformity — assess the knowledge on the dentofacial deformity. The perception of facial attractiveness and the need for treatment were assessed based on visual analog scores given to each of the 12 selected cases.

These questions were designed based on earlier studies for assessing the knowledge and perception of dentofacial deformity and orthognathic surgery.[1,5,10,25] Content validity was assessed, and the mean item-content validity index (I-CVI) and the scale-content validity index (S-VCI) were found to be relevant (CVI > 0.7). The pretesting of the questionnaire was done on 20 randomly selected patients attending the polyclinic for dental treatment. The questionnaire was finalized after modifying ambiguous questions based on the validity assessment.

The collected data was entered and analyzed using the Statistical Package for the Social Sciences (SPSS) Version 22.0. The respondents' knowledge of dentofacial deformity was evaluated using a chi-square test, whereas mean FAS and mean TNS were analyzed using an independent *t*-test. Pearson correlation was used to measure the strength and the direction of the linear relationship between FAS and TNS.

Results

Twelve lateral cephalometric radiographs of healthy males and females were examined, traced, and divided into three groups according to the severity of their dentofacial deformity based on the ANB angle, which indicates the magnitude of a jaw discrepancy. A paired *t*-test was used to test the inter-examiner calibration between two cephalogram tracers. The results showed no significant difference in the tracing reading of all the cephalometric variables between the two examiners with *p*-value > 0.05.

In total, 100 respondents were selected for this study. Table 2 shows the distribution of the respondents according

Fig. 1. Facial photographs of selected cases included in the questionnaire.

Table 2.
Demographic background of respondents

	Dental ($n = 50$)	Non-dental ($n = 50$)	Total percentage ($n = 100$)	p-value
Gender				0.682
Male	18	21	39	
Female	32	29	61	
Age				[a]0.001
18 – 30 years	43	25	68	
31 – 45 years	6	13	19	
> 45 years	1	12	13	
Race				0.242
Malay	50	47	97	
Chinese	—	3	3	
Religion				0.213
Islam	50	47	97	
Buddhist	—	2	2	
Others	—	1	1	
Education level				[a]0.002
Post-degree level	1	2	3	
Degree level	37	17	54	
Diploma	6	16	22	
Pre-University	2	1	3	
Secondary school	4	11	15	
Others	—	3	3	

[a]p-value < 0.05; Independent t test.

to their gender, age, race, religion, education level, and dental background. Fifty of the respondents had a dental education background and the remaining respondents did not have any dental background. There was no significant difference in the respondents based on gender, race, and religion ($p > 0.05$). The majority of the respondents were from the same age group, with 68% of them being in the age group 18-30 years ($p < 0.05$). There was a statistically increased percentage of participants with degree and diploma as their highest level of education.

In general, the responses to items regarding dentofacial deformity affecting facial appearance, malocclusion, speech, mastication, social health and its surgical treatment suggest that more than 70% of the respondents had knowledge. However, only 33% of the respondents indicated that severe dentofacial deformity could not be corrected by orthodontic treatment alone. The percentage of the respondents having knowledge on dentofacial deformity based on dental background is presented in Table 3 and Fig. 2. It was found that respondents with a dental background were more aware of

Table 3.
Percentage of correct knowledge on dentofacial deformity based on dental background

Questionnaire Items	Total ($N = 100$) (%)	Dental ($N = 50$)	Non-dental ($N = 50$)	p-value
Q1. Facial appearance	78	95% (48)	70% (35)	[a]0.001
Q2. Malocclusion	80	95% (48)	64% (32)	[a]0.000
Q3. Speech	71	88% (44)	54% (27)	[a]0.001
Q4. Mastication	72	84% (42)	60% (30)	[b]0.024
Q5. Social health	70	90% (45)	50% (25)	[a]0.000
Q6. Orthodontic treatment	33	45% (23)	20% (10)	[a]0.000
Q7. Surgical treatment	77	95% (48)	58% (29)	[a]0.000

[a]p-value < 0.01; χ^2 test.
[b]p-value < 0.05; χ^2 test.

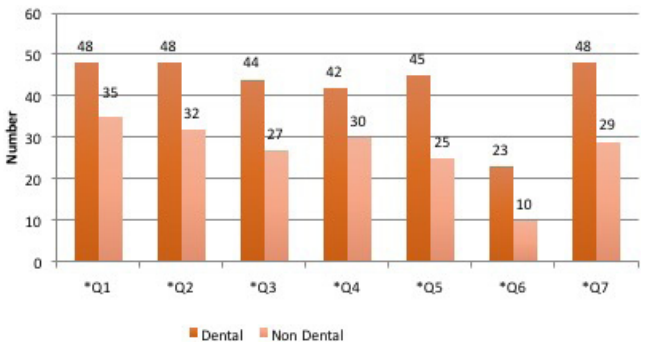


Fig. 2. Number of correct responses between dental and non-dental background.

the conditions presented by questions than those without a dental background. A significant number of dental respondents had knowledge of items regarding facial appearance, malocclusion, speech, mastication, social health, and surgical treatment, with their correct responses ranging from 84% to 95%. On the contrary, only 50%–70% of non-dental respondents could correctly mark the same questionnaire items (p-value < 0.05). However, when asked about the correction for severe dentofacial deformity, only 45% and 20% of the dental and non-dental respondents, respectively, responded that severe dentofacial deformity cannot be corrected by orthodontic treatment alone.

In general, the mean FAS and the mean TNS calculated for each group of the dentofacial deformity for all respondents were recorded in Table 4. The mean FAS for severe, borderline, and normal cases was 4.0, 5.6, and 6.4, respectively. There was no significant difference in FAS in the severe, borderline, and normal groups with p-value > 0.05. In the case of TNS, no significant difference was found between severe, borderline, and normal groups, given the mean TNS for severe, borderline, and normal cases was 6.6, 4.4, and 3.4, respectively. Although statistically not significant, the severe group revealed relatively lower mean FAS and relatively higher TNS than the other groups.

In Table 5, the mean perceived FAS for dental and non-dental respondents was compared. In severe cases, the mean perceived FAS of the dental respondents was 3.7, while non-dental respondents scored 4.3. The mean perceived FAS of dental and non-dental respondents for the normal group was 6.1 and 6.7, respectively. The p-values showed no significant difference in the mean FAS of dental and non-dental respondents in all cases ($p > 0.05$). The results indicated that there was an agreement in the

Table 4.
Mean perceived Facial Appearance Score (FAS) and perceived Treatment Need Score (TNS) in total respondents

	Mean FAS (SD)	[a]p-value	[b]Mean TNS (SD)	[b]p-value
Severe	4.0 (1.6)		6.6 (2.2)	
Borderline	5.6 (1.4)	0.064	4.4 (1.8)	0.406
Normal	6.4 (1.5)		3.4 (1.6)	

[a]p-value > 0.05 One-way ANOVA between three groups within FAS.
[b]p-value > 0.05 One-way ANOVA between three groups within TNS.

Table 5.
Comparison of mean of perceived FAS of dental and non-dental respondents using independent t-test

	Mean FAS of dental	Mean FAS of non-dental	p-value
Severe	3.7 (1.4)	4.3 (1.9)	[a]0.075
Borderline	5.4 (1.3)	5.9 (1.5)	[a]0.065
Normal	6.1 (1.4)	6.7 (1.6)	[a]0.051

[a]p-value > 0.05; Independent t test.

Table 6.
Comparison of mean of perceived TNS of dental and non-dental respondents using Independent t test

	Mean TNS of dental	Mean TNS of non-dental	p-value
Severe	6.7 (2.1)	6.4 (2.2)	[a] 0.579
Borderline	4.7 (1.8)	4.1 (1.8)	[a] 0.152
Normal	3.5 (1.7)	3.3 (1.6)	[a] 0.488

[a]p-value > 0.05; Independent t test.

Table 7.
Correlation between perceived FAS and perceived TNS for different dentofacial deformity and dental background

		Mean FAS	Mean TNS	Pearson correlation, r	p-value
Severe	Dental	3.7	6.7	−0.599	[a]0.000
	Non-dental	4.3	6.4	−0.235	0.100
Borderline	Dental	5.4	4.7	−0.531	[a]0.000
	Non-dental	5.9	4.1	−0.463	[b]0.001
Normal	Dental	6.1	3.5	−0.396	[b]0.004
	Non-dental	6.7	3.3	−0.168	0.243

[a]p-value < 0.01, Pearson correlation.
[b]p-value < 0.05, Pearson correlation.

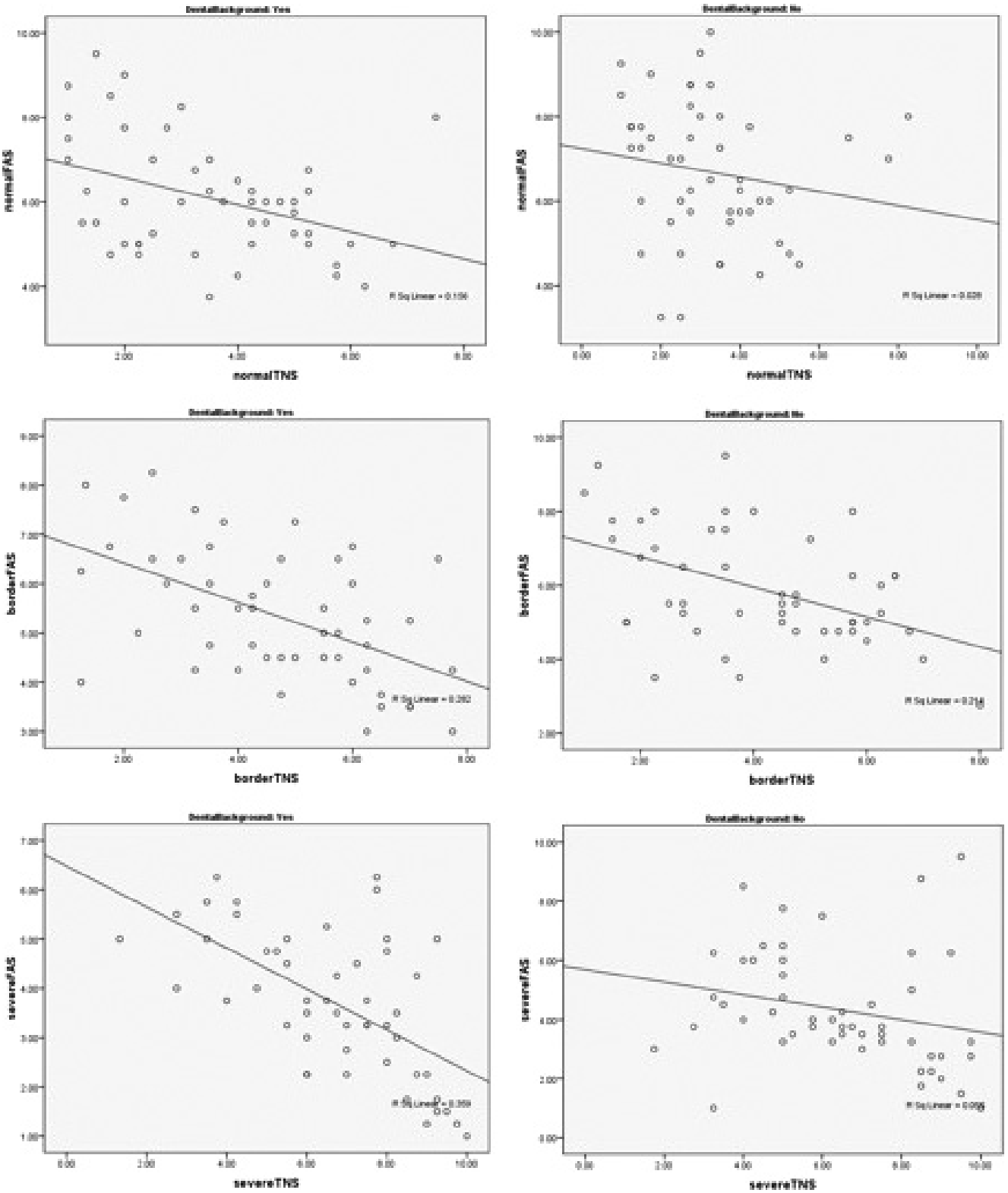


Fig. 3. Correlation between perceived FAS and perceived TNS for different severity of dentofacial deformity and dental background.

perceived FAS of the respondents with a dental background and without a dental background.

