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Editorial

Dear all,

I am proud to announce that our journal Dental Bites has been elated to a higher level through the assignment of ISSN 2394-9848(Print). I congratulate the Editorial team and especially Dr. Sameera G. Nath, Associate Editor for her continued and relentless effort put forward to achieve this status for our Journal within a short period of time. Now it is our responsibility to uphold the standard of publications every time.

The Volume II Issue 1 of Dental Bites is in your hands ready to be turned and read. I congratulate and appreciate the contributors for continuously and constantly supporting and supplying the vital elements for the timely publication and circulation, maintaining the integrity and the quality in its contents.

Clinical Dentistry is a combination of science and art. The paradigm shift of Clinical Dentistry from experience-based to evidence-based requires a good clinician to think like a scientist. We should make our treatment decision based on evidences derived from data analysis rather than one's own experience, because such experience can be biased.

When you publish your paper in a journal, you raise yourself to a higher level: you're contributing a fraction of your new knowledge to the literature database, which may be carried on to the next generation.

I once again congratulate all the contributors for their work. Finally the credit goes to all members of the Editorial Board for moulding this journal into a professionally acceptable form. Looking forward and anxiously waiting for the next issue.

Yours,
Sd/-
Dr.Kunjamma Thomas
Chief Editor

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MULTIPLE CYSTIC SWELLINGS IN THE FLOOR OF THE MOUTH – A CASE REPORT

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Abstract

Oral ranula is a type of mucocele occurring in the lateral side of the floor of the mouth which is closely related to vital structures like the sublingual gland & lingual nerve. While diagnosing, careful differential diagnosis should be carried out to rule out the other lesions occurring in the floor of the mouth like the lipoma, dermoid cyst, abscess, salivary gland lesions and vascular lesions. Treatment by incision, simple marsupialization, and excision of the ranula alone have a high recurrence rate, whereas excision of the sublingual gland with or without the ranula is almost always successful. Here we report a case of a 17-year-old female patient who presented with a cystic swelling in the floor of the mouth that was documented to be oral ranula. Following excision, another cystic swelling developed on the contralateral side that was diagnosed as oral ranula, and subjected to excision.

Key words: Ranula, mucocoele, cystic swelling, mucus extravastion phenomenon, mucus retention cyst

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Introduction

Mucoceles are one of the most common benign soft tissue masses present in the oral cavity. By definition, mucoceles are cavities filled with mucus.[1] They are characterized by single or multiple, spherical, fluctuant nodules which are generally asymptomatic.[2]

When located on the floor of mouth, mucoceoles are termed as 'ranula', the name derived from the typical swelling that resembles the air sacs of the frog 'ranatigrina'. Ranulas usually arise in the body of the sublingual gland and occasionally in the ducts of Rivini or in the Wharton's duct.[3]

Mucoceles are believed to result from mechanical trauma to the excretory duct of the salivary glands, causing duct transection or rupture, with consequent extravasation of mucin to the connective tissue stroma (mucus extravasation phenomenon, MEP). In addition, mucus might be retained in the duct and/or acinus as a result of duct obstruction (mucus retention phenomenon, MRP).[2]

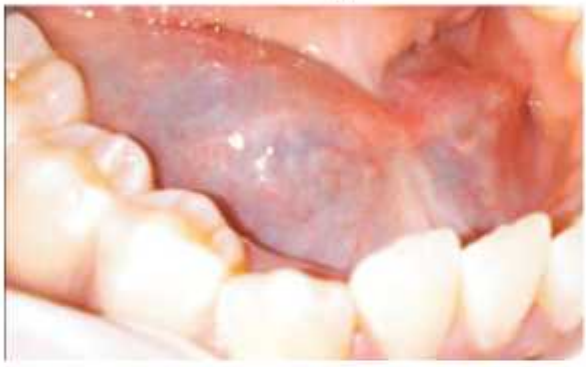
Case Report

A 17 year old female reported to the outpatient department with a chief complaint of painless swelling below the tongue on the right side, for the past one month. History revealed that the swelling has gradually increased in size to the present size. No history of previous trauma or surgery in the area present. She reported history of mild dull pain during food intake since 3 days. There was no

history of fever, xerostomia, upper respiratory tract infection, or any difficulty in swallowing, speech or mastication.

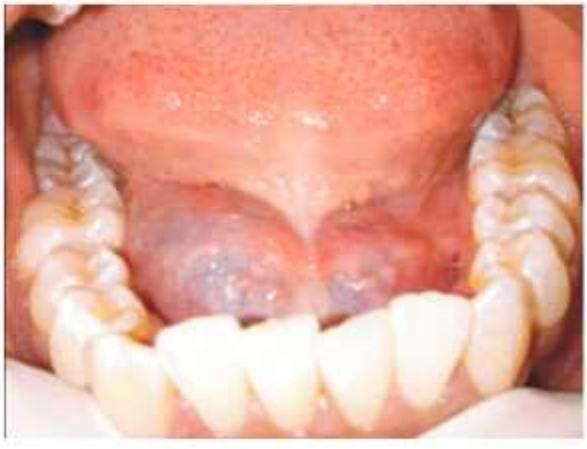
On examination, a 3 x 2 cm bluish fluctuant swelling was seen in the floor of the mouth on the right side, extending across the midline (Fig. 1).

Fig 1: Fluctuant swelling in the floor of the mouth -right side



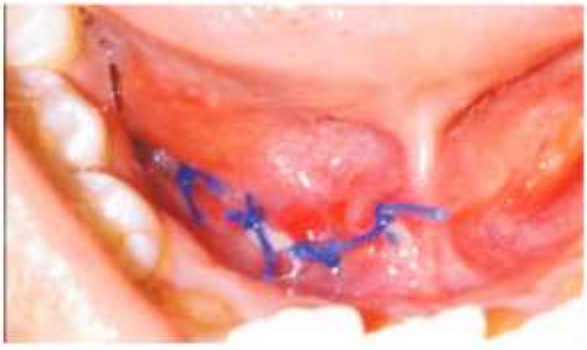
The swelling was non-tender, soft in consistency and no discharge was elicited. The tongue was displaced superiorly (Fig. 2).

Fig 2: Superiorly displaced tongue



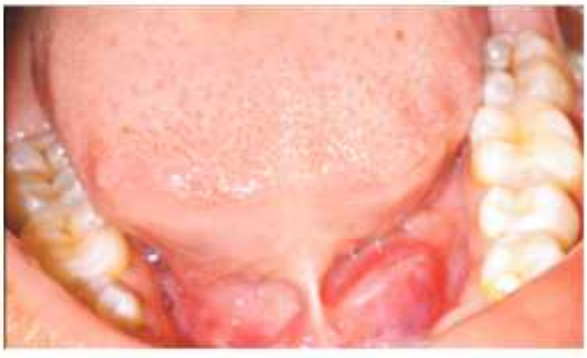
Based on history and clinical findings, a provisional diagnosis of "ranula" was given. Radiographic examination revealed no evidence of obstruction or calculi. FNAC of the cystic swelling yielded mucus. After preoperative investigations, surgical excision of ranula along with the right sublingual gland was carried out under general anaesthesia. Sutures were placed (Fig. 3). Patient was kept under observation

Fig 3: Immediate post surgical view



Four weeks later, a 1cm x 0.5 cm bluish cystic swelling was noted in the floor of the mouth on the left side. Swelling was not associated with any pain (Fig. 4). Plain radiography revealed absence of calculi or obstructions. FNAC revealed presence of mucinous content within the swelling, confirming the diagnosis of ranula.

Fig 4: Ranula on the left side



Surgical excision of the second ranula was done under general anesthesia, along with removal of ipsilateral sublingual salivary gland and duct, which were sent for histopathological examination (Fig. 5).

Histopathology revealed presence of salivary gland tissue and in between connective tissue, showing eosinophilic area resembling mucin with few mucinophages (Fig. 6). Patient was kept under observation, and no new lesion was noted postoperatively.

Fig 5: Surgical removal of the second ranula

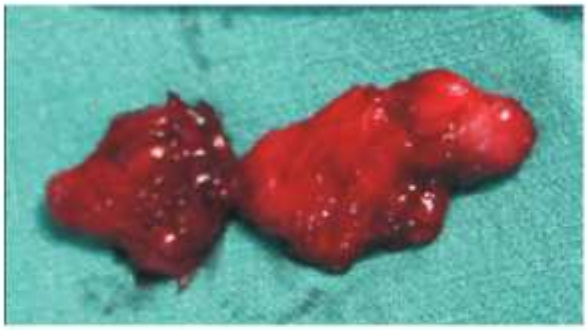
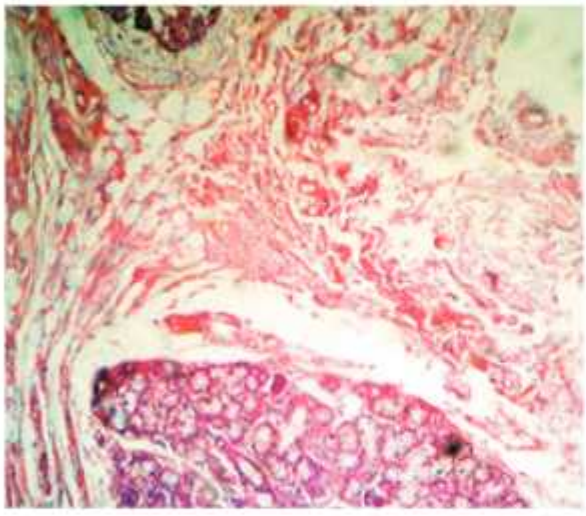