The comparison of the mean TNS calculated for dental and non-dental respondents is shown in Table 6. The results indicate no significant difference in the perceived TNS for dental and non-dental respondents with p-value > 0.05. For normal cases, the TNS of dental and non-dental respondents was relatively low (3.5 and 3.3, respectively), while for the severe group, it was high; dental respondents scored 6.7 and non-dental 6.4.

The correlation between the perceived FAS and the perceived TNS for different dentofacial deformity and dental background is presented in Table 7. All groups showed a statistically significant correlation between FAS and TNS, except for severe and normal cases by non-dental respondents ($p > 0.05$). There were significant correlations between the perceived FAS and TNS among dental respondents regardless of the severity of the cases, with a strong negative correlation in severe and borderline cases ($r = -0.599$ and $r = -0.531$, respectively). However, the correlation for severe and normal cases in non-dental respondents was weak, with the Pearson correlation coefficient, r, of -0.235 and -0.168, respectively. Figure 3 shows the strength and the direction of the linear relationship between FAS and TNS of dental and non-dental respondents for each severity group.

Discussion

The key findings of this study were (1) the majority of respondents had sound general knowledge related to dentofacial deformity regardless of their dental background, with 70% correct answers in all but one questionnaire item regarding treatment with orthodontics; (2) respondents with dental background had better knowledge on dentofacial deformity; (3) the perception of facial attractiveness and treatment needs were the same in different severity of dentofacial deformity regardless of dental background; and (4) there was a strong negative correlation between perceived facial attractiveness and treatment needs in all groups of severity for dental respondents and in severe and borderline groups for non-dental respondents.

Understanding patients' perception of facial attractiveness is the most crucial part of any orthodontist and maxillofacial surgeon practice, as the perception of facial attractiveness varies based on gender, age, social and educational background.[1,2,26] Various studies regarding the awareness and perception of dentofacial appearance in different educational backgrounds reported that laypersons without dental education background and non-regular dental attenders scored least, whilst orthodontic patients scored the highest in perceiving dentofacial appearance.[1,26,27] People with dental education were reported to be more aware of aesthetics during their dental education. Not only that, orthodontic patients showed more interest and had high aesthetics expectations. In addition, a previous study done by Tufekci *et al.* also reported that those who had dental background were found to be more conscious of their skeletal profile, and the perception of beauty and attractiveness can be influenced by the level of specialty.[27] This is in agreement with the current study whereby the dental respondents reported significantly more knowledge in dentofacial deformity when compared to the non-dental respondents.

A previous study done by Ngeow *et al.* reported poor acceptance of the public for surgery. The refusal to accept cosmetic surgery is thought to be caused by the different socio-economic and socio-cultural status among the Malaysians.[23,28] This is evident in the current study where the majority of the respondents perceived that skeletal discrepancies could be corrected by orthodontic treatment. This indicated that the public had generally poor knowledge of dentofacial deformity and its treatment options. This can also explain how the public has low acceptance toward orthognathic surgery as the treatment for dentofacial deformity.

In contrast, some people refrain from undergoing orthognathic surgery because of the in-depth knowledge they have about the risks of complications, burden of care, and lack of internal motivation.[29] A study done by Hagensli *et al.* looked at why patients avoid orthognathic surgery. They found that 52% of the unoperated patients opted out of the elective surgery because their malocclusion and skeletal deformity was not particularly severe compared to the scope of surgical treatment.[30] Moreover, the lack of external motivation and support from family and friends also led to the refusal of treatment. Financial problems can also cause a deferment of interceptive treatment, possibly leading to a severe skeletal discrepancy in adulthood.[11]

In an article written by Sousa, A. D., less attractive people faced more judgment and reactions from other people due to their facial deformity.[31] Although the current study did not show any significance of perceived facial attractiveness and perceived treatment needs of different severity groups, there was a significantly strong correlation between perceived facial attractiveness and perceived treatment needs in severe and borderline cases. In this study, we found a negative correlation between facial attractiveness and treatment needs, whereby a lower perceived facial attractiveness score in severe dentofacial deformity showed a higher perceived treatment need. This indicated that when the perceived facial attractiveness was low, there was a high perceived treatment need. This is in agreement with the general indication of orthognathic surgery to correct dentofacial deformity to improve facial aesthetics.[22]

In conclusion, respondents with dental background showed sound knowledge about dentofacial deformity.

The perception of facial attractiveness and treatment needs of patients with dentofacial deformity is not influenced by dental background. In addition, a poorly attractive person with dentofacial deformity was perceived to have a higher need for orthognathic surgery. Despite these findings, the conclusion made from the study needs to be carefully interpreted as external validity lacks strength. The authors recommend that this study should be expanded to other parts of the country to gain a wider representation of facial aesthetics among the Malaysian population.

Ethical Approval

The approval to conduct this questionnaire-based study was obtained from the International Islamic University Malaysia (IIUM) Research Ethics Committee (IREC-760).

Patient Consent

Written patient consent for clinical photographs had been obtained to publish clinical photographs.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors report no conflicts of interest related to this study.

Funding

This work was supported by the International Islamic University Malaysia under the Research Initiative Grant Scheme [RIGS17-021-0596].

Acknowledgements

The authors thank the members of the Editorial Advisory Board for the careful review and approval of these guidelines.

Questionnaire for the study "Perception on facial appearance of dentofacial deformity"

Background of the Study

The dentofacial deformity is a condition that affects the position, size, shape, or orientation of the facial skeleton. This abnormal skeletal pattern is caused by an imbalance in skeletal growth due to genetic problems, congenital problems, pathologic conditions, or trauma. Although uncommon, this condition results in an imbalance of facial harmony and malocclusion and causes improper chewing, speech impediments, impaired breathing, as well as psychosocial challenges. It can be treated with combined orthodontic treatment and orthognathic surgery, which can improve the physiological function and have a positive psychosocial benefit. In Malaysia, a limited number of cases have been reported for dentofacial deformity treated by surgery when compared to other developed countries. In the past decade, the small number of surgery is thought to be due to differences in socio-cultural and religious beliefs among Malaysians. The other reason could be the lack of awareness of this condition and the available treatment. Nevertheless, there has been a slight increase in the prevalence of dentofacial deformity treated by orthognathic surgery in this country. Therefore, it will be of added value for both orthodontists and oral and maxillofacial surgeons to understand the level of perception and the status of knowledge about the disorder through this questionnaire survey.

Aim of Study

The aim of this study is to conduct a questionnaire survey to quantitatively evaluate the perception and knowledge of dentofacial deformity and to differentiate them between participants with a dental background and without a dental background.

Research Intervention

This research involved the participation of selected patients attending Orthodontic Specialist Clinic, Kulliyyah of Dentistry, IIUM Kuantan Campus, with a clinical presentation of malocclusion and various forms and severities of dentofacial deformity. Full face photographs of the selected patients were used for the study and included in the questionnaire. These photographs were seen by 100 participants to answer the questions for the survey.

Information to Survey Participants

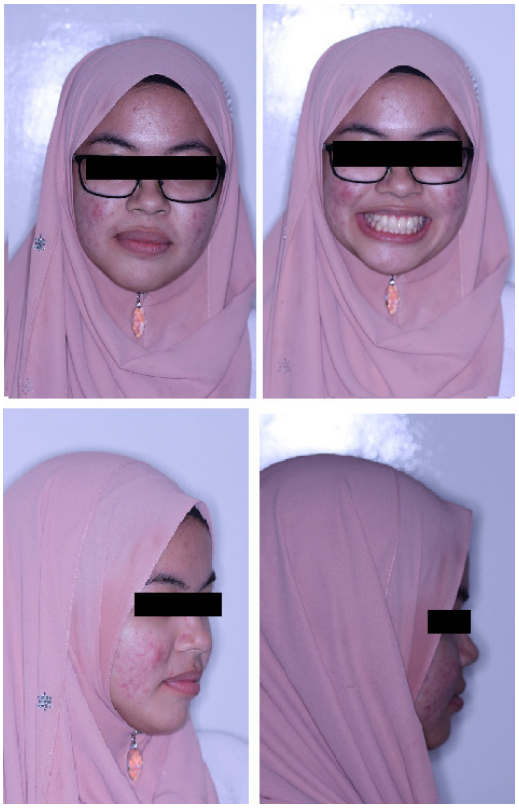
Facial appearance and attractiveness are sensitive issues. Patients' photographs constitute an important part of medical records in orthodontic and oral surgery units. Such photographs can aid in the diagnostic process and long-term follow-up. They are also beneficial for the use of teaching and research purposes. Patients involved in this study have given their consent to display their photographs to the respondents of this survey questionnaire. Photos in

this booklet are entirely private and confidential, and they should only be used by the researchers involved in this study.

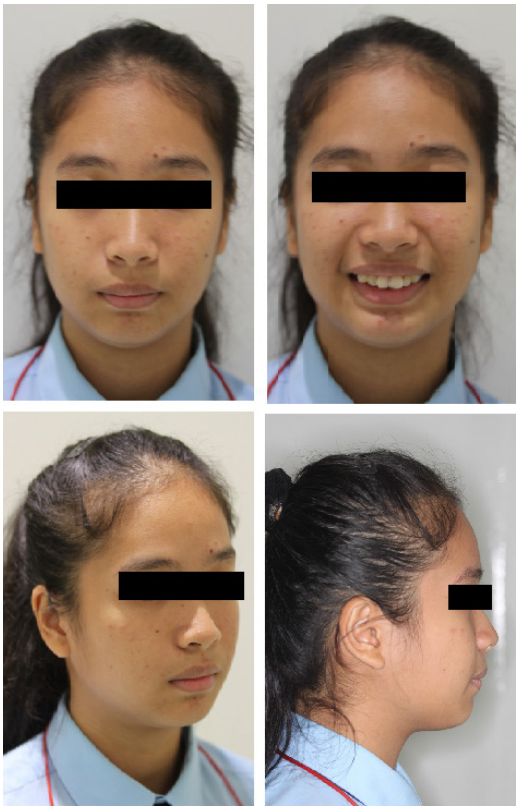
Confidentiality

Under Personal Data Protection Act 2010, patients may possess the rights to protect the confidentiality of their personal data, regarding collection, custody, retention, management, control, use (including analysis or comparison), non-disclosure, erasure, and/or dealing with or disposing of any personal data in or for this study.

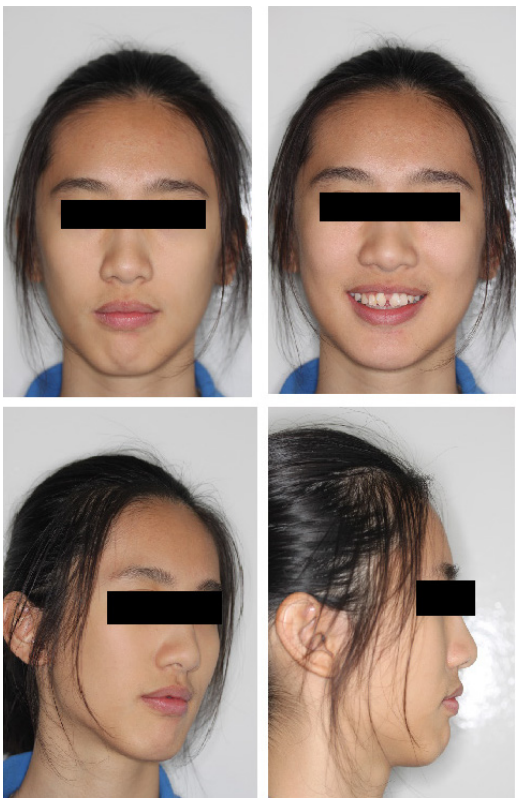
(a)



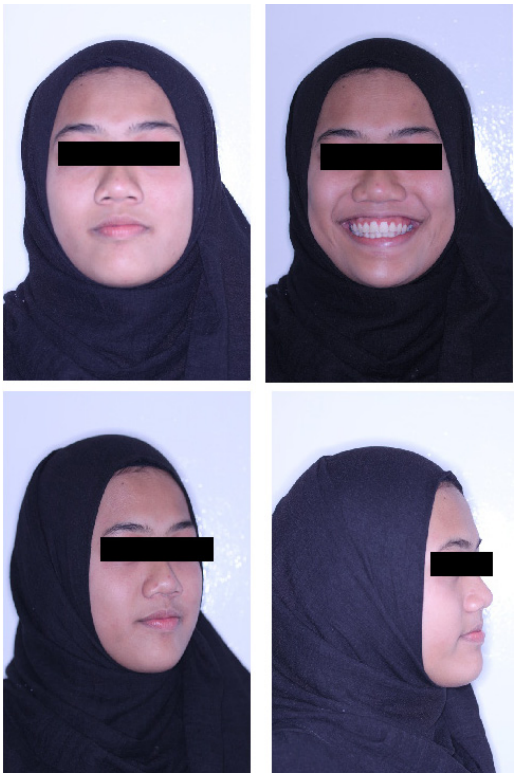
(b)



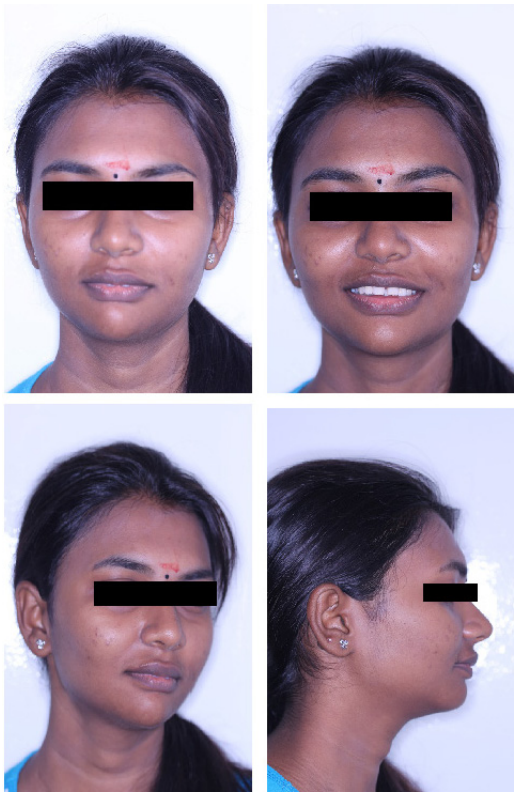
(c)



(d)

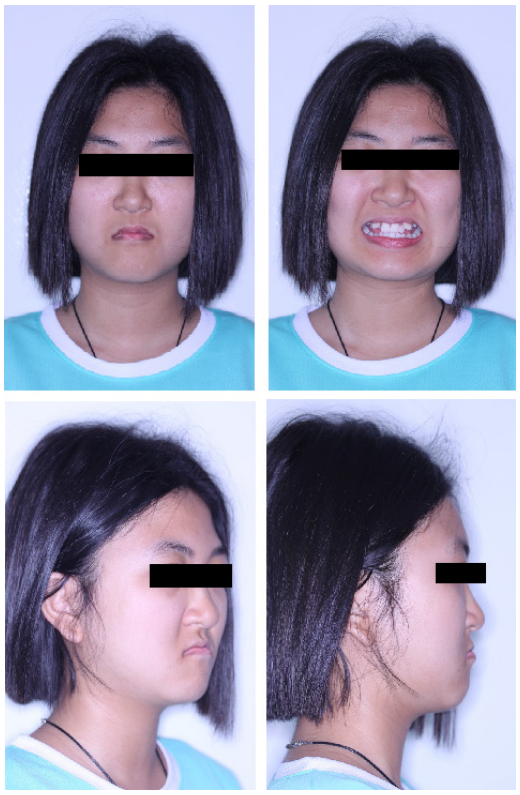


(e)



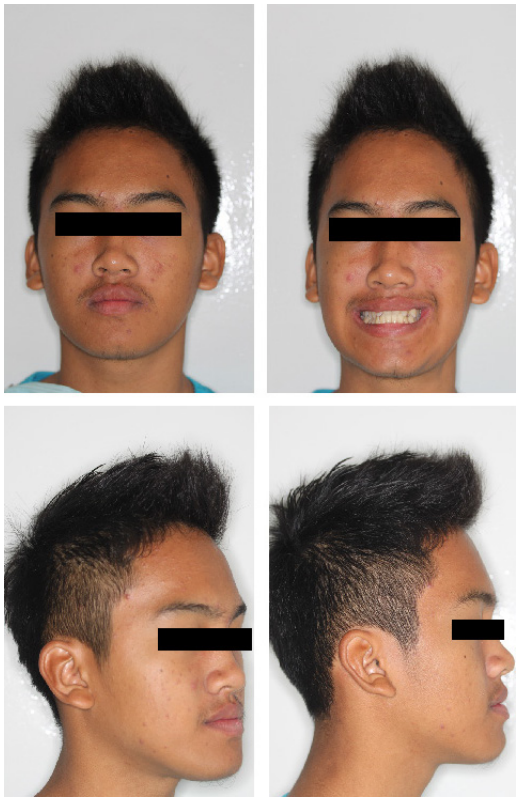
(f)

(g)

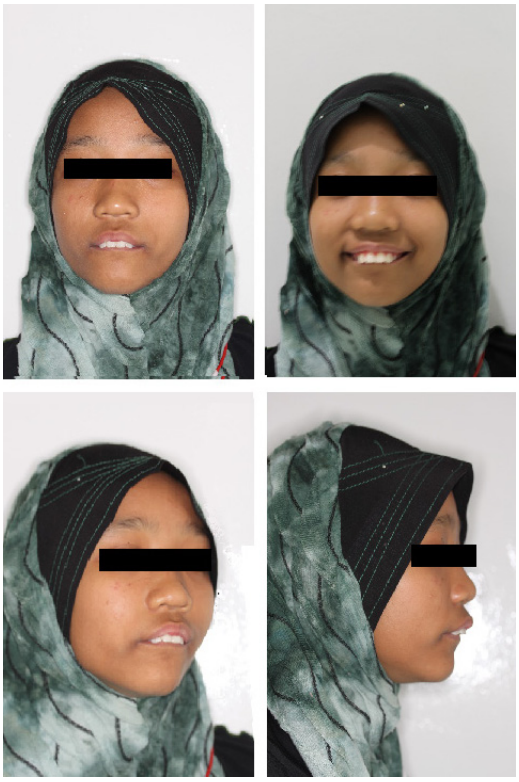


(h)

(i)

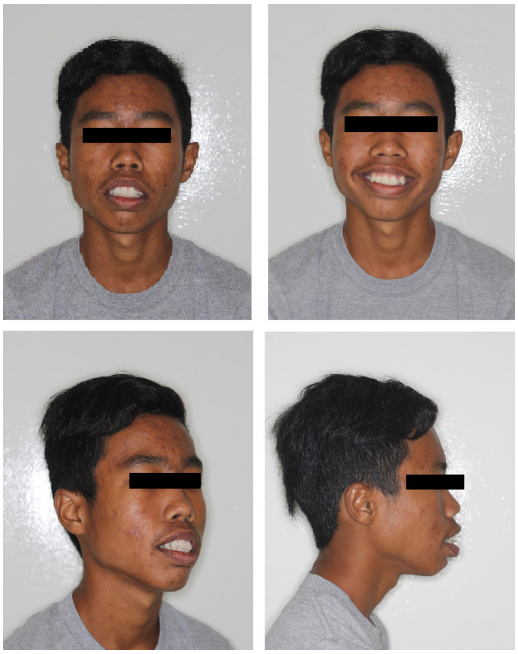


(j)



(k)

(l)



References

[1] Phillips C, Tulloch C, Dann C. Rating of facial attractiveness. *Community Dent Oral Epidemiol* 1992;**20**:214–20.

[2] Mirjam H, Gernot G. The ideal of facial beauty: A review. *J Orofac Orthop* 2006;**68**:6–16.

[3] Ackerman JL, Proffit WR, Sarver DM. The emerging soft tissue paradigm in orthodontic diagnosis and treatment planning. *Clin Orthod Res* 1999;**2**:49–52.

[4] Oh HS, Korn EL, Zhang X, Liu Y, Xu T, Boyd R *et al.* Correlations between cephalometric and photographic measurements of facial attractiveness in Chinese and US patients after orthodontic treatment. *Am J Orthod Dentofac Orthop* 2009;**136**(762):e1-e14.

[5] Bullen RN, Kook Y, Kim K, Park JH. Self-perception of the facial profile: An aid in treatment planning for orthognathic surgery. *J Oral Maxillofac Surg* 2014;**72**(4):773–8.

[6] Garvill J, Garvill H, Kahnberg K, Lundgren S. Psychological factors in orthognathic surgery. *J Cranio Maxillofac Surg* 1992;**20**(1):28–33.

[7] Profitt W, White R, Sarver D. In: Profitt WR, Sarver DM. Contemporary Treatment of Dentofacial Deformity. St Louis: CV Mosby, 2003.

[8] Murphy C, Kearns G, Sleeman D, Cronin M, Allen P. The clinical relevance of orthognathic surgery on quality of life. *Int J Oral Maxillofac Surg* 2011;**40**(9):926–30.

[9] Lew KK. Attitudes and perceptions of adults towards orthodontic treatment in an Asian community. *Community Dent Oral Epidemiol* 1993;**21**:31–5.

[10] Soh J, Chew MT, Wong HB. An Asian community's perspective on facial profile attractiveness. *Community Dent Oral Epidemiol* 2007;**35**:18–24.

[11] Jacobson A.Psychological aspects of dentofacial esthetics and orthognathic surgery. *Angle Orthod* 1984;**54**(1):18–35.

[12] Nicodemo D, Pereira M, Ferreira L. Effect of orthognathic surgery for class III correction on quality of life as measured by SF-36. *Int J Oral Maxillofac Surg* 2008;**37**(2):131–4.

[13] Brook PH, Shaw WC. The development of an index of orthodontic treatment priority. *Eur J Orthod* 1989;**11**:309–20.

[14] Shaw WC, Richmond S, O'Brien KD. The use of occlusal indices: A European perspective. *Am J Orthod Dentofac Orthop* 1995;**107**:1–10.

[15] Johansson AM, Follin ME. Evaluation of the aesthetic component of the Index of orthodontic treatment need by Swedish orthodontists. *Eur J Orthod* 2005;**27**:160–6.

[16] Mitchell L.*An Introduction to Orthodontics*. Oxford, UK: Oxford University Press, 2013.

[17] Gupta A, Shrestha RM. A review of orthodontic indices. *Orthod J Nepal* 2014;**4**(2):44–50.

[18] Flanary CM, Barnwell GM, Alexander JM. Patient perceptions of orthognathic surgery. *Am J Orthod* 1985;**88**(2):137–45.

[19] Proffit WR, Turvey TA, Phillips C. Orthognathic surgery: A hierarchy of stability. *Int J Adult Orthod Orthognath Surg* 1996;**11**:191–204.

[20] Cunningham SJ, Gilthorpe MS, PHN. Are orthognathic patients different? *Eur J Orthod* 2000;**22**:195–202.

[21] Kim S, Park S. Incidence of complications and problems related to orthognathic surgery. *J Oral Maxillofac Surg* 2007;**65**(12):2438–44.

[22] Hupp JR, Ellis E, Tucker MR. Contemporary Oral and Maxillofacial Surgery. *St Louis: Elsevier*, 2014.

[23] Ngeow WC, Ong ST, Siow KK, Lian CB. Orthognathic surgery in the University of Malaya. *Med J Malaysia* 2002;**57**(4):398–403.

[24] Kamaluddin JM, Cobourne MT, Sherriff M, Bister D. Does the Eastman correction over or under adjust ANB for positional changes of N? *Eur J Orthod* 2012;**34**:719–23.

[25] Lew KK, Soh G, Loh E. Ranking of facial profiles among Asians. *J Esthet Dent* 1992;**4**(4):128–30.

[26] Kokich VO, Kokich VG, Kivak HA. Perceptions of dental professionals and laypersons to altered dental esthetics: Asymmetric and symmetric situations. *Am J Orthod Dentofac Orthop* 2006;**130**:141.

[27] Tufekci E, Jahangiri A, Lindauer SJ. Perception of profile among laypeople, dental students and orthodontic patients. *Angle Orthod* 2008;**78**(6):983–7.

[28] Ong M.Spectrum of dentofacial deformities: A retrospective survey. *Ann Acad Med Singapore* 2004;**33**(2):239–42.

[29] Alolayan AB, Leung YY. Risk factors of neurosensory disturbance following orthognathic surgery. *PLoS One* 2014;**9**(3):e91055.

[30] Hågensli N, Stenvik A, Espeland L. Patients offered orthognathic surgery: Why do many refrain from treatment? *J Cranio Maxillofac Surg* 2014;**42**(5):e296-e300.

[31] Sousa AD.Psychological issues in oral and maxillofacial reconstructive surgery. *Br J Oral Maxillofac Surg* 2008;**46**(8):661–4.