Fig 6: Histopathology



Discussion

Oral mucoceles can affect patients of all ages, with the highest incidence in the second decade of life. No gender predilection has been reported.[3]

Oral mucoceles located on the floor of the mouth are termed ranulas. A ranula manifests as a cup-shaped fluctuant bluish swelling on the floor of the mouth.[2] The characteristic deep blue color results from tissue cyanosis and vascular congestion associated with the stretched overlying tissue and the translucent character of the accumulated fluid beneath. The intensity of color depends on the size of the lesion, its proximity to the surface, and the elasticity of the overlying tissue.[1]

Ranulas tend to be larger than mucoceles located in other regions of the mouth, growing to some centimeters in diameter. Depending on size and location, patient may present external swelling and relate discomfort, interference with speech, mastication, and swallowing.[2]

According to sites of the primary swelling, ranulas may be classified into 3 clinical types: oral ranula (intraoral swelling only), plunging ranula (submandibular and/or submental swelling without intraoral swelling), and mixed ranula(intraoral and extraoral swelling).[4]

Ranulas commonly originate from the deeper areas of the body of the sublingual gland, followed to a lesser degree by the retention cysts from the ducts of Rivini. Less often, retention cysts of the opening of Wharton's duct have been reported.[1]

Mucus extravasation triggers a secondary inflammatory reaction predomi nantly consisting of mononuclear cells in surrounding connective tissue, followed by a granulation tissue-type reaction that culminates in the formation of a fibrous capsule around the mucin deposit, conferring a cyst-like appearance to the lesion.[2]

The causes of ranula formation were thought to be trauma or surgery to the floor of the mouth, neck region which may be a cause for the rupture of the sub lingual gland acini or cause obstruction of the sublingual gland ducts which results in mucous extravasation.[3]

The sublingual salivary gland, being aspontaneous secretor, produces a continuous flow of mucus even in the absence of nervous.

In a case of ranula, a balance exists between sublingual secretory activity and the attempts of the body to limit the extravasation by inflammatory fibrosis and by removal of mucus by macrophages.[6]

Thorough history taking and examination of the lesion is crucial for diagnosing oral mucoceles correctly. Diagnosis may require routine radiographs, ultrasonography or advanced diagnostic methods computed tomography and magnetic resonance imaging for better visualizing the form, diameter, position and determination of the origin of the lesion. Fine needle aspiration is a useful diagnostic technique, especially when differential diagnosis of angiomatous lesion is involved. High amylase and protein content may be revealed by the chemical analysis.[3]

Histopathology of ranula ranges from acute inflammation intermingling with the mucus collection to patterns of mature lesions with scarce amounts of mucus and connective tissue fibrosis. The lesion may show hyperplastic parakeratinized stratified squamous epithelium, small cystic spaces containing mucin and mucusfilledcells, areas of spilled mucin surrounded by a granulation tissue and sebaceous cells in the connective tissue. Presence of salivary gland tissue and sialomucin is diagnostic.[3]

Oral mucocele shall be differentiated from lipoma, oral hemangioma, oral lymphangioma, benign or malignant salivary gland neoplasms, venous varix, irritational fibroma, orallymphoepithelial cyst, gingival cyst of adults, soft tissue abscess, cystice rcosis, and pyogenic granuloma.[7] The treatment shall be either complete excision, marsupialization, dissection, cryosurgery, carbon dioxide lasers, electrocautery, intralesional injection of sclerosing agent OK432 or steroid injection. However, recurrence can occur and a further surgical intervention becomes necessary.[3]

Conclusion

Effective treatment of salivary gland disorders requires accurate diagnosis of the specific disease. Newer advancements in the field of imaging, aid the clinician in making a proper diagnosis. The key to understanding the ranula and its management is to understand the complex anatomy of the floor of mouth and the balance that exists therein.

Acknowledgement

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XYLITOL IN THE PREVENTION OF DENTAL CARIES: A REVIEW OF THE CURRENT UNDERSTANDING

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Abstract

The principle concern for dental professionals has been increasing worldwide prevalence of dental caries. Advances in research have focused on finding an alternative to sugars which is the main etiological dietary factor in dental caries. Xylitol, a caloric sugar substitute, has gained importance in the promotion of oral health. The purpose of this review is to provide an overview of xylitol in caries prevention. Studies have shown xylitol to be a non acidogenic sugar substitute with a specific anticariogenic action against Streptococcus mutans. Xylitol has shown the ability to beneficially influence the remineralization of carious lesions and in addition its long term use inhibited the transmission of mutans Streptococci from mother to child. Consistent scientific evidence from numerous studies suggests a caries preventive effect when xylitol is used habitually. However there is need for more rigorous clinical trials of xylitol that takes into consideration the multifactorial etiology of dental caries.

Key words: xylitol, dental caries, prevention, sugar alcohol, polyol.

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Introduction

Sugar is used widely in foods because of its sweetness, however sugars' are the most important dietary factor in the etiology of dental caries.[1] Epidemiological studies like the Vipeholm Study, Hopewood House study, World War II food rationing, Hereditary Fructose Intolerance etc have given classic evidence of the role of sugars in the etiology of dental caries. Since 1940's, the principle concern for dental professionals have been increasing worldwide prevalence of dental caries.

The 'Turku' sugar studies fired the search for non-cariogenic sugar substitutes.[2] The main health benefits of sugar substitutes in food and drink are their contribution in controlling weight, diabetes and in promoting oral health. Given the prevalence of dental caries especially in developing countries,[3] the role of sugar substitutes as an adjunct to other methods of prevention is of great public health significance.

Among the sugar substitutes Xylitol is the most widely studied and most commonly used sugar substitute. Taking this into consideration, the present review was undertaken to understand the role played by xylitol in the prevention of dental caries.

Methodology

An electronic search was conducted using PubMed with following terms "xylitol AND dental caries", "caries prevention", "plaque reduction" Streptococcus mutans suppression". Relevant papers published in English were identified after review of the abstracts.

Classification of sugar substitutes

The Sugar substitutes can be broadly categorized into Caloric and Non-caloric sugar substitutes based on their caloric value at use.[4]

The Caloric sugar substitutes are as sweet as sucrose and provide nearly as many calories. They are further categorized into Monosaccharides, Disaccharides and Polysaccharides. The monosaccharides and disaccharides belong to the family of 'Sugar alcohols'.

The monosaccharides are Xylitol, Sorbitol, Erythritol and Mannitol. The disaccharides comprise of Lactitol, Maltitol, Isomalt. Hydrogenated Starch Hydrolysates make up the polysaccharide category.

The Non-caloric sugar substitutes are many times sweeter than sucrose and provide negligible calories. They can be categorized into Synthetically derived and Naturally occurring. The Synthetically derived sugar substitutes comprise of Saccharin, Cyclamate, Aspartame, Acesulfame-K, Sucralose, Neotame and Alitame. The Naturally occurring sugar substitutes are Stevia sweeteners, Thaumatin, Monellin, Miraculin, Neohesperidine, Glycyrrhizin, Brazzein and Lo Han Guo.

Xylitol

Xylitol, a pentose alcohol, was first discovered from Beech chips by a German scientist, Emil Fischer and at the same time isolated from wheat and oat straw, by a French chemist, MG Bertrand in 1891.[3] It occurs naturally in fruits (strawberries, plums, raspberries) and vegetables (lettuce, cauliflower, mushrooms).

Xylitol has sweetness similar to that of sucrose leaving a cool aftertaste in the mouth and supplies 40% fewer calories than sucrose.[4]The dental effects of xylitol were first recognized in Finland through studies on animal models. The first human studies showing the relationship between plaque and xylitol as well as safety of xylitol was conducted in 1975.[3]

Xylitol in Dental caries prevention

Numerous research since have shown xylitol to be noncariogenic.[4] Regular xylitol use has shown to affect the levels of various oral microflora.

Studies of xylitol use in the form of chewing gums[5], tablets[6] and gummy bear snacks[7] in different population groups showed inhibition of levels of various acidogenic bacteria in both plaque and saliva. The amount of growth inhibition varied depending on the frequency of xylitol use and initial levels of Streptococcus mutans.

These studies also revealed a specificity of xylitol's anticariogenic action towards the growth of pure strains of Streptococcus mutans. However Van Loveren C in his review concluded that not all studies of xylitol showed a similar mutans reducing effect.[8]

Apart from its effect on Streptococcus mutans, many in vitro investigations have shown xylitol to be hypo or non acidogenic. In the in vitro study by Haukioja A et al[9] in 2008 the fall in plaque pH observed, 30 minutes following a sucrose challenge, was lowest for xylitol group when compared to the glucose, sorbitol and lactose groups.The caries preventive effects of xylitol is mainly attributed to development of a 'futile cycle' in mutans Streptococci and other micro organisms in the oral cavity.[10-15]

In vitro studies have shown that Streptococcus mutans and Lactobacillus caseii incorporate xylitol intracellularly as Xylitol-5-phosphate and the accumulation of this metabolite results in inhibition of glycolytic enzymes, resulting in low production of energy not enough for bacterial maintenance, development and acid production.