Singapore Dental Journal, Vol. 39 (2019) 53–56

DOI: 10.1142/S2214607519720015

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Case Report

A novel non-invasive retentive approach of an interim auricular prosthesis: A case report

Abdullah Kamel Abdullah*, Amro Mohammed Moness Ali†,§, Amal Mohammed Elsawy‡

*Assistant Lecturer of Prosthetic Dentistry, Prosthetic Dentistry Department, Faculty of Dentistry, Minia University, Egypt

†Lecturer of Paediatric and Community Dentistry, Paediatric and Community Dentistry Department, Faculty of Dentistry, Minia University, Egypt

‡Professor, Department of Clinical Dental Science Prosthodontic Division, Faculty of Dentistry, Princess Nourah Bint Abdulrahman University, Saudi Arabia

Keywords:
Microtia
Interim auricular prosthesis
Retention
Hair hoop

A B S T R A C T

Auricular reconstruction is a challenging issue. It can either be performed surgically or by the use of prosthesis. Definitive auricular prosthesis can be retained by craniofacial implants. Temporary (interim) prosthesis can be retained using adhesives, engaging anatomical undercuts and using mechanical means of retention-like spectacles. This case report proposes a new mechanical means of retention for a temporary auricular prosthesis, which can be suitable for non-eyeglass wearing females or for female patients who refuse to wear eyeglass for retaining their prosthesis.

Introduction

Ear anomalies are attributed to either congenital (either syndromic or non-syndromic), acquired (injury, infarction, exposure to certain chemicals, malnutrition, etc.) or even unknown causes.[1] The deformities may range from complete absence (anotia) to a small, malformed lobule (microtia). Reconstruction of ear deformities includes surgical reconstruction or prosthetic restoration. Size, aetiology of the defect, and patient's concern are the major factors that are considered for the management and selection of prosthesis type.[2] Auricular plastic surgical reconstruction is a major challenge with the probability of complications. In contrast, prosthetic rehabilitation has excellent aesthetic outcomes and poses minimal risks of morbidity, and it is the solution of choice but with certain limitations.[3] Means of retention of prosthesis include adhesives, osseointegrated implants and anatomically retained and/or mechanical retained prostheses.[4,5] The aim of any prosthetic reconstruction, as was in this case, is to construct a properly retained temporary prosthesis that is aesthetically acceptable, as long as the patient can afford the cost of implant-retained prosthesis or perform plastic surgical reconstruction.

§Corresponding author: Amro Mohammed Moness Ali, Lecturer of Paediatric and Community Dentistry, Paediatric and Community Dentistry Department, Faculty of Dentistry, Minia University, Egypt, E-mail: amromoness@mu.edu.eg, ORCID: 0000-0002-1249-2175.

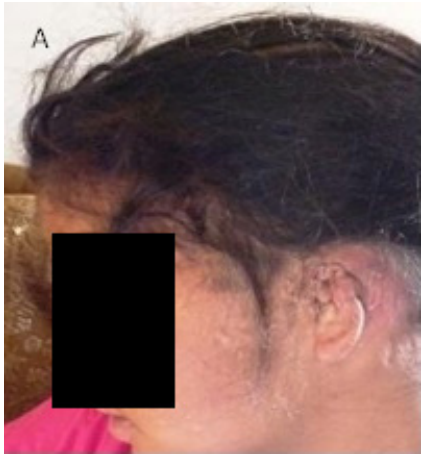


Fig. 1. (A) External view of the left microtia. (B) Right ear.

Case Report

An eight-year-old female child without any hearing impairment presented with an auricular defect (microtia), which was the result of a burns injury. (Fig. 1). The case was referred to a private prosthodontic clinic from the plastic surgery department of the Faculty of Medicine, Sohag University, Egypt, in order to construct an interim auricular prosthesis. After patient's initial assessment, detailed discussions were held with her parents about all possible treatment strategies and taking the parents concern about expenditure into consideration, the child's psychological status, and the parents' refusal of the child wearing eyeglass, which is a common method for retaining temporary auricular prosthesis.

Method

Preparation for impression

Microtia, adjacent skin and hair near the defect area and contralateral ear were protected by applying petrolatum gel (Vaseline, Unilever, UK). A piece of gauze was placed at the opening of the external auditory canal to prevent the entry of the impression material. Three lines representing the superior, middle and inferior border of the normal right ear were marked and transferred from the right to the left side of the face. These lines were transferred on to the working model to act as a guide during sculpting of the wax pattern.

Impression procedures and wax model preparation

After the area of defect was boxed using modelling wax (Anutex toughened pink dental modelling wax, ADP Ltd., England), a flowable mix of irreversible hydrocolloid (Cavex Holland BV, Haarlem, the Netherlands) was used (Fig. 2), and a dental stone was used as a supportive material for the

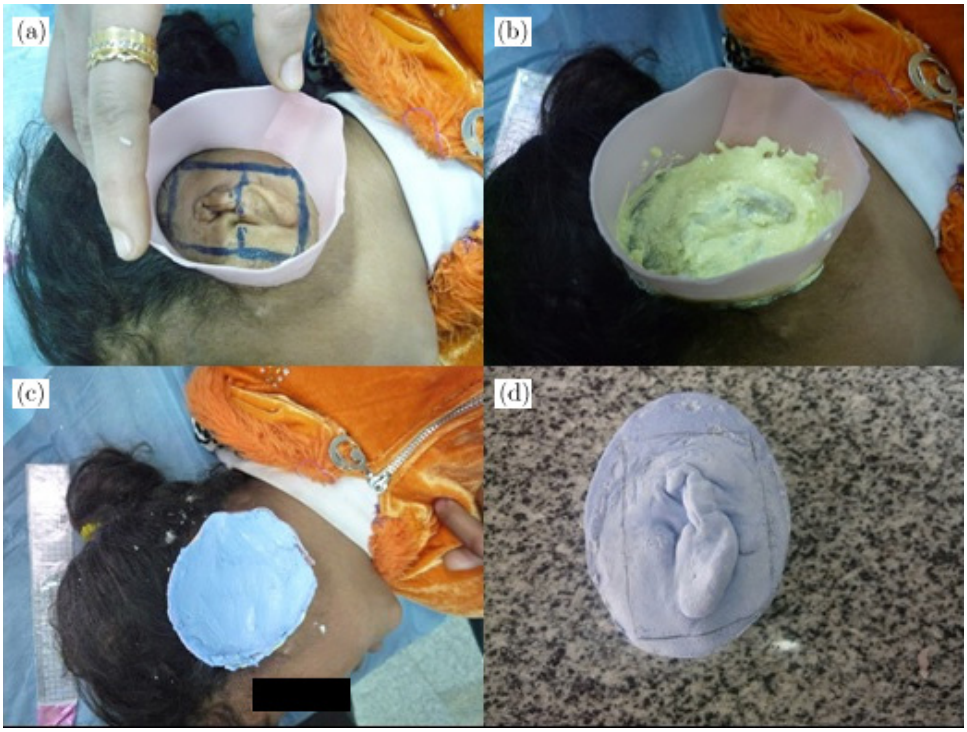


Fig. 2. (a) Markings for the extension of the ear. (b) Irreversible hydrocolloid impression of the defect. (c) Support of the impression with stone. (d) Stone working model.

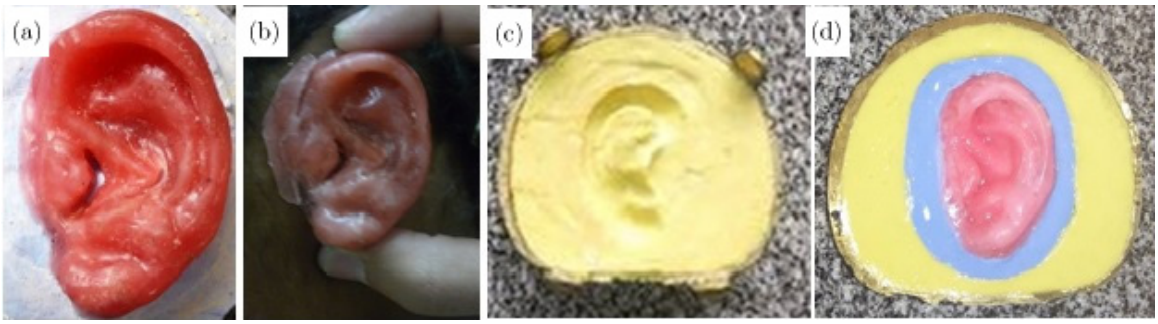


Fig. 3. (a) Wax pattern of the ear prosthesis. (b) Try-in on the patient. (c&d) Investing the wax pattern.

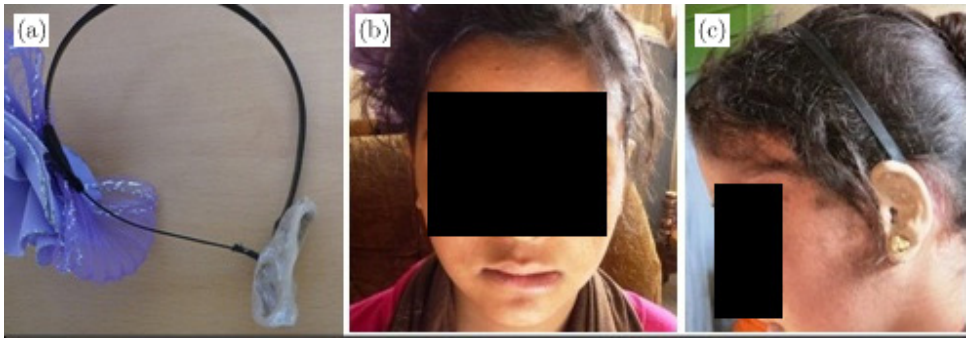


Fig. 4. (a) prosthesis attached to a metallic hair hoop. (b) Frontal view of the prosthesis in position. (c) Lateral view of the prosthesis in position.

preparation of impression. Then, the impression was removed with care, boxed and poured with dental stone.

To obtain a wax model, wax sculpting of the left ear was performed (Figs. 3(a) and 3(b)) using the image of the normal right ear. Then, this wax prosthesis was placed on the patient and checked for proper fit on the tissues and proper alignment with the right (normal) ear.

Mould fabrication

The wax was invested in the denture flask using irreversible hydrocolloid. (Figs. 3(c) and 3(d)) After the material was set, a wax pattern was retrieved. A mixture of clear self-curing acrylic resin (Acrostone, WHW, England) with cosmetic skin foundation pigments was used to make the prosthesis. Multiple mixtures were made with known amounts of pigment and assessed with the photograph of each mix until a required skin shade was obtained. After the required shade was obtained, an adequate amount of polymer and monomer were mixed with pigments to fill the mould. The mix was left to polymerize completely. Then, the prosthesis was deflasked, trimmed and completed. Finally, the prosthesis was checked on the patient's ear.

Adhesion of the acrylic auricular prosthesis to a hair hoop

The prosthesis was attached to a metallic hair hoop using cyanoacrylate (CC-33 strain gauge cement, Kyowa Electronic Instruments Co., Japan). The skin surrounding the defect was well protected to avoid any tissue damage by cyanoacrylate using a separating medium. Camouflaging of the ear prosthesis was made by attachment of earrings to the prosthesis and the normal ear (Fig. 4).

Discussion

Deformities such as acquired microtia result in unpleasant appearance with subsequent social problems during childhood and increased risk of serious psychological consequences during adulthood.[6] Auricular prosthesis, when properly constructed, can play a significant role in ear reconstruction.[7] Epithesis is an acceptable temporary treatment measure that can be used in children till the definitive treatment could be carried out.[8]

A wax pattern was obtained by making an impression and cast of the defective side using the contralateral ear as a

reference and sculpting the wax pattern by using a commonly known method.[9] In the present case, sculpting in-situ was performed because no donor technique using an ear of similar side and size was possible due to the presence of microtia. Acrylic resin is a traditional material of choice for interim epitheses fabrication, as it is an economically feasible option with better tear strength than silicon. Elastic duplicating material (irreversible hydrocolloid) is used for the investing of the wax prosthesis to allow for easy removal of the sculpted ear without damage, which can be used in final prosthesis construction or for reconstruction of interim prosthesis if any damage occurred in the first one.

The use of self-curable acrylic resins allows for rapid evaluation of multiple trials of staining until the required shade was obtained. Taking into consideration the impact of wearing an eyeglass on child's self-perceptions[10] coupled with the parents feeling that their daughter would be wearing spectacles, in the present case study, a novel means of retention was selected that was more suitable for our female patient and readily accepted by the parents and community. In addition, cyanoacrylate was preferred as an adhesive between the epitheses and the hair hoop, because it is well known that adhesion between cyanoacrylic glue and stain steel is good.[11]

The cumulative effects of skin foundation application and use of earring as a camouflage/distraction provided an aesthetically acceptable appearance, which was cost-effective.

References

[1] Bartel-Friedrich S, Wulke C. Classification and diagnosis of ear malformations. *GMS Curr Top Otorhinolaryngol Head Neck Surg* 2007; **6**:Doc05.

[2] Bento RF, Kiesewetter A, Ikari LS, Brito R.Bone-anchored hearing aid (BAHA): indications, functional results, and comparison with reconstructive surgery of the ear. *Int Arch Otorhinolaryngol* 2012;**16**:400–5.

[3] Baluch N, Nagata S, Park C, Wilkes GH, Reinisch J, Kasrai L *et al.* Auricular reconstruction for microtia: a review of available methods. *Plast Surg (Oakv)* 2014;**22**:39–43.

[4] Lemon JC, Kiat-Amnuay S, Gettleman L, Martin JW, Chambers MS. Facial prosthetic rehabilitation: preprosthetic surgical techniques and biomaterials. *Curr Opin Otolaryngol Head Neck Surg* 2005;**13**:255-62.

[5] Chung RW, Siu AS, Chu FC, Chow TW. Magnet-retained auricular prosthesis with an implant-supported composite bar: a clinical report. *J Prosthet Dent* 2003;**89**:446–9.

[6] Li D, Chin W, Wu J, Zhang Q, Xu F, Xu Z *et al.* Psychosocial outcomes among microtia patients of different ages and genders before ear reconstruction. *Aesthetic Plast Surg* 2010;**34**:570–6.

[7] Mandelbaum RS, Volpicelli EJ, Martins DB, Park SH, Dubina E, Ishiyama A *et al.* Evaluation of 4 outcomes measures in microtia treatment: exposures, infections, aesthetics, and psychosocial ramifications. *Plast Reconstr Surg Glob Open* 2017;**5**:e1460.

[8] Federspil PA. The role of auricular prostheses (epitheses) in ear reconstruction. *Facial Plast Surg* 2015;**31**:626–32.

[9] Reisberg DJ, Habakuk SW. Hygiene procedures for implant-retained facial prostheses. *J Prosthet Dent* 1995;**74**:499–502.

[10] Walline JJ, Jones LA, Sinnott L, Chitkara M, Coffey B, Jackson JM *et al.* Randomized trial of the effect of contact lens wear on self-perception in children. *Optom Vis Sci* 2009;**86**:222–32.

[11] Lambert RL. Retentive properties of stainless steel pins cemented with ethyl cyanoacrylate. *J Prosthet Dent* 1975;**34**:187–191.

Singapore Dental Journal, Vol. 39 (2019) 57–61

DOI: 10.1142/S2214607519720027

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Preservation of the superficial temporal artery during resection of a pseudoaneurysm: A case report and review of the literature

Wee Hsuan Ng*, Wai Seng Chan†, Eugene Hze-Khoong Poh†, Fredrik Petersson‡

*Department of Oral and Maxillofacial Surgery, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828

†Department of Oral and Maxillofacial Surgery, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828

‡Department of Pathology, National University Hospital, 5 Lower Kent Ridge Rd, Singapore 119074

Keywords:
Superficial temporal artery
Pseudoaneurysm
Aneurysm
Trauma
Surgical ligation
Preservation of main artery

A B S T R A C T

The superficial temporal artery (STA) is a structure that is particularly vulnerable to injury, given its prominent location in the head and neck region. Pseudoaneurysms of this artery may be encountered during the management of maxillofacial trauma. This article presents a review of the relevant literature on this topic. One of the common surgical interventions includes ligation of the entire feeding artery, which compromises the corresponding blood supply. Preservation of the main trunk of the STA can be achieved in certain cases; one such case is detailed in this report.

Introduction

Although the earliest documented case of a superficial temporal artery (STA) pseudoaneurysm was in the 17th century by Bartholin,[1] STA pseudoaneurysms remain a rare occurrence. More than 95% of reported cases have been attributed to blunt trauma, while spontaneous occurrences accounted for the remaining 5%.[2]

The STA originates from the external carotid artery and passes over the posterior part of the zygomatic arch before bifurcating into the frontal and the parietal branches. It has a relatively superficial course that predisposes it – particularly the frontal branch – to injury. Furthermore, its tethering to a dense connective tissue layer and the absence of a protective layer of overlying muscles restrict its mobility and prevent shock absorption from blunt trauma.[3] A pseudoaneurysm occurs when there is a breach of the wall of the main vessel. The pressure within the artery causes extravasation of blood into the surrounding tissues, creating a fibrous capsule continuous with the vessel wall (Fig. 9).

We present a case that demonstrates this phenomenon, and elaborate on the diagnosis and subsequent management of this relatively uncommon injury.

Case Report

A 18-year-old Chinese male was referred to our emergency department for a hemispherical swelling over his right temporal fossa, following a collision with a metal pole 5 days ago. On examination, he had no other injuries or

*Corresponding author: Wee Hsuan Ng, Department of Oral and Maxillofacial Surgery, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828, E-mail: weehsuan90@gmail.com.

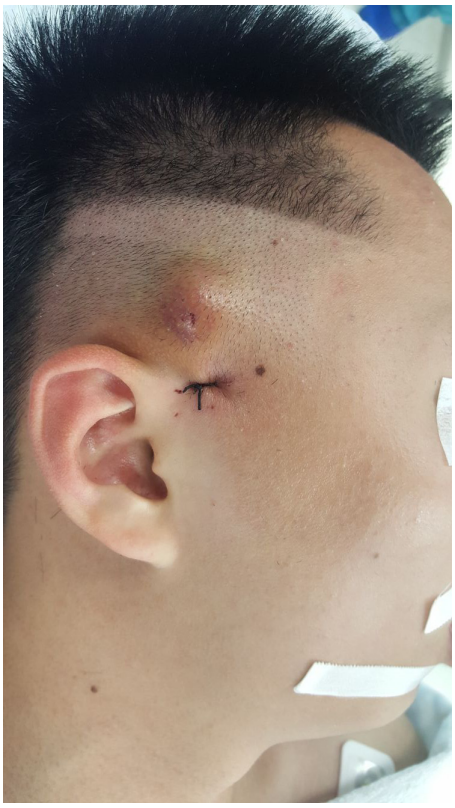


Fig. 1. Initial Presentation of the Pulsatile Lesion over the Right Temporal Region. Note the Deep 2/0 Black Silk Suture Placed Proximal to the Lesion, Previously Placed in an Attempt to Compress the Feeding Artery.

neurological deficits and the 4 cm × 4 cm mass was found to be pulsatile, turbid, and erythematous. A chairside aspiration yielded 15 mL of bright red arterial blood with immediate refilling, while firm digital compression inferior to the lesion resulted in the obliteration of pulsation within the mass. Hinging on a differential diagnosis of a pseudoaneurysm of the STA, a deep 2/0 silk suture was passed percutaneously at the inferior aspect of the lesion in an attempt to compress the proximal end of the artery. Pulsation within the lesion ceased, and a second aspiration was performed, leading to a significant reduction in its size and no discernible immediate refilling. However, during the following day's review, there was a recurrence of the swelling and the detection of a faint pulse.

Treatment options offered to the patient included a conventional endovascular embolization by interventional radiologists or a surgical exploration and resection of the pseudoaneurysm under general anaesthesia. Due to time constraints, both patient and his parents elected on the latter, and surgery was scheduled on the next day. A semi-circumscribed "question mark" incision posterior-superior to the lesion was made and a full thickness skin and

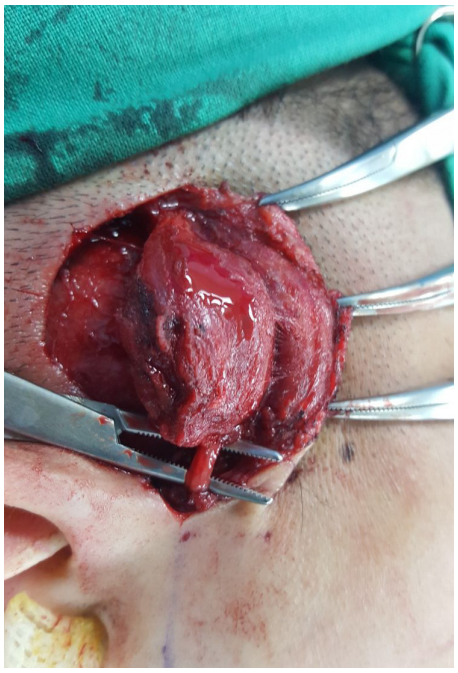


Fig. 2. Exposing the Superficial Temporal Artery (STA) (Above the Haemostat) and the Pseudoaneurysm through a Temporal Incision and an Anteriorly Reflected Full-Thickness Skin Flap.

subcutaneous flap was carefully raised in the posterior-anterior direction, taking care to avoid the temporal branch of the facial nerve crossing anteriorly. Dissection proceeded just beneath the plane of the temporoparietal fascia toward the pseudoaneurysm, and the proximal end of the STA supplying it was identified and preserved (Fig. 2). Careful dissection of the pseudoaneurysm and exposure of the STA revealed a sub-centimetre point of origin along the artery that was subsequently ligated. The entire pseudoaneurysm

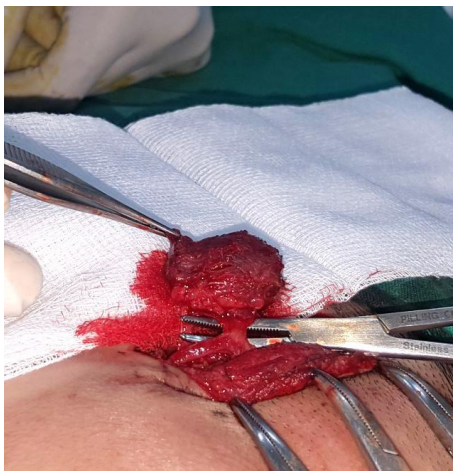


Fig. 3. Pseudoaneurysm Dissected Completely to Reveal the Point of Its Connection with the STA (Above the Haemostat).

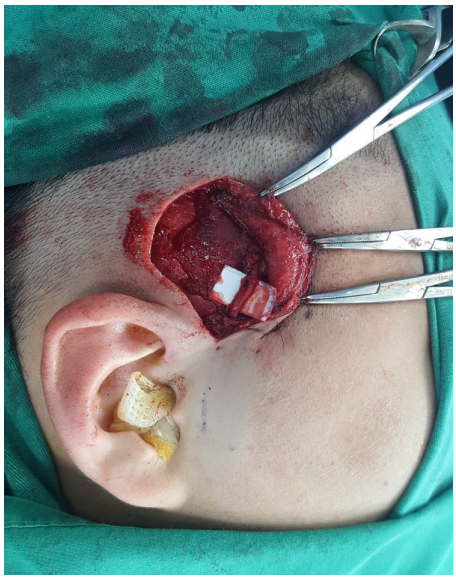


Fig. 4. Preservation of the STA (Above a Piece of White Background) Following the Ligation and Resection of the Pseudoaneurysm.

was then carefully dissected off the superficial layer of the temporalis fascia completely (Fig. 3). A double forceps patency test of the artery was performed over the exact site of the lesion to ascertain the patency of the STA. Valsava manoeuvres were performed thereafter to verify complete haemostasis before the incision site was closed in layers without the need for drains. The operation took 110 minutes with a blood loss of <50 mL. Following an uneventful overnight stay, the patient was discharged the next day. His subsequent weekly and monthly reviews were

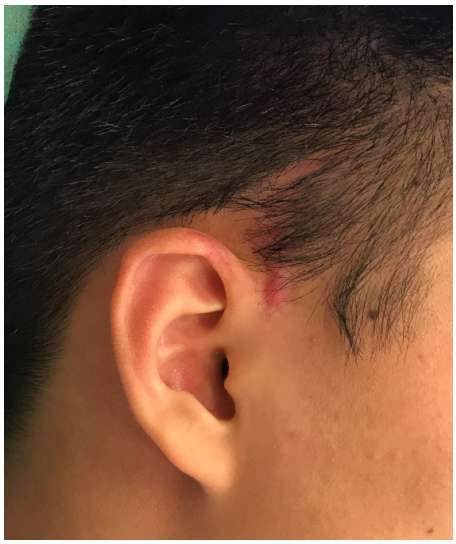


Fig. 5. Healing of Skin Incision 6 Months after Surgery.