Xylitol's ability to influence the remineralization of demineralized enamel was first observed in the classic "Turku" sugar studies which had shown reversal of enamel lesions in the xylitol group.[2] Others had shown that a five time daily use of Xylitol gum by children with dental caries resulted in a rehardening of enamel lesions and a 10-27% rehardening of dentinal lesions.[16,17]Thedegree of remineralization doubled with the addition of Casein phosphopeptide-amorphous calcium phosphate to xylitol gums.[18]A similar enhanced remineralization of artificial enamel lesions was also observed on addition of 5% xylitol to 500 ppm of Sodium Fluoride tooth paste.[19]

Early acquisition of cariogenic bacteria in children increases the risk for developing dental caries lesions. Habitual consumption of Xylitol chewing gums by mothers when their child was 6- 18 months of age showed mutans Streptococcus colonization was low to non- significant and reduced dmf and defs scores at two years of age.This effect was attributed to a selection for xylitol resistance strains with reduced adhesion to tooth surfaces upon long term consumption of xylitol thereby inhibiting the transmission of mutans streptococci from mother to child.[20-22]

Long term consumption of xylitol showed a selective emergence of xylitol resistant mutans Streptococci that were less virulent and less cariogenic than parent strains.[23]A 24 month study in China among 8-9 year old children in public elementary schools showed decrease in the plaque and salivary levels of Streptococcus mutans, reduction in size of colonies, decrease in sticky substance secretion and a decrease in expression of gtfB gene needed for extracellular polysaccharide synthesis following regular use of xylitol chewing gums.[24]

A 40 month double blind cohort study in Belize compared the effect of xylitol chewing gum to sorbitol gum use by children on the caries reductions and levels of Streptococcus in plaque and saliva. Greatest reductions were observed for xylitol group than the combined xylitol-sorbitol groups.[25] A similar study by Haresaku S et al[26]in 2007comparing regular xylitol chewing gum use to maltitol gums observed that unlike xylitol, long term use of maltitolpromotes growth of Streptococcus mutans.The investigation by Makinen KK et al on various sugar alcohol tablet use by mentally

challenged individuals showed enhanced buffering capacity, salivary flow as well as reduced salivary and plaque levels of streptococcus mutans for combinations of xylitol and pure xylitol tablet groups when compared with groups using combinations of sorbitol and erythritol tablets.[6]

Sugar alcohols like erythritol, sorbitol, maltitol, and mannitol are considered to be non acidogenic, however, xylitol seems to show superior anticariogenic effect. This may be due to the specific action of xylitol on Streptococcus mutans which is not observed in other sugar alcohols.

The ideal effective dose and frequency of xylitol for caries prevention was determined from studies using xylitol gums at concentrations ranging from 1.3 g to 14 g. The maximum anticaries activity of xylitol was seen at concentrations not less than five grams per day chewed for a minimum of five minutes in a minimum of three divided doses and upto a concentration of 14 g without significant side-effects such as osmotic diarrhea and abdominal distress.[25,27]

Clinical efficacy of xylitol

Many reviews have addressed the question of clinical effectiveness of xylitol in the prevention of dental caries. A systematic review of original randomized controlled trials and observational studies of polyol chewing gum on dental caries by Deshpande A and Jadad AR[28] found a preventive fraction of 58% for xylitol and 52% for xylitol- sorbitol blends.

A recent review by Milgrom P et al[29] identified xylitol, as a safe dental caries preventive agent when incorporated into chewing gum or confectionaries when used habitually by mothers prenatally or after delivery and suggests use of a slow release vehicle for xylitol to prevent S mutans transmission. However the authors concluded that the research on xylitol still failed to address how xylitol can be effectively utilized to prevent the global dental caries problem.

The American Academy of Pediatric Dentistry recognizes the benefits of caries prevention with xylitol and recommends use of xylitol for long term caries pathogenic suppression in high risk patients.[30]

However, the review by Loveren CV[8] suggests that the caries preventive effect of xylitol might be due on stimulation of salivary flow when used in chewing gums and lozenges. Hence the conclusions from clinical trials of xylitol need to be interpreted with caution.

Conclusion

Dental caries is a reversible disease if treated in the early stages. The consistent scientific evidence from numerous studies suggests a caries preventive effect when xylitol is used habitually. However there is need for more rigorous clinical trials of xylitol that takes into consideration the multifactorial etiology of dental caries and which focuses on integration of xylitol as a part of regular oral hygiene maintenance for the prevention of public health problem of dental caries.

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PHOTODYNAMIC THERAPY

*Dr. Anjhana Narayanan, **Dr. Santhosh V.C., ***Dr. Sanara P.P.,****Dr. Sreekanth P.

Abstract

Conventional treatment for periodontopathy can greatly reduce the bacterial load and achieve an optimal therapeutic effect in many cases. However, chemotherapeutic therapy may be accompanied by side effects. Therefore, alternatives for an efficient adjunctive removal of periodontal bacteria have been proposed. This review is on one alternative to conventional periodontal therapy based on the principles of photodynamic therapy.

Key words: periodontitis, inflammation, photodynamic therapy

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Introduction

Periodontitis is caused by bacterial infection and is accompanied with signs of inflammation, bleeding on probing and pronounced attachment loss. Prevention of periodontitis is based on suppression of periopathogenic bacteria and reduction of inflammatory signs.

Conventional treatment for perio dontopathy (scaling and root planing in conjunction with or without antibiotics) can greatly reduce the bacterial load and achieve an optimal therapeutic effect in many cases.[1] However, chemotherapeutic therapy may be accompanied by side effects such as gastrointestinal disorders, or may at least temporarily lead to the development of bacterial resistance.[2] For these reasons, patient compliance may also be jeopardized. Therefore, alternatives for an efficient adjunctive removal of periodontal bacteria have been proposed.

Photodynamic therapy (PDT) has emerged in recent years as a non – invasive therapeutic modality for the treatment of various infections by bacteria, fungi, and viruses. This therapy is defined as an oxygen-dependent photochemical reaction that occurs upon light – mediated activation of a photosensitizing compound leading to the generation of cytotoxic reactive oxygen species, predominantly singlet oxygen.[3]

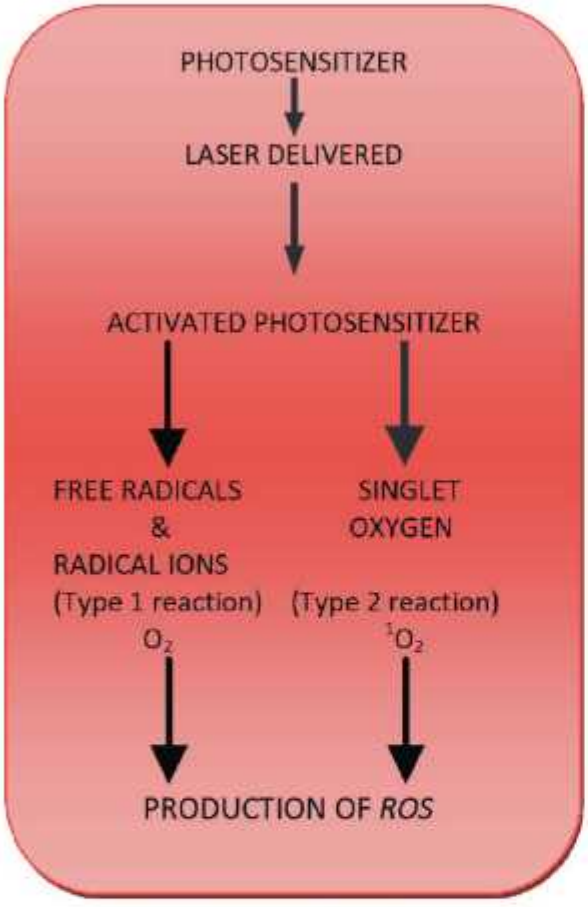
The potential of photodynamic therapy to oral bacteria began to be investigated in the 90's when Dobson and Wilson analyzed the bacterial reduction of S. sanguis, A. actinomycetemcomitans, F. nucleatum and P. gingivalis.[4]

Principle of Photodynamic therapy

The knowledge of the preferred uptake and accumulation of some dyes (mostly porphyrins) into tumor tissues stimulated the introduction of PDT into clinical practice. PDT is based on the principle that on irradiation with light in the visible range of the spectrum, the dye (photo sensitizer) is excited to its triplet state, the energy of which is

transferred to molecular oxygen.[5] The triplet state photo sensitizer can react with biomolecules in two different pathways - type I and II.

Fig 1: Principle of PDT



Type I reaction involves producing free radicals which interact with endogenous molecular oxygen to produce highly reactive oxygen species (ROS) which are harmful to cell membrane integrity, causing irreparable biological damage.[4]

Type II reaction produces singlet oxygen which can interact with a large number of biological substrates inducing oxidative damage on the cell membrane and cell wall. Photo sensitizer induces apoptosis in mitochondria and necrosis in lysosomes and cell membranes.[4]Singlet oxygen has a short lifetime in biological systems and a very short radius of action (0.02 mm). Hence, the reaction takes place within a limited space, leading to a localized response; thus making it ideal for application to localized sites without affecting distant cells or organs.

Photo sensitizers

Chemically, many photo sensitizers belong to dyes and porphyrin-chlorine groups. PDT[6] uses several photoactive components with optimal properties such as:

- Highly selective
- Low toxicity and fast elimination from skin and epithelium
- Absorption peaks in the low-loss transmission window of biological tissues
- High quantum yield of singlet oxygen production
- High solubility in water, injection solutions and blood substitutes
- Storage and application light stability
- Should bind with bacteria and plaque without causing any cosmetic issues, such as unwanted staining of gingiva and other soft tissues.

Types of photosensitizers[6]

a) **Dyes**: Tricyclic dyes with different meso-atoms: methylene blue, toludine blue O and acridine orange; and phthalocyanines – aluminum disulphonated phthalocyanine and cationic Zn(II) phthalocyanine.

b) **Chlorines:** chlorine e6, stannous (IV) chlorine e6, chlorine e6-2.5 N-methyl-d-glucamine (BLC1010), polylysine

and polyethyleneimine conjugates of chlorine e6.

c) **Porphyrins**: haematoporphyrin HCl, photofrin and 5-aminolevulinic acid (ALA), benzoporphyrin derivative (BPD)

d) **Xanthenes**: erythrosine

e) **Monoterpene**: azulene

In antimicrobial PDT, photo sensitizers used are toluidine blue O and methylene blue. Toluidine blue O is a solution that is blue–violet in color. It stains granules within mast cells and proteoglycans/ glyco saminoglycans within connective tissues. Methylene blue is a redox indicator that is blue in an oxidizing environment and becomes colorless upon reduction. Methylene blue combined with light has been reported to be beneficial in killing the influenza virus, Helicobacter pylori, and C. albicans.[5]

Photo sensitizers can also be activated by low power visible light at a specific wavelength. Human tissues transmit red light efficiently at wavelengths of 630 nm and 700 nm and these correspond to light penetration depths from 5 mm to 15 mm respectively.[7]

Activation of the photo sensitizer is dependent on the total light dose, the dose rates, the depth of light penetration and the localization of target area. Sources of light delivery vary depending on the location and morphology of the lesion. The light should be uniform and should deliver precise calculation of the delivered dose. Fibre-optic catheters with terminal cylindrical diffusers or lenses are often used. The tip of the fibre can be formed into various shapes allowing for diffusion in all directions or for focus.[6]

Practical advantages of PDT

1. Safe for human tissue
2. Inexpensive, instant results
3. No patient compliance
4. Versatile
5. Systemic antibiotics cannot get into dead or damaged tissues
6. Even if antibiotic works, it may take several days
7. PDT has broad therapeutic window
8. Eradicates pathogens in biofilm
9. Eliminates development of resistance
10. Destroys secreted virulence factors

Fig 2: Advantages of PDT

Application of Photodynamic Therapy in Dentistry [4]

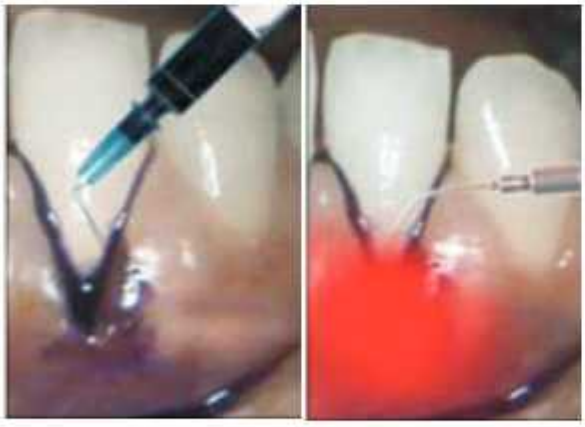
- As an adjunctive to conventional mechanical therapy
- Detoxification of endotoxins such as lipopolysaccharide
- Bacteria associated with periodontal disease can be killed through photosensitization with toulidine blue o by irradiating with helium – neon soft laser
- In the surgical management of peri – implantitis
- Is effective for the treatment and prevention of dental caries.

- Effective as an adjunct to conventional endodontic disinfection treatment to destroy the bacteria that remain even after irrigation with sodium hypo chlorite
- Combined with endodontic treatment in patients with necrotic pulp infected with microflora resistant to a previous antibiotic therapy
- In efficient treatment to kill multi-drug resistant microorganisms

Application in Periodontics

Antimicrobial PDT can be considered as an adjunctive to conventional mechanical therapy. The liquid photo sensitizer placed directly in the periodontal pocket can easily access the whole root surface before activation by the laser light through an optical fiber placed directly in the pocket.

Fig 3: Application of PDT for periodontal therapy



A photo sensitizer is applied in the area to receive PDT. The pocket is irradicated for a second time using PDT. (Figure courtesy: General Dentistry, March/April2010)

Antimicrobial properties are achieved by following mechanisms:

- Polysaccharides present in extracellular matrix of oral biofilm are highly sensitive to singlet oxygen and susceptible to photodamage. Breaking the biofilm may inhibit plasmid exchange involved in transfer of antibiotic resistance and disrupt colonization.
- PDT may increase oxygenation of gingival tissues by 21–47 per cent and inhibits the growth of anaerobic bacteria.
- Gram positive bacteria are more susceptible to photoinactivation than Gram negative bacteria. The structural variations in their cytoplasmic membrane are responsible for the enhanced susceptibility of Gram positive bacteria to binding to photo sensitizers
- The selective uptake of photo sensitizers by bacteria can be enhanced by conjugation with various peptides beneficial in targeting bacteria or particular virulence factors. For example, Poly-l-lysine (pL)–chlorine e6 conjugates kill P. gingivalis without affecting the viability of epithelial cells

Adverse effects

The risk and side effects of antimicrobial PDT are basically classified into two categories. Those which are related to the effect of light energy and those related to photo sensitizer and the photo chemical reaction.

The use of protective glasses by the patient, the operator and the assistant is recommended. With regard to photo sensitizers and photochemical reactions, it is important to apply antimicrobial photodynamic therapy to stain and kill selectively the targeted bacteria without adversely affecting the surrounding periodontal tissues[6]

Perspectives and Future Directions

The numerous studies indicate that PDT appears to be most efficient for treatment of localized and superficial infections. Thus, infections in the oral cavity such as mucosal and endodontic infections, periodontal diseases, caries, and periimplantitis are potential targets.

PDT will not replace antimicrobial chemotherapy, but may improve the treatment of oral infections, accelerating and lowering the cost of the treatment. Development of new photo sensitizers, more efficient light delivery systems, and further studies are required to establish the optimum treatment parameters

Conclusion

Antimicrobial PDT seems to be a unique and interesting therapeutic approach towards periodontal and endodontic therapy. The numerous in vitro studies have clearly demonstrated the effective and efficient bactericidal effect of PDT. There is a great need to develop an evidence based approach to the use of PDT for the treatment of periodontitis, peri-implantitis, and endodontic therapy. It would be prudent to say that there is an insufficient evidence to suggest that PDT is superior to the traditional modalities of periodontal therapy. Further, randomized long term clinical studies and meta analyses are necessary to demonstrate the beneficial effect of antimicrobial photodynamic therapy, and in comparison with conventional methods. Antimicrobial photodynamic therapy may hold promise as a substitute for currently available chemotherapy in the treatment of periodontal disease.

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NEED OF THE HOUR: UPDATE ON ANTICOAGULANT & ANTIPLATELET THERAPY

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Abstract

Continuous oral anticoagulant therapy has been used to decrease the risk of thromboembolism for more than half a century, prolonging the lives of thousands of patients. Many physicians recommend interrupting continuous anticoagulant therapy for dental surgery to prevent hemorrhage. Many authorities state that dental extractions can be performed with minimal risk in patients who are at or above therapeutic levels of anticoagulation. There are sound legal reasons to continue therapeutic levels of warfarin for dental treatment. This article aims to provide an understanding on the current protocol undertaken in the treatment consideration for dental patients on anticoagulants.

Key words: dental treatment, anticoagulants, antiplatelet therapy,aspirin

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Introduction

Continuous oral anticoagulant therapy has been used to decrease the risk of thromboembolism for more than half a century, prolonging the lives of thousands of patients. Many physicians recommend interrupting continuous anticoagulant therapy for dental surgery to prevent hemorrhage.

Many authorities state that dental extractions can be performed only after stoppage of eth anticoagulant drug prior to dental procedures. One must balance the risks of primary or recurrent thromboembolism if these drugs are stopped, against the risk of bleeding if these drugs are continued. But,there are sound legal reasons to continue therapeutic levels of warfarin for dental treatment.

The perioperative management of patients taking oral anticoagulant or antiplatelet drugs for primary or secondary prevention of arterial or venous thrombosis is a common and important problem. This article aims to provide an understanding on the current protocol undertaken in the treatment consideration for dental patients on anticoagulants

Anticoagulants[1]

Anticoagulants are agents that prevent the formation of blood clots, by affecting blood coagulation factors. The mechanism of action of anticoagulation varies depending on the agent. They are used to treat thrombotic and thromboembolic disease such as stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism.

Anticoagulants mainly include:

- *Coumarins and Indandiones*
- *Factor Xa Inhibitors*
- *Heparins*
- *Thrombin Inhibitors*

Coumarins and indandiones[1]

Warfarin, is a coumarin. It is an oral anticoagulant that inhibits Vitamin K epoxide reductase, an enzyme that that recycles oxidized vitamin K. Vitamin K is an activator of coagulating factors II, VII, IX and X, so by decreasing the availability of Vitamin K synthesis of these factors are decreased.

Warfarin is used to treat blood clots in cases of deep vein thrombosis or pulmonary embolism. It is also used to prevent thrombosis in patients at high risk, such as in atrial fibrillation, heart attack and knee or hip surgeries.