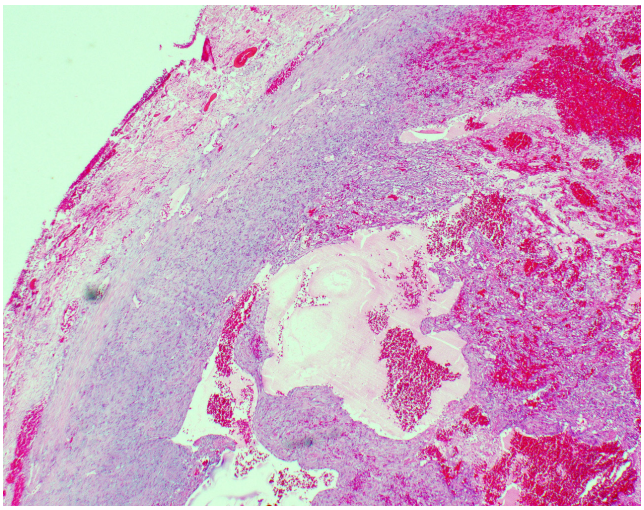


Fig. 6. Haematoxylin and Eosin (H&E) Staining of Resected Pseudoaneurysm, under Low Power Magnification, Demonstrating a Partly Recanalised Thrombosed Blood Vessel.

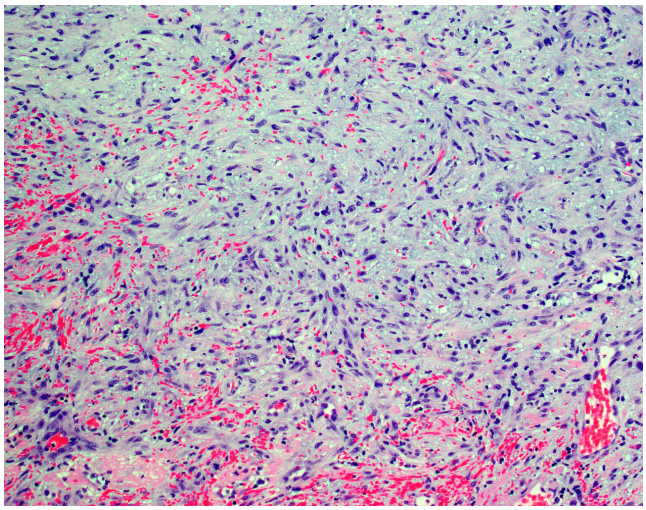


Fig. 7. Haematoxylin and Eosin (H&E) Staining of Resected Pseudoaneurysm, under Medium Power Magnification, Showing Normal Layers of the Artery Being Replaced by Granulation Tissue Composed of Reactive Myofibroblasts, Inflammatory Cells, and Capillaries Set in an Oedematous–Myxoid Background.

unremarkable with no facial palsy or evidence of recurrence, with hypertrophic scar formation hidden within the hairline (Fig. 5).

Histopathological examination confirmed a pseudoaneurysm measuring 3 cm $\times$ 2 cm $\times$ 1.5 cm with a thrombosed vascular wall and partial recanalization as well as prominent inflammatory and fibrous changes within the wall (Figs. 6–8).

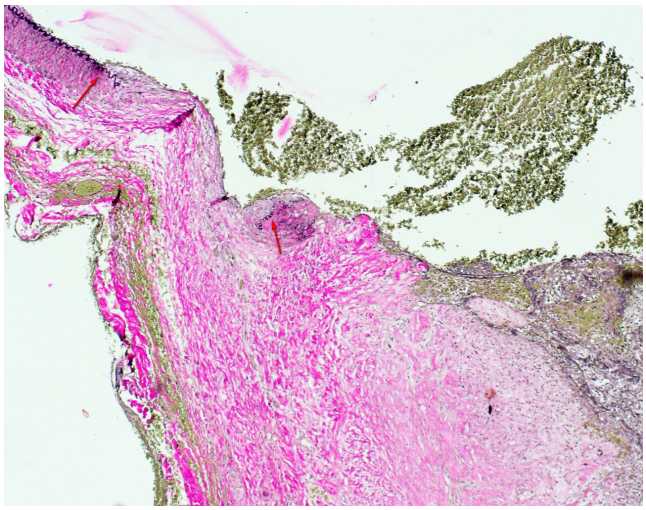


Fig. 8. Verhoeff's Elastin Stain of Resected Pseudoaneurysm, under Low Power Magnification. At the Junction between the Pseudoaneurysm and the Normal Artery, the Elastic Lamina (Arrows) Was Identified.

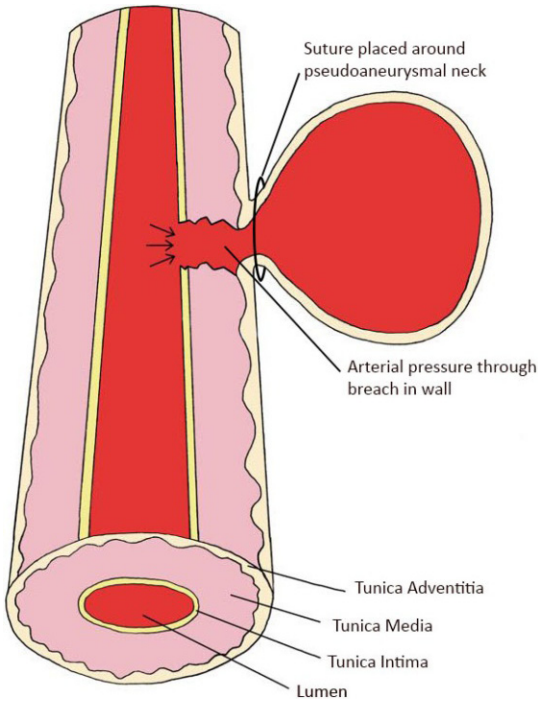


Fig. 9. Diagram Demonstrating the Formation of a Pseudoaneurysm and Subsequent Ligation of the Pseudoaneurysm Alone, Maintaining the Patency of the Main Vessel.

Discussion

Clinical signs and symptoms of an STA pseudoaneurysm are often fairly obvious, allowing for a largely straightforward diagnosis. They typically present with a well-defined swelling over the temporal fossa that may be pulsatile, and auscultation may reveal a thrill or bruit.[4] Coupled with a history of blunt force trauma to the region, these pathognomonic findings are often sufficient for an accurate diagnosis.[5] Angiography, duplex ultrasound, CT, and MRI scans may be employed to confirm the diagnosis and determine the treatment approach.[4]

Treatment modalities range from conservative monitoring or compression, endovascular embolisation, thrombin injection or stent graft insertion, as well as definitive surgical resection. Conservative management invariably requires close and frequent follow-up due to its unpredictability and risk of propagation or rupture, while endovascular approaches have a higher morbidity, risks, and varying degrees of success.[4,6,7] A transfemoral endovascular approach to the STA usually involves passing a percutaneous needle, a guide wire, and then a catheter into the femoral artery. The catheter is threaded through the arteries, guided by contrast and X-rays, and navigated into the lumen of the offending aneurysm. Embolization of the aneurysm can then be achieved with various materials such as detachable coils, liquid agents, sclerosing agents, particulate agents, microspheres, or foam.[6,7] Varying complications have been known to result from endovascular approaches, including temporofacial pain, soft tissue necrosis, migration of embolic material, stroke, blindness, air embolism, thrombosis, infection, pseudoaneurysm of the femoral artery access, recurrence of vascular malformation, and perforation.[4,6,7] Surgical treatment has been shown to have a higher success rate with relatively fewer complications. It usually involves ligation and resection of the artery, with or without an arterial graft, at a point proximal to the pseudoaneurysm.[4,5] This article documents the first reported case where the STA was preserved without the need for grafting or secondary repair following the isolation and resection of an associated pseudoaneurysm, thereby preserving the perfusion of surrounding tissues nourished by the STA. Potential complications with such an approach include a weakened or narrowed STA, which may result in a recurrence of the pseudoaneurysm or formation of a thrombus. Hence, careful surgical handling of the artery and close post-operative observation are paramount. Resection of the pseudoaneurysm alone may not be possible if careful dissection at its point of origin reveals that it emanated from a wide defect of the STA. In such instances, the total ligation and excision of the STA or the insertion of a bypass graft or endovascular stent may be required.

Conclusion

STA pseudoaneurysms can be easily and readily diagnosed without subjecting patients to unnecessary radiation from conventional CT angiograms, thus making substantial

savings of costs and time. Ligation and resection of the pseudoaneurysm to maintain the patency of the STA can be a viable treatment modality given its superficial location that permits a relatively simple surgical approach. Careful case selection, tissue handling, and post-operative monitoring are crucial to avoid arterial wall ruptures or recurrences of the pseudoaneurysm.

References

[1] Bartholin T. Epistolarum medicinalium centuria. Hague Comitum 1644:53.

[2] Sharma A, Tyagi G, Sahai A, Baijal SS. Traumatic aneurysm of superficial temporal artery. *Neuroradiology.* 1991;**33**(6):510–2.

[3] Kim SW, Kim EJ, Sung KY, Kim JT, Kim YH. Treatment protocol of traumatic pseudoaneurysm of the superficial temporal artery. *J Craniofac Surg.* 2013;**24**(1):295–8.

[4] Van Uden DJ, Truijers M, Schipper EE, Zeebregts CJ, Reijnen MM. Superficial temporal artery aneurysm: diagnosis and treatment options. *Head Neck.* 2013;**35**(4):608–14.

[5] Webber CM, Wind GG, Burton RG. Pseudoaneurysm of the superficial temporal artery: report of a case. *J Oral Maxillofac Surg* 1997;**55**(2):166–9.

[6] Health Quality Ontario. Coil embolization for intracranial aneurysms: an evidence-based analysis. *Ont Health Technol Assess Ser* 2006;**6**(1):1.

[7] Bilbao JI, Martínez-Cuesta A, Urtasun F, Cosín O. Complications of embolization. *Semin Intervent Radiol* 2006;**23**(2):126–42. Copyright© 2006 by Thieme Medical Publishers, Inc. New York, NY.

[8] Grasso RF, Quattrocchi CC, Crucitti P, Carboni G, Coppola R, Zobel BB. Superficial temporal artery pseudoaneurysm: A conservative approach in a critically ill patient. *Cardiovasc Intervent Radiol.* 2007;**30**(2):286–8.

Singapore Dental Journal, Vol. 39 (2019) 63–68

DOI: 10.1142/S2214607519720039

SINGAPORE DENTAL JOURNAL
https://www.worldscientific.com/worldscinet/sdj

Parotid gland oncocytosis: Multifocal adenomatous oncocytic hyperplasia variant — A case report in Singapore

Chee Seng Lee*, Eugene Hze-Khoong Poh†, Venkateswaran Kotamma‡, Tsu Ken Loy§, Hsun Tau Chow¶

*Registrar in Oral and Maxillofacial Surgery, Dental Surgery Department, Khoo Teck Puat Hospital, Singapore

†Senior Consultant in Oral and Maxillofacial Surgery, Dental Surgery Department
Khoo Teck Puat Hospital, Singapore

‡Consultant from the Department of Laboratory Medicine of Khoo Teck Puat Hospital, Singapore

§Private Dental Practitioner, Co-Founder of Luminous Dental Group, Singapore

¶Oral Surgeon in Galmi Hospital, Niger

Keywords:
Parotid gland
Oncocytosis
Multifocal adenomatous oncocytic hyperplasia
Salivary gland tumours

A B S T R A C T

Oncocytosis is a rare, benign, non-neoplastic lesion that can be further classified into diffuse oncocytosis or multifocal adenomatous oncocytic hyperplasia. This tumour has been estimated to account for 0.1% of all parotid gland tumours.[1] Here, we report a rare case of a patient who presented to the Oral and Maxillofacial Surgery Department with a 3-cm swelling of his left parotid gland. Histopathological results from a superficial parotidectomy revealed the lesion to be a multifocal adenomatous oncocytic hyperplasia of the parotid gland. A description of this rare disease and its management are included in this article.