Warfarin is an extremely effective anticoagulant but there are a few drawbacks. It can interact with certain foods and can it cause serious interactions with many commonly used medicines. Regular blood monitoring (International Normalized Ratio-INR) is done to check for effectiveness and safety.

Factor Xa Inhibitors[1]

Factor Xa inhibitors are anticoa gulants that block the activity of clotting factor Xa and prevents blood clots developing or getting worse. Factor Xa is generated by both the extrinsic and intrinsic coagulation pathways; it activates prothrombin to thrombin, which activates the final components of the coagulation pathway to form clots.

Factor Xa inhibitors are generally used as prophylaxis in patients having hip and knee replacement surgery, where blood clots can form and lead to deep vein thrombosis and pulmonary embolism.

Heparins[1]

Heparin is an injectable anticoagulant that activates antithrombin III, which inhibits thrombin and factor Xa, factors necessary in the final stages of blood clotting cascade.

There are two types of heparins: high molecular weight heparins and low molecular weight heparins.High molecular weight heparins require daily blood monitoring to check the aPTT. Low molecular weight heparins give a better anticoagulant response and do not need daily blood monitoring.

Heparin is used to treat or prevent clots in conditions where there is a high risk of clot formation and thromboembolism, such as in atrial fibrillation, myocardial infarction, deep vein thrombosis, knee and hip surgery and so on.

Thrombin Inhibitors[1]

Thrombin inhibitors are anticoa gulants that bind to and inhibit the activity of thrombin therefore prevent blood clot formation. Thrombin inhibitors inactivate free thrombin and also the thrombin that is bound to fibrin. Thrombin has many important functions in the clotting pathway, so it is a good target for anticoagulants drugs.

Thrombin inhibitors are used to prevent arterial and venous thrombosis. They can be used to prevent and treat deep vein thrombosis, or used as prophylaxis in atrial fibrillation to avoid thromboembolism.

Antiplatelet Therapy

Aspirin irreversibly inhibits platelet function via the acetylation of cyclo-oxygenase-1. Clopidogrel, a thienopyridine, selectively inhibits adenosine diphosphate-induced platelet aggregation.[2] The effect of

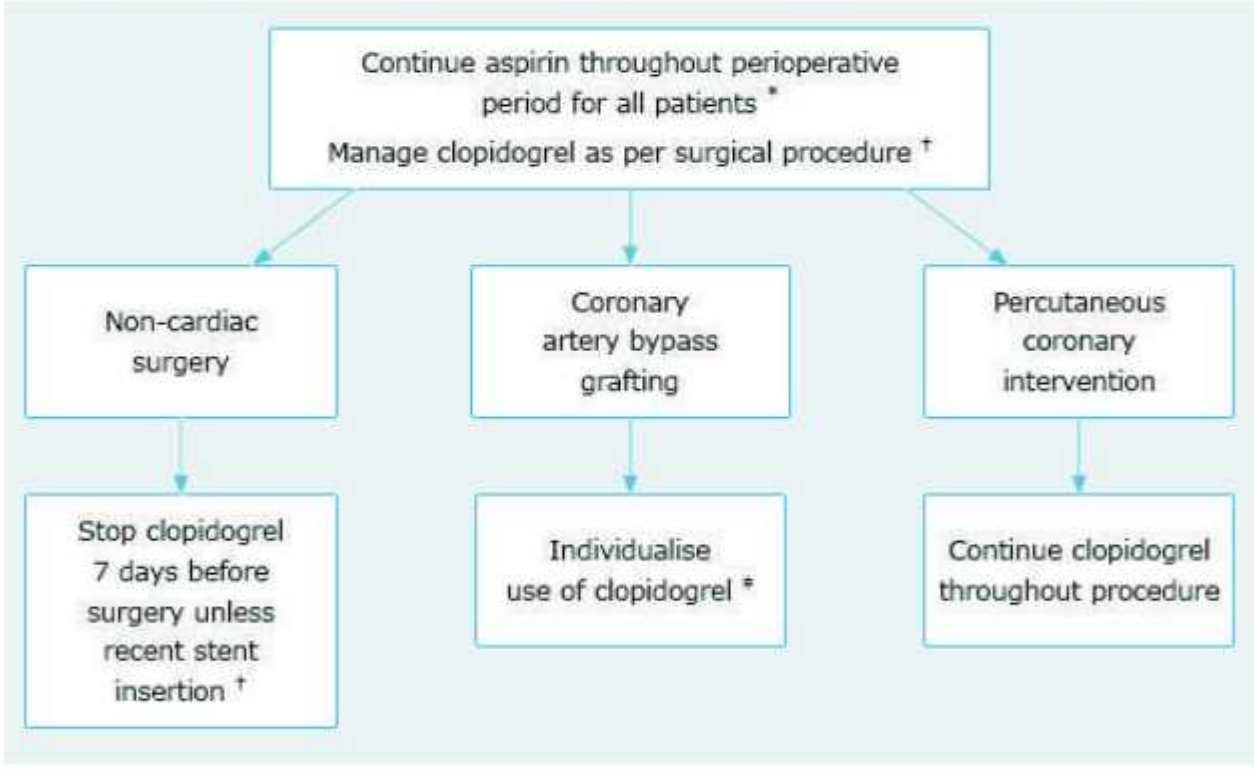
both drugs lasts for the lifespan of the platelet (approximately 7–10 days). Although it seems logical to stop either drug 7–10 days before an elective procedure, platelet function is only one of the many important mechanisms of coagulation necessary for adequate haemostasis. Aspirin can be continued for most procedures but whether or not clopidogrel can be safely continued depends on the risk of recurrent thrombosis versus bleeding.

Risk of perioperative bleeding

1. Antiplatelet drugs

Clinical studies have shown that patients who have taken aspirin preope ratively have an increased risk of postoperative bleeding after cardiac and non-cardiac surgery. Use of aspirin within seven days of coronary artery bypass grafting has been associated with increased blood loss and the need for re-operation, but this does not increase mortality. However, another study showed that aspirin use in the five days before coronary artery bypass grafting was associated with a lower risk of postoperative mortality, without a concomitant increase in re-operation for bleeding or the need for blood transfusion.[3] This applied to a range of aspirin doses, 100 mg to 975 mg daily.

Fig 1:Perioperative management of patients receiving aspirin and/or clopidogrel [2-4]



* Except neurosurgery

† For patients with a bare metal coronary stent requiring surgery within six weeks of insertion, or with a drug-eluting stent requiring surgery within 12 months of stent placement, it is recommended that aspirin and clopidogrel be continued in the perioperative period. Discussion with cardiologist is recommended.

‡ Discussion with cardiologist recommended

It is generally considered safe to continue aspirin throughout the perioperative period, for both cardiac and non-cardiac surgery, unless there is a significant bleeding risk (Fig. 1).

The use of clopidogrel throughout the perioperative period is more controversial. Some studies have shown an increased risk of major bleeding with the use of clopidogrel within five days of coronary artery bypass grafting.[4]

While recognising the increased risk of bleeding complications after coronary artery bypass grafting, some experts recommend a more tailored approach depending on individual risk with respect to ischaemic complications and bleeding.[5]

Patients with coronary stents *in situ* have a high thrombotic risk if antiplatelet drug therapy is interrupted. Elective non-cardiac surgery should therefore be avoided after stent placement when patients are most prone to thrombosis. This is during the first six weeks for bare metal stents, and during the first 12 months for drug-eluting stents.[6] For patients without coronary stents who are not at high risk of cardiac events, clopidogrel can be ceased 5–7 days before surgery. It is often routine clinical practice to consult the patient's cardiologist before stopping the drug.

Clopidogrel should be resumed following the procedure as soon as there is adequate haemostasis, usually the morning after surgery

2. Oral Anticoagulant drugs

The most common indications for oral anticoagulant therapy are atrial fibrillation, the presence of a mechanical heart valve, and venous thromboembolism. Warfarin is the most common oral anticoagulant prescribed for the treatment and prophylaxis of venous or arterial thromboembolism.

The mean half-life of warfarin activity is approximately 40 hours and the anticoagulant effect lasts 2–5 days. For most patients, the therapeutic target for the

Table 1:Patient risk stratification for perioperative arterial or venous thromboembolism[6]

High risk	Any mechanical heart valve
	Atrial fibrillation with $CHADS_2$* score >2 or history of stroke or transient ischaemic attack or rheumatic valvular heart disease
	Recent venous thromboembolism (within 3 months)
	Recurrent venous thromboembolism receiving long-term anticoagulation
Low risk	Atrial fibrillation with $CHADS_2$ score of < 2 and no history of stroke or transient ischaemic attack
	Single venous thromboembolism occurring >3 months ago and with no other risk factors

$CHADS_2$ score for non –valvular atrial fibrillation : **Congestive heart failure (past or current) – 1 point,hypertension – 1 point,**A**ge ⩾ 1 point,**D**iabetes -1 point,**S**troke(ischemic), transient ischemia attack or thromboembolism- 2 points. [Courtesy: Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, et al. The perioperative management of antithrombotic therapy.Chest 2008;133: 299S-399S.]*

international normalised ratio (INR) range is 2.0–3.0. For patients with a mechanical heart valve, the recommended INR range is 2.5–3.5.

When considering how to manage patients on warfarin who require surgery, it is helpful to weigh up the risk of bleeding versus the risk of thromboembolism (Table 1). This requires consideration of:

- indication for anticoagulation
- history of any thrombotic events
- type of surgery and its associated risks of bleeding and thromboembolism, particularly with respect to posto perative venous thromboembolism.

The patient's management is guided by the risk of thromboembolism (Fig. 2). The options include:

- if low risk, stop warfarin five days before surgery (that is, missing four doses before the day of surgery) to allow the INR to drop to less than 1.5, then resume it on the evening of the procedure if there is no evidence of bleeding.
- if high risk, stop warfarin and start heparin (unfractionated heparin infusion or low molecular weight heparin) before and after the surgery, during the period when the INR is below the therapeutic range.This option is referred to as 'bridging' anticoagulation. Heparin is usually started on the third morning after the last dose of warfarin when the INR becomes sub therapeutic.

Stopping Heparin Preoperatively [6,7]

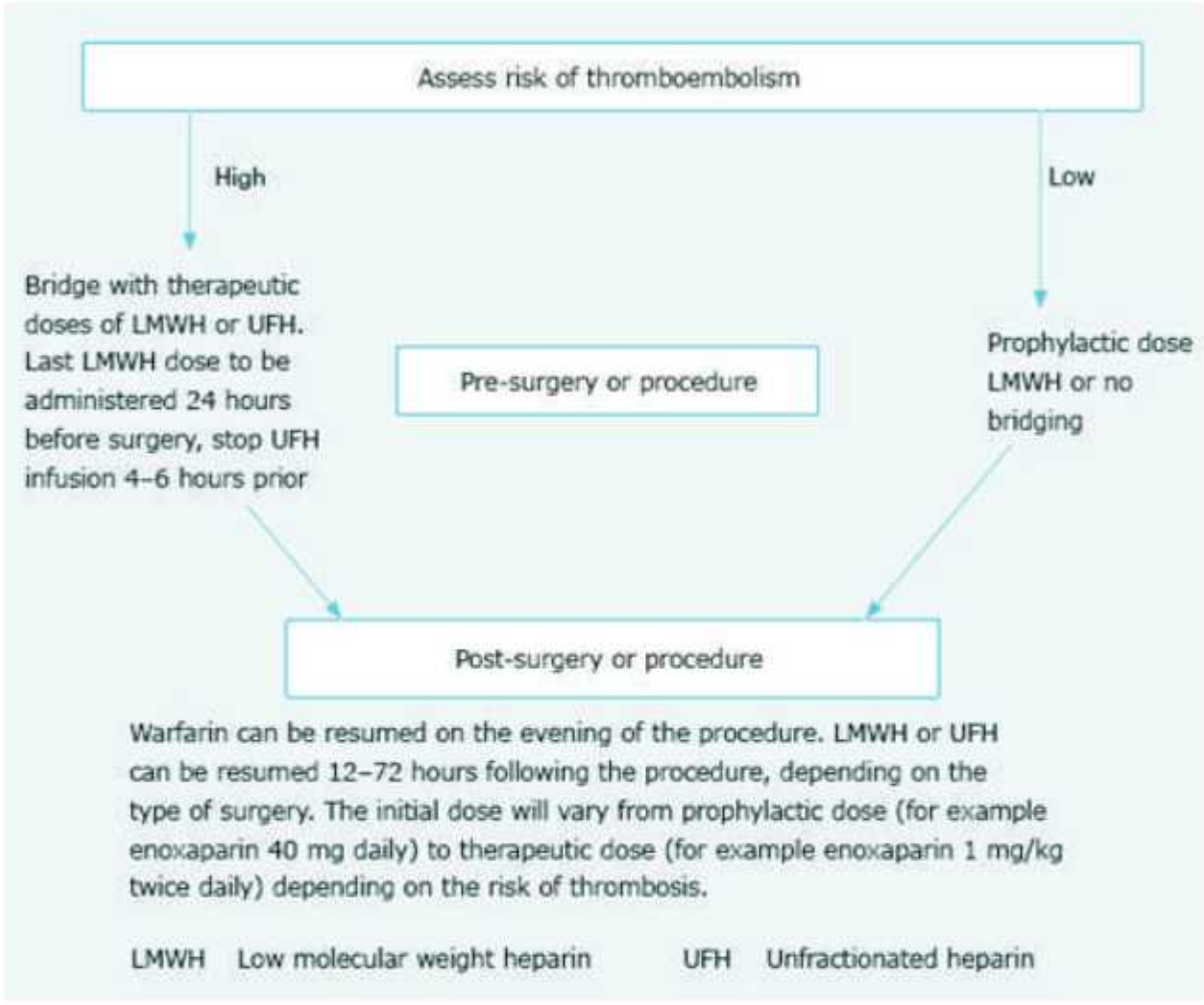
For patients who receive bridging anticoagulation with therapeutic doses of low molecular weight heparin, the last dose should be administered at least 24 hours before the procedure. There is evidence suggesting that there will be a residual anticoagulant effect if low molecular weight heparin is given too close to the time of the procedure. It is recommended that the last preoperative dose be half the usual total daily dose. For unfractionated heparin, it is recommended that the infusion be stopped 4–6 hours before the procedure.

Resuming Heparin Postoperatively [6-10]

The factors that affect the risk of postoperative bleeding include the timing of the anticoagulant dose after surgery, the dose of anticoagulant and the type of surgery along with its associated bleeding risk. The following recommendations take all of these factors into consideration:

- warfarin can be resumed on the evening of the procedure (regardless of whether the procedure is performed in the morning or afternoon), at the usual maintenance dose (no loading dose)
- low molecular weight heparin or unfractionated heparin can be resumed 12–24 hours following the procedure for minor surgery. For major surgery, the first dose should be 24–72 hours post surgery.
- The initial dose will vary from the prophylactic dose (for example, enoxaparin 40 mg daily) to the therapeutic dose (for example, enoxaparin 1 mg/kg twice daily) depending on the risk of thrombosis, and the risk of bleeding. This needs to be individualised for each patient.

Fig 2: **Perioperative management of patients receiving warfarin for atrial fibrillation, venous thromboembolism or mechanical heart valves** [2-4]



Procedures

Dental/Dermatological/Ophthalmologic Procedures

It is usually safe to continue aspirin around the time of the procedure. However, clopidogrel should be stopped 5–7 days before the procedure unless the patient has had a recent stent insertion.

Warfarin can usually be continued in patients having minor dental procedures (single or multiple tooth extraction and root canal procedures), minor dermatological procedures (including excisions of skin lesions) and minor ophthalmological procedures (including cataract extraction). Dentists can consider co-administration of an antifibrinolytic drug such as tranexamic mouth wash.

Other Anticoagulant Drugs

There are an increasing number of patients participating in clinical trials that evaluate the efficacy and safety of other oral anticoagulants such as rivaroxaban and

dabigatran for the treatment and prevention of venous and arterial thrombosis. Rivaroxaban, a direct Factor Xa inhibitor, has a half-life of 4–9 hours. Dabigatran has a longer half-life of 14–17 hours.[11] Bridging anticoagulation with a heparin can be used if indicated. This can be started 24 hours after the last dose of rivaroxaban or dabigatran.

To stop or to continue therapy for the procedures??[6-10]

Ambulatory dental surgery in patients with hemostatic alterations, and who use oral anticoagulant drugs (OAC) has become a constant practice over the last few years, demanding a specific approach by the dentist and interdisciplinary interaction with the various health teams that follow up the patient.[2]

There is discussion on how to perform dental treatment safely in patients on anticoagulants. Some time ago, the American College of Cardiology (ACC) and the American Heart Association (AHA) developed a set of practical guidelines that propose to develop, review, and update protocols for cardiovascular diseases and assist with clinical procedures. Some protocols suggest stopping use of the drug, in addition to the administration of vitamin K or heparin before procedures with potential for hemorrhage. However, these alterations may increase the chance of an episode of thromboembolism in patients.[12,13]

None of these schemes is risk-free, which makes it imperative to carry out a complete evaluation of the patient's systemic condition, follow up of his/her degree of anticoagulation, and classification of the amplitude of surgical trauma involved in the dental procedure to be performed.

Protocols have been researched to guarantee a treatment that prevents the occurrence of hemorrhages, and at the same time, not expose the patient to the risk of thromboembolism. Interrupting anticoagulant therapy, thereby exposing the patient to an unnecessary risk of thromboembolism, is not a cautious attitude. Many authors have demonstrated that it is safe to perform the majority of dental surgical procedures without risk of severe hemorrhages when the International Normalized Index (INR) is within the therapeutic levels.[14]

Patients who use OAC have their therapy monitored by measuring the Prothrombin Time (PT). This test measures the time for clot formation from VII factor activation to fibrin coagulum formation. Due to variations in the methodology, reagents, and instruments used in each laboratory, a normalization ratio was established for PT measurements (INR).[15] There is increased risk of thromboembolic events when the INR is below the therapeutic level; when it is above, the risk of hemorrhages increases dramatically, particularly in the elderly.[16,17]

Based on the facts set forth, a proposal was made to evaluate the quantity and severity of hemorrhagic episodes after tooth extraction in patients on anticoagulant medications and who have been under medical and dental treatment at the Hemotherapy and Hematology Center (HEMOCENTRO) of the State University of Campinas, SP, Brazil (UNICAMP) for an uninterrupted period of 48 months. In patients who make continuous use of oral anticoagulant drugs, it is imperative to carry out careful anamnesis, as well as a

multiprofessional clinical evaluation with regard to the risk and control of hemorrhagic or thromboembolic episodes.[18]

It is imperative to have the patient's degree of anticoagulation under medical control, and it must be checked periodically to verify whether the necessary hemostatic therapeutic level is being maintained. For this purpose, the prothrombin time is used, the result of which may be expressed in seconds, in prothrombin activity or in INR, which must be performed in a maximum interval of 4 weeks, as recommended by the American College of Chest Physicians.[14] Generally speaking, the therapeutic interval of INR should remain between 2.0 and 3.5, but depending on the type of disease presented by the patient, higher INR values are considered therapeutic.[16-18]

Lippert and Gutschik[19] published recommendations in which the INR should not be higher than 4.0, and preferably lower than 3.0, before the patient on an anticoagulant is submitted to dental procedures with high risk of bleeding.