Introduction

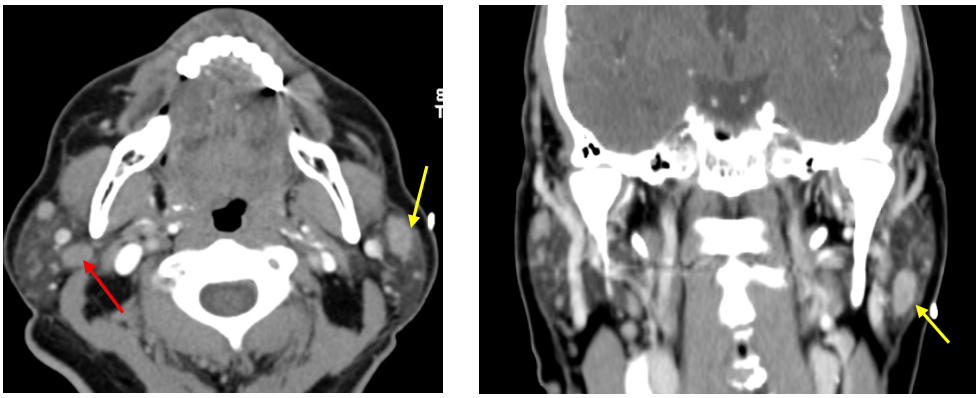
Oncocytes are epithelial cells with abundant, granular, eosinophilic cytoplasm and a central pyknotic nucleus packed with mitochondria. They were first described by Shaffer in 1897[2] and further characterised by Hamperl in 1931.[3] Oncocytes have been observed in the salivary glands, thyroid, parathyroid, pituitary gland, nasal cavities, sinuses, ocular caruncle, lacrimal glands, buccal mucosa, eustachian tube, larynx, oesophagus, liver, pancreas, and kidneys,[4] and they range in presentation from hyperplasia to malignancy.

Here, we report a case of a patient with multifocal adenomatous oncocytic hyperplasia of the parotid gland and describe the characteristics and management of this rare disease.

Case presentation

A 64-year-old Chinese male presented to a general dentist in private practice with the chief complaint of a painless left facial swelling at the parotid region, which had manifested several weeks before. He was then referred to

*Corresponding author: Chee Seng lee's, Registrar in Oral and Maxillofacial Surgery, Dental Surgery Department, Khoo Teck Puat Hospital, Singapore



Figs. 1 and 2. Computed tomography scans (axial and coronal slices, respectively) showing a homogenous enhancing mass within the left parotid gland (indicated by a yellow arrow) with a few other tiny enhancing nodules. Multiple oval-shaped enhancing nodules were seen in the right parotid gland, with a dominant one in the deep lobe (indicated by a red arrow).

the Oral and Maxillofacial Surgery Department of Khoo Teck Puat Hospital for management. He did not exhibit dysphagia, paraesthesia, pain, pre-prandial enlargement, or cervical lymphadenopathy. He was a non-smoker with no history of radiation exposure to the head and neck region. On examination, the swelling was firm, painless, and well-circumscribed, measuring approximately 3 cm. It was slightly mobile on palpation within the tail of the left parotid gland with normal overlying skin. His submandibular glands, nasopharynx, and oropharynx were normal and not injected.

A fine needle aspiration cytology (FNAC) of the left parotid gland was performed, but the cytological results were inconclusive. A contrast-enhanced (Omnipaque 350) computed tomography (CT) scan of his parotid gland and neck was performed, and the scans revealed an elongated, enhancing nodule in the superficial lobe of the left parotid gland, measuring 1.5 cm by 0.9 cm, along with a few other small enhancing nodules. The right parotid gland also had multiple oval-shaped enhancing nodules with a dominant one in the deep lobe, measuring 1.3 cm by 0.9 cm. The provisional diagnosis of the left nodule was Warthin's tumour (Figs. 1 and 2).

The treatment plan was for a left superficial parotidectomy for histopathological analysis before determining the course of action for the smaller lesion in the deep lobe of the right parotid gland.

The superficial parotidectomy was performed under general anaesthesia without administering any muscle relaxants. A modified Blair approach was used, and a subplatysmal flap was raised in continuity with the superficial muscular aponeurotic system to expose the parotid gland capsule. The greater auricular nerve was found to be coursing through the tumour and was sacrificed. Using the tragal pointer, the posterior belly of the digastric muscle and the mastoid aspect of the sternocleidomastoid muscle as landmarks, the root of the facial nerve and the pes anserinus were exposed for an anterograde facial nerve dissection. The tumour-containing superficial parotid gland was then carefully dissected from all 5 branches of the facial nerve. A nerve integrity monitor was used to verify the preservation of all 5 facial nerve branches throughout the operation. A size #10 Redivac drain was inserted away from the facial nerve, and the incision site was closed in layers with 4/O Vicryl (Polyglactin 910, Ethicon Inc.) and 6/O Prolene (Polypropylene, Ethicon Inc.) sutures. Tetracycline ointment was applied over the incision site. The estimated total blood loss was approximately 100 mL. As the patient was observed to be well with minimal overnight drainage, the drain was removed and he was discharged the following day (Figs. 3–5).

Histopathological sections of the resected specimen revealed salivary tissue with a brown solitary nodule measuring 2 cm by 1.6 cm by 0.9 cm. Adjacent to the main nodule were multiple brown nodules ranging from 0.1 to 0.3 cm. Microscopically, the nodules consisted of benign oncocytic cellular proliferation in keeping with oncocytosis, without evidence of malignancy. The histopathological findings were compatible with the diagnosis of multifocal adenomatous oncocytic hyperplasia (Figs. 6–11).

At his 1-week review visit, the patient was able to close his left eye with effort but had difficulty raising his left eyebrow. There was also slight weakness of his left cheek on smiling. He was diagnosed with a House–Brackmann grade III facial nerve palsy with no significant facial asymmetry at rest. Vitamin B12 supplements were prescribed, and the patient was instructed to perform facial muscle exercises. He reported full recovery and complete restitution of his facial nerve function within 2 months, but complained of a mild gustatory sweating which did not affect his daily life. There was also minimal scarring and no obvious hollowing at the operative site. He was reviewed again at 6 months with no clinical evidence of recurrence or any other post-

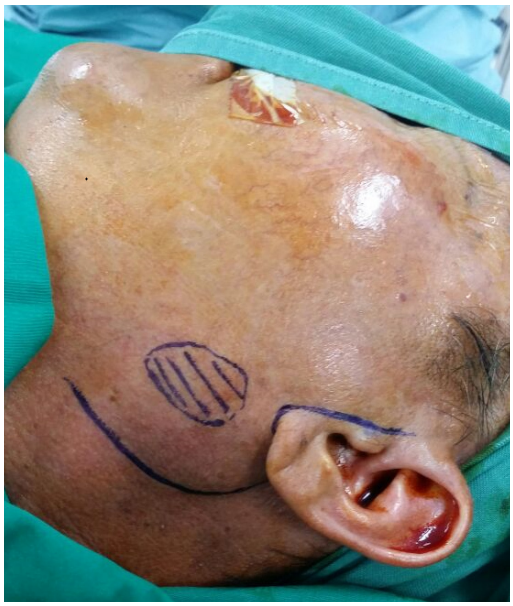


Fig. 3. Preoperative view of incision design (Modified Blair approach) and marking of the left parotid gland swelling.

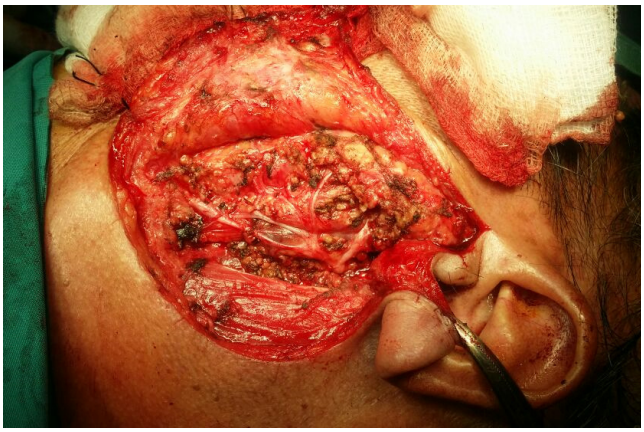


Fig. 4. Intact branches of the facial nerve after superficial parotidectomy.

operative complications, and was advised to have yearly radiological assessments of the nodule in the deep lobe of his right parotid gland, with an option for an ultrasound or CT-guided FNAC.

Discussion

The World Health Organization classifies parotid oncocytic neoplasms into 3 categories: oncocytosis, oncocytoma, and oncocytic carcinoma.[5]

Oncocytosis is considered to be a non-neoplastic, hyperplastic change that may present as a generalised enlargement of the salivary gland. It has been estimated to account for 0.1% of all parotid gland tumours.[1] Oncocytosis has been further categorised into multifocal adenomatous oncocytic hyperplasia (MAOH) and diffuse hyperplastic oncocytosis (DHO).[6]

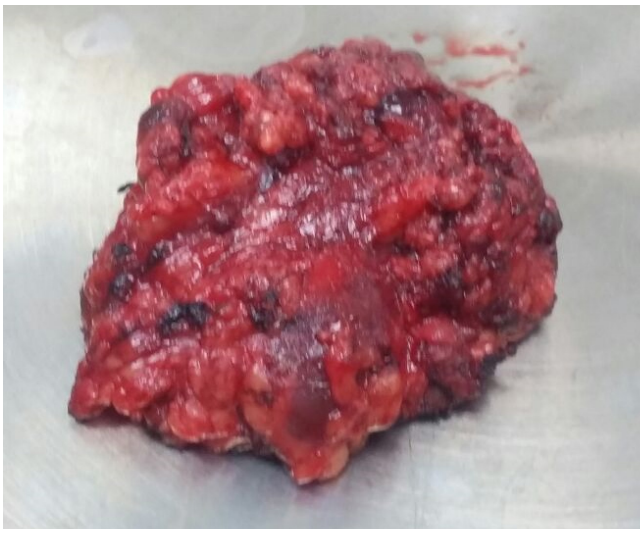
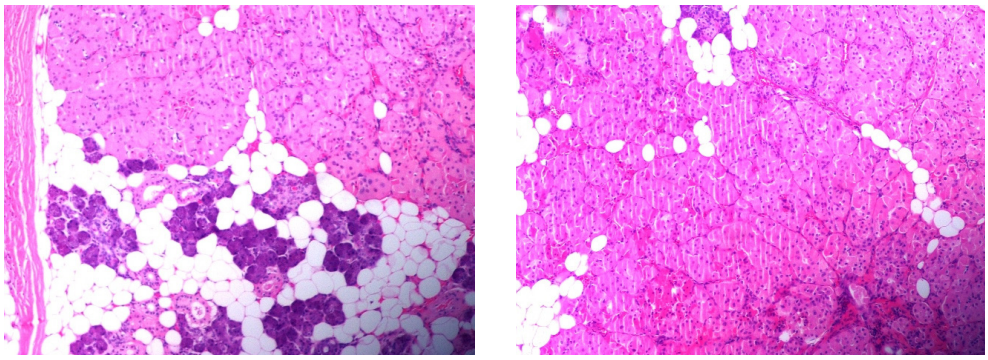


Fig. 5. Excised specimen measuring 5 cm in the greatest diameter.

MAOH in the salivary glands is a rare, benign condition representing multifocal oncocytic proliferation of the duct system, comprising only 0.1% of all parotid gland diseases.[7] It is mainly diagnosed in women and in the sixth decade of life. Macroscopically, MAOH can be described as multinodular non-encapsulated oncocytic foci measuring 0.1–1.0 cm. These foci possess inclusions of salivary gland remnants and ductal oncocytic metaplasia occasionally. Histologically, the nodules consist of bland, polyhedral cells with round, centrally located nuclei, eosinophilic granular cytoplasm and conspicuous cell borders. Unlike oncocytomas, the nodules of MAOH have incomplete capsules. The multinodular growth may mimic malignancy, but the presence of oncocytic proliferation in intercalated ducts and ductules assists in the diagnosis of this benign condition.[8] MAOH is best treated by complete resection as it is not responsive to irradiation.[9] Partial resection likely heightens the probability for recurrences.

DHO represents a rare, non-tumorous condition in which almost the entire salivary gland is engorged with oncocytes. Most cases of DHO occur in the parotid gland, in adults who are 60 years or older, with no evidence of gender predilection.[10] Macroscopically, the excised specimen is non-encapsulated and appears tan-brown in colour, with a gradual transition from a normal parotid parenchyma to an oncocytic region. Microscopically, the glandular lobuli shows complete oncocytic metaplasia of acinar cells and ductal epithelia. Diffuse hyperplastic oncocytosis can only be diagnosed following histopathological confirmation of an



Figs. 6 and 7. Histopathological slides of oncocytosis of the left parotid gland (haematoxylin and eosin staining; 4× low power view) showing benign oncocytic cellular proliferation without nuclear atypia.