The recommendations of some authors for various dental surgical procedures indicate that for simple extractions, or when minimal bleeding is expected, an INR lower than 4.0 is acceptable. For cases of moderate bleeding, included and impacted third molar surgeries or multiple extractions, the INR should be reduced; in cases where greater hemorrhage is expected, an INR lower than 3.0 is indicated; and when the INR is over 5.0, no surgeries should be performed.[16,17]

Elderly patients are among those who most benefit from anticoagulant treatment; however, they are also among those with the greatest risk of hemorrhagic complications.[20-22] We can emphasize that the patient was elderly (72 years of age) which corroborates the literature stating that they are the patients most susceptible to hemorrhages.

Many authors are sufficiently concerned to point out the necessity of using an atraumatic surgical technique and the application of local conventional measures to control hemostasis, in which the adequate suture is extremely important.[20-22]

Maintenance of the anticoagulant medication has been recommended by an increasing number of researches, which observed a minimal incidence of hemorrhagic episodes after surgeries, in which the patients' values in PT and/or in INR were within the therapeutic indexes.[20-31] This protocol has been even further reinforced by authors who emphasize the use of local hemostatics, affirming their efficiency in the prevention and control of postoperative hemorrhages.[23,24] These guidelines are also recommended by the British Committee for Standards in Hematology, which states the risk of bleeding in these patients when maintaining the INR between 2 and 4 is low for dental surgeries, and that the interruption of anticoagulant therapy would not be justified due to the increase in the risk of thrombosis.

It is imperative to evaluate the risks of transoperative and postoperative hemorrhage, as well as the amount of surgical trauma to which this patient would be subjected in order to establish an adequate attendance protocol. Therefore, we point out that performing a surgical procedure with the least amount of trauma possible, strict observance of all the steps of the surgical procedure, including

adequate suturing, and the patient's compliance with the postoperative recommendations must be primordial factors to consider at all times in all patients, and especially in those on anticoagulant medications.

Conclusion

Controversy has always surrounded the correct management of patients therapeutically anticoagulated with warfarin who require dental extractions. The risk of bleeding must be weighed up against the risk of thromboembolism when deciding whether to interfere with a patient's warfarin regimen. An improved understanding of the importance of fibrinolytic mechanisms in the oral cavity has resulted in the development of various local measures to enable these patients to be treated on an outpatient basis.

Extractions in patients on oral anticoagulants must be performed in the least traumatic manner possible. It is not necessary to stop anticoagulant therapy to perform extractions. Local hemostatic techniques such as obliterative sutures alone are sufficient. In reviewing the available literature, there are no well-documented cases of serious bleeding problems from dental surgery in patients receiving therapeutic levels of continuous warfarin sodium therapy, but there were several documented cases of serious embolic complications in patients whose warfarin therapy was withdrawn for dental treatment.

Many authorities state that dental extractions can be performed with minimal risk in patients who are at or above therapeutic levels of anticoagulation. There are sound legal reasons to continue therapeutic levels of warfarin for dental treatment. Although there is a theoretical risk of hemorrhage after dental surgery in patients who are at therapeutic levels of anticoagulation, the risk appears to be minimal, the bleeding usually can be easily treated with local measures, and this risk may be greatly outweighed by the risk of thromboembolism after withdrawal of anticoagulant therapy.

For minor procedures, antiplatelet and oral anticoagulant drugs can usually be continued. For other elective cardiac and non-cardiac surgery, aspirin can be continued during the perioperative period. Clopidogrel should usually be withheld for non-cardiac surgery unless the patient is at high risk of cardiac events, and in this case the management should be individualised and discussed with a cardiologist. Warfarin and other oral anticoagulants should be stopped according to their half-lives and bridging anticoagulation with a heparin introduced as indicated.

The perioperative management of patients taking oral anticoagulant or antiplatelet drugs for primary or secondary prevention of arterial or venous thrombosis is a common and important problem. One must balance the risks of primary or recurrent thromboembolism if these drugs are stopped, against the risk of bleeding if these drugs are continued.

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HOST MODULATION THERAPY TO RESTRICT PERIODONTAL DESTRUCTION

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Abstract

Bacterial biofilms have been shown to be the primary aetiological factor in the initiation of gingival inflammation and subsequent destruction of periodontal tissues. But this is not sufficient to explain disease initiation and progression. The major component of destruction associated with periodontal disease is the result of activation of the host's immuno-inflammatory response to the bacterial challenge. The present topic highlights various host modulation therapeutic agents and ongoing development of pharmacotherapies that specially target host response mechanism.

Key words: bacterial challenge, host modulation, periodontitis

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Introduction

Periodontitis is a health concern for centuries and are the most important causes of pain, discomfort, and tooth loss in adults.[1] Bacterial biofilms have been shown to be the primary aetiological factor in the initiation of gingival inflammation and subsequent destruction of periodontal tissues. Although chronic bacterial and endotoxin exposure is a prerequisite for gingival inflammation and periodontal tissue destruction to occur, its presence alone accounts for a relatively small proportion (i.e. 20%) of the variance in disease expression.

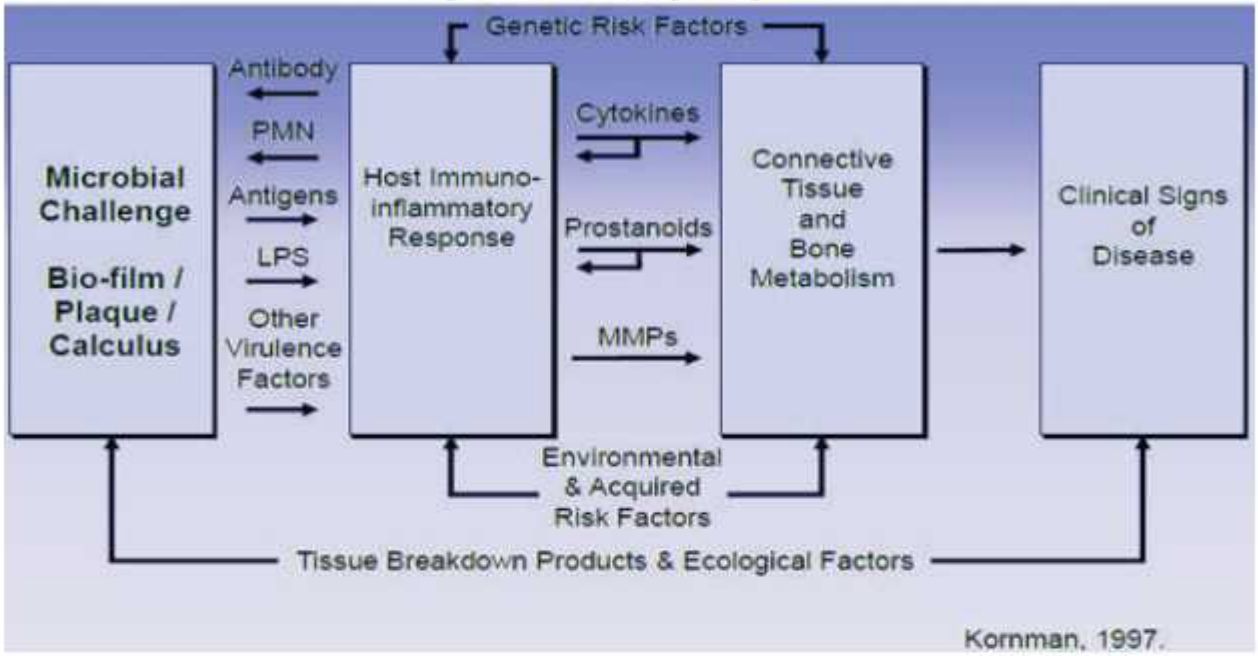
According to a novel model of pathogenesis, this is not sufficient to explain disease initiation and progression. The major component of soft- and hard tissue destruction associated with periodontal disease is the result of activation of the host's immuno-inflammatory response to the bacterial challenge.[2]

It seems hard to believe that the same host response factors are responsible both for the defence, as well as the appearance of the disease. The present topic highlights various host modulation therapeutic agents and ongoing development of safe and effective pharmacotherapies that specially target host response mechanism.

Introduction of such pharmo cotherapies as an adjunct to the traditional periodontal therapies represent a 'new integrated approach' in long-term treatment and management of Periodontitis. The future holds much promise for the host modulation as an important tool not only for the management of Periodontitis, but also for the clinical practice of periodontal medicine.[3]

Host response in the periodontium is the defense mechanisms in periodontal tissues against bacterial infections.

Fig 1: Periodontal pathogenesis



Definition and rationale

HOST RESPONSE MODULATION (HOST MODULATION-HMT)

Host Modulation is a treatment concept that aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or down regulating destructive aspects of the host response and up regulating protective or regenerative responses.

The concept of host modulation was first introduced to dentistry by Williams in 1990 and Golub *et al*. in 1992 and later on expanded by many researchers. The rationale behind this approach is to aid the host in its fight against infectious agents by supplementing the natural inherent defense mechanisms or to modify its response by changing the course of inflammatory systems. Compared to other weapons against infection, host response modulation potentially has fewer side-effects, is not invasive, and does not require complicated application methods.

Periodontal pathogenesis

The diagram (Fig 1) makes it clear that direct bacterial destruction of bone and connective tissue is not a primary component of disease, thereby emphasizing the critical role of the host response. The microbial challenge presented by subgingival plaque results in an upregulated host immune-inflammatory response in the periodontal tissues that is characterized by the excessive production of inflammatory cytokines (e.g. IL, TNF-α), prostanoids (e.g. PGE2) and enzymes [including the matrix metallo proteinases (MMPs)]. These proinflammatory mediators are responsible for the majority of periodontal breakdown that occurs, leading to the clinical signs and symptoms of disease Acquired and environmental risk factors, such as diabetes mellitus, cigarette smoking and

stress, as well as genetically transmitted traits, such as interleukin-1 (IL-1) gene polymorphisms, may accentuate the host inflammatory response to the bacterial challenge and, eventually, the susceptibility to the disease.[4,5]

Perhaps more important than the levels of any single inflammatory mediator in the periodontal tissues is the relative balance between pro-inflammatory and anti-inflammatory cytokines and enzymes. Thus, pro-inflammatory mediators, such as prostaglandins and many cytokines, are balanced by anti-inflammatory cytokines and lipoxins. The destructive activities of MMPs are balanced by their inhibitors, the tissue inhibitors of metalloproteinases. Imbalances between pro-inflammatory and anti-inflammatory activities in the periodontal tissues are a major determinant of periodontal destruction.

The purpose of host modulatory therapy is to restore balance between, on the one hand, pro-inflammatory mediators and destructive enzymes, and, on the other hand, anti-inflammatory mediators and enzyme inhibitors.Host modulation therapy options include-systemic administration and local delivery.

A. Systemically administered HMT agents

Systemically administered HMT agents can be broadly divided into those agents which modulate the immune response, those which modulate arachidonic acid metabolites, those which modulate nitric oxide synthase activity, those which modulate bone remodelling , those which modulate the cell signalling pathways, and other agents .

1. Modulation of immune response

- **Pro-inflammatory cytokine inhibition**

Based upon the increased expression of IL-1 and TNF in inflamed gingiva and GCF of periodontitis patients, several studies have suggested that increased production of these cytokines may play an important role in periodontal tissue destruction.[6] To counteract tissue destruction and maintain homeostasis, cytokine antagonists such as IL-1 receptor antagonist (IL-1Ra) or soluble TNF receptors can competitively inhibit receptor-mediated signal transduction.[7,8]

Pentoxifylline(PTX), a methylxanthine derivative, specially blocks the synthesis of TNF-α, among other cytokines, by inhibiting gene transcription, thereby reducing the accumulation of TNF-α mRNA. The protective effect of PTX could be explained by its capacity to inhibit the production of inflammatory cytokines or to stimulate anti-inflammatory cytokine production.[9]

Some examples of TNF-α antagonists are: infliximab, etanercept, natalizumab, adalimumab. IL-1receptor antagonists include- anakinara.

- **Modulation of MMP Activity**

Matrix metalloproteinases encompass a family of zinc- and calcium-dependent endopeptidases secreted or released by a variety of host cells that function at neutral pH and utilize the various constituents of extracellular matrix as their substrates.The major Antiproteinase used in periodontal treatment is tetracycline (TC).

Sub antimicrobial dose doxycycline (SDD) is at present, the only systemic host response

modulator specifically indicated as an adjunctive treatment for periodontitis. Doxycycline Hyclate (**Periostat**) is available as 20-mg capsule, prescribed twice daily for a period of 3 to 9 months.

Effects of doxycycline as HMT agent (adapted from Golub etal):

1. Direct inhibition of active MMPs by cation chelation (dependent on Ca^{2+} and Zn^{2+} binding properties)
2. Inhibits oxidative activation of latent MMPs (independent of cation-binding properties)
3. Down regulates expression of key inflammatory cytokines (IL-1, IL-6, TNF-α, PGE2)
4. Scavenges and inhibits production of reactive oxygen species produced by neutrophils
5. Inhibits MMPs and reactive oxygen species thereby protecting α1-proteinase inhibitor, and thus indirectly reducing tissue proteinase activity
6. Stimulates fibroblast collagen production
7. Reduces osteoclast activity and bone resorption
8. Inhibits osteoclast MMP

Limitation of SDD

Normal homeostasis of collagen metabolism may get affected.

2. Modulation of arachidonic acid (AA) metabolites

AA is a 20-carbon polyunsaturated fatty acid (eicosanoid) liberated from membrane phospholipids by the action of phospholipase A2. Free AA is metabolized via either the cyclooxygenase (COX) or the Lipo oxygenase pathways. AA is enzymatically oxidized by either COX to form unstable cycloendo peroxide intermediates (PGG2 and PGH2) leading to prostanoid synthesis (prostaglandins, prostacyclin and thromboxane) or by the action of LO to form the LTs and other monohydroxy-eicosatetraenoic acids. [2] NSAIDS and pro resolving lipid mediators belong to this category.

Prostaglandin E2 is a key inflammatory mediator in periodontal disease as it upregulates osteoclastic bone resorption and prostaglandin E2 levels are significantly increased in the tissue and gingival crevicular fluid of patients with periodontal disease compared to healthy controls.

Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandins by blocking the cyclo-oxygenase pathway of arachidonic acid metabolism.[10]

Disadvantages of NSAIDS

- GIT upset
- Gastrointestinal hemorrhage (due to decreased platelet aggregation)
- Renal& Hepatic impairment

Rebound phenomenon- once patients cease taking NSAIDs, a return to, or even acceleration of, the rate of bone loss seen prior to drug therapy occurs.

Proresolving lipid mediators are derived mainly from neutrophils nad macrophages which include – lipoxin, resolvin, protectin and maresin(Table 1).

Table 1: pro resolving lipid mediators

LIPOXIN Omega-6 fatty acid Derived from neutrophil	• limits PMN recruitment, chemotaxis, and adhesion to the site of inflammation. • Induce neutrophil apoptosis • Enhance monocyte/ macrophage clearance of apoptotic neutrophils • Monocyte- phlogistic to non phlogistic
RESOLVIN (Resolution-phase nteraction products) Omega-3 fatty acid Derived from neutrophil	• Stop PMN infiltration and transmigration • Reduce cytokine expression on microglia cells
PROTECTIN Omega-3 fatty acid Derived from neutrophil	• stop PMN infiltration • reduce cytokine expression and • Improved wound healing in mouse models.
MARESIN Omega-3 fatty acid Derived from macrophages	• Macrophage mediated resolution of inflammation • Potent up regulation of efferocytosis

1. Modulation of Nitric Oxide Synthase (NOS) activity

NO is a short lived molecule involved in host defence that can be toxic when present at high levels & has been implicated in a variety of inflammatory conditions. Produced from L-Arginine by a family of iso–enzymes called NO synthases. Inducible NO synthase (iNOS) is generated for longer periods by cells in immune system. Cytokines and other bacterial products stimulate the expression of iNOS and interferes with periodontal disease progression. Eg: tetracyclines.

A. Modulation of bone remodelling

- **Anti-inflammatory agents**

Arachadonic acid metabolites are pro-inflammatory mediators that have been implicated in a variety of bone resorptive processes including chronic periodontitis. These mediators can be inhibited by a variety of NSAIDS.

- **Bisphosphonates**

Bisphosphonates are bone sparing agents with a chemical structure related to pyrophosphate. 1st Generation (alkyl side chains) –Etidronate. 2nd Generation (amino terminal group)- Alendronate & pamidronate. 3rd Generation (cyclic side chains) - Risedronate.

The antiresorptive properties of bisphosphonates change according to their side chains& their potency increases from first to third generation. Activities of Bisphosphonates on Osteoclast Function can be seen at tissue level , cellular level and molecular level.

At tissue level –

1. ↓ bone turnover due to ↓ bone resorption
2. ↓ number of new bone multicellular units
3. Net positive whole body bone balance

At cellular level-

1. ↓ osteoclast recruitment
2. ↑ osteoclast apoptosis

3. ↓ osteoclast adhesion
4. ↓ depth of resorption site
5. ↓ release of cytokines by macrophages
6. ↑ osteoblast differentiation &number

At molecular level-

1. Inhibit mevalonate pathway(can result in perturbated cell activity and induction of apoptosis)
2. ↓ post-translational prenylation of GTP-binding proteins.

Side effects:

1. GI upset
2. Esophageal ulcerations
3. Bisphosphonate induced osteonecrosis

At the present time, there are no bisphos phonate drugs that are approved and indicated for use as adjuncts in the treatment of periodontal disease.

- ***RANK/RANKL/OPG axis***

Inhibition of RANKL function with OPG significantly reduced the number of osteoclasts and alveolar