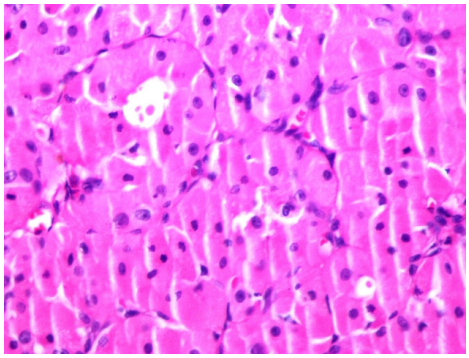


Fig. 8. Histopathological slides of oncocytosis of the left parotid gland (haematoxylin and eosin staining; 10× high power view) showing benign oncocytic cellular proliferation without nuclear atypia.

unencapsulated lesion with the entire gland that is replaced by oncocytic cells. The recommended treatment for DHO is surgical excision.[11]

Oncocytoma is the most common type of oncocytic neoplasm and accounts for approximately 1% of parotid gland tumours. They usually present as a well-circumscribed, encapsulated lesion, comprising an organoid pattern with a thin capillary network, with features of adjacent tissue compression. It has been described to be a potentially recurrent benign epithelial tumour[12] or the neoplastic counterpart of DHO. Oncocytomas are commonly detected between the sixth through eighth decades of life with no gender predilection, and occur within the parotid gland in 80% of the cases. They commonly present as solitary, slow-growing, painless masses that are firm, multilobulated and mobile on palpation.[13,14] Facial paralysis rarely occurs, and oncocytic carcinoma should be suspected if facial palsy is observed. While Warthin's tumour has been shown to have a strong association with cigarette smoking, oncocytomas have been reported to be preceded by radiation exposure.[12,15]

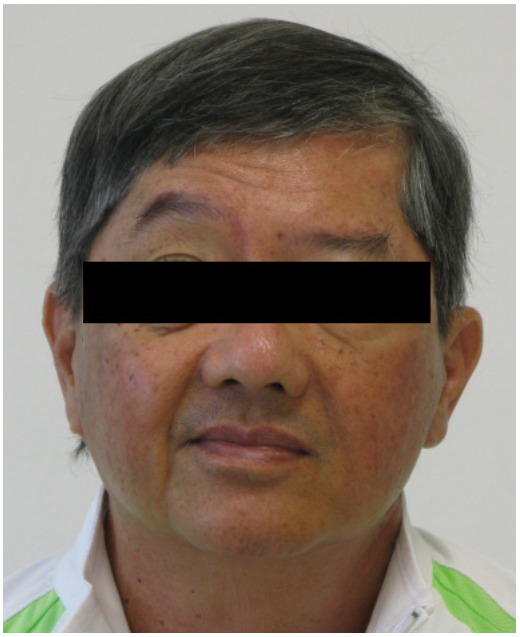


Fig. 9. Immediate postoperative frontal view of the patient, showing weakness over his left eyebrow and a slight weakness of his left cheek.

Oncocytomas of the parotid gland appear as a well-defined homogenous parotid mass in CT scans. In magnetic resonance imaging (MRI), these tumours appear hypodense on T1 and T2 sequences due to their high cellularity and low free water content.[16,17] In contrast, the more common Warthin's tumour can be differentiated from oncocytomas by the former's decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images.[17]

FNAC for oncocytomas demonstrates epithelial cells in sheets and papillary clusters, with an attempt at acinus formation with little or no lymphoid cells. Single cells have also been observed to be present in greater abundance.

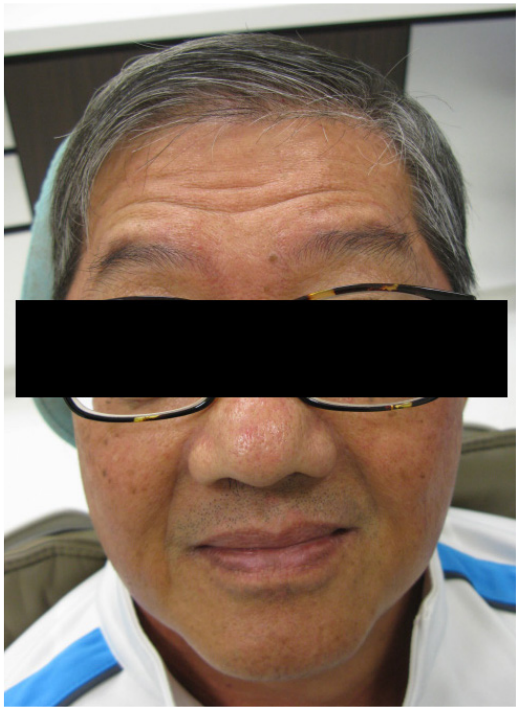


Fig. 10. Three-month postoperative frontal view of the patient, showing full recovery of his facial nerve function.

Both Warthin's tumour and oncocytomas also share similar cystic changes and lymphocytic/oncocytic infiltrates FNAC results from some Warthin's tumours that have fewer lymphocytes and more oncocytes may be cytologically indistinguishable from oncocytoma or oncocytosis. The sensitivity of FNAC for diagnosing oncocytomas was reported to be a dismal 29% in a study by Capone *et al.,*[14] and histopathological analysis remains as the gold standard for an accurate diagnosis. Histologically, oncocytomas are composed of monotonous sheets of oncocytes, frequently with a central scar. Although rare, oncocytomas can undergo malignant transformation to oncocytic carcinomas.[18]

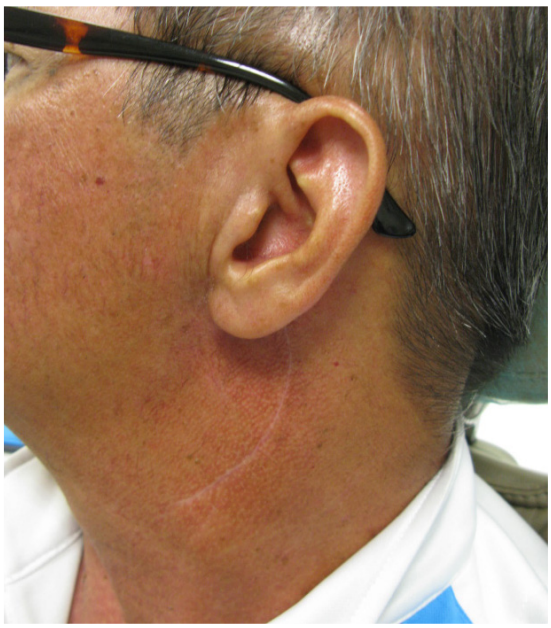


Fig. 11. Six-month post-operative review showing minimal scarring of the incision site.

Oncocytic carcinoma was first reported by Bauer and Bauer in 1953 and is the rarest type of oncocytic neoplasia.[19] It reportedly accounts for 11% of all oncocytic salivary gland neoplasms, 0.5% of all epithelial salivary gland malignancies, and 0.18% of all epithelial salivary gland tumours.[20] Oncocytic carcinoma can be recognised by its morphologic features of cellular pleomorphism, necrosis, frequent mitoses, and infiltrative growth and metastasis.

Oncocytic neoplasms can be difficult to differentiate from other salivary gland tumours. Areas of oncocytic metaplasia can be present within a variety of salivary gland tumours such as basal cell adenoma, pleomorphic adenoma, myoepithelioma, cystadenoma, canalicular adenoma, polymorphous low-grade adenocarcinoma, Warthin's tumour, acinic cell carcinoma, and mucoepidermoid carcinoma.[21] A 16-year retrospective review by Capone *et al.* of 561 parotidectomies reported a 3.7% incidence (21 cases) of oncocytic neoplasms, of which 61.9% were oncocytomas (13 out of 21), 28.6% were oncocytosis (6 out of 21), and 9.5% were oncocytic carcinomas (2 out of 21).[14] Various oncocytic subtypes have been reported to occur simultaneously, which blurs the definitive boundaries of specific differential diagnosis for each subtype and raises the concept of a progression model with a progressive transition between these oncocytic lesions.[14]

In conclusion, MAOH is a rare, benign lesion that should be treated by a complete resection. Recurrences may be more prevalent for partially resected lesions, and continual long-term surveillance is recommended in lieu of the small risk of malignant transformation.

Acknowledgements

The authors would like to appreciate Dr Kotamma for her histopathological analyses and scientific contributions, and acknowledge Dr Loy Tsu Ken for his clinical astuteness in identifying and referring the patient to our department.

References

[1] Watson W, Fu Y, Canalis R. Transitional features of benign and malignant oncocytic tumors: report of two cases. *Am J Otol* 1996;**17**:335–9.

[2] Schaffer J. Beiträge zur Histologie menschlicher Organe. Sitzungsber Akad Wiss Wien Math Naturwiss Kl, Ab, 1897:353.

[3] Hamperl H. Onkozyten und Geschwulste der Speicheldrusen. *Vircows Archiv Pathol* 1931;**282**:724–36.
[4] Kontaxis A, Zanarotti U, Kainz J, Beham A. Diffuse hyperplastic oncocytosis of the parotid gland. *Laryngorhinootologie* 2004;**83**: 185–8.
[5] Hanna E, Suen J. Neoplams of the salivary glands. In: Cummings C, Freidrickson J, Harker L *et al.* editors. *Otolaryngology — Head and Neck Surgery*, 3rd edition. St Louis: Mosby, 1998:1256.
[6] Mandel L, Carrao V. Bilateral parotid diffuse hyperplastic oncocytosis: Case report. *J Oral Maxillofac Surg* 2005;**63**:560–2.
[7] Politi M, Toro C, Cian R, Robiony M, Zerman N. Case Report Multifocal adenomatous oncocytic hyperplasia of the parotid gland. *Oral Oncology Extra* 2005;**41**(8):183–7.
[8] Ghandur-Mnaymeh L. Multinodular oncocytoma of the parotid gland: A benign lesion simulating malignancy. *Human Pathol* 1984;**15** (5):485–6.
[9] Lidang-Jensen M. Multifocal adenomatous oncocytic hyperplasia in parotid glands with metastatic deposits or primary malignant transformation. *Path Res Pract* 1989;**185**:514–21.
[10] Takeda Y. Diffuse hyperplastic oncocytosis of the parotid gland. *Int J Oral Maxillofac Surg* 1986;**15**:765–8.
[11] Shellenberger TD, Williams MD, Clayman GL, Kumar AJ. Parotid gland oncocytosis: CT findings with histopathologic correlation. *Am J Neuroradiol* 2008;**29**(4):734–6.
[12] Palmer T, Gleeson M, Eveson J, Cawson R. Oncocytic adenomas and oncocytic hyperplasia of salivary glands: A clinicopathological study of 26 cases. *Histopathology* 1990;**16**:487–93.
[13] Davy C, Dardick I, Hammond E, Thomas M. Relationship of clear cell oncocytoma to mitochondrial-rich (typical) oncocytomas of parotid salivary gland: An ultrastructural study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1994;**77**:469–79.
[14] Capone R, Ha P, Westra W, Pilkington T, Sciubba J, Koch W *et al.* Oncocytic neoplasms of the parotid gland: A 16-year institutional review. *Otolaryngol Head Neck Surg* 2002;**126**:657–62.
[15] Elhosseiny A. Salivary Glands. In: Koss LG, Melamed MR. *Koss' Diagnostic Cytology and its Histopathological Basis*, 5th edition. Philadelphia: Lippincott Williams and Wilkins 2006:1240–1.
[16] Som P, Shapiro M, Biller H, Sasaki C, Lawson W. Sinonasal tumors and inflammatory tissues: Differentiation with MR imaging. *Radiology* 1988;**167**:803–8.
[17] Som P, Biller H. High-grade malignancies of the parotid gland: Identification with MR imagings. *Head Neck Radiol* 1989;**173**:823–6.
[18] Laurian N, Zohar Y, Kende L. Malignant oncocytoma. *J Laryngol Otol* 1977;**91**:805–8.
[19] Bauer W, Bauer J. Classification of glandular tumors of the salivary glands: Study of 143 cases. *Arch Pathol* 1953;**55**:328–46.
[20] Ellis G, Auclair P, Gnepp D, Goode R. Surgical Pathology of the Salivary Glands. Saunders W Philedelphia, 1991:455–88.
[21] Becker K, Donath K, Seifert G. Diffuse oncocytosis of the parotid gland. Definition and differential diagnosis. *Laryngol Rhinol Otol (Stuttg)* 1982;**61**(12):691–701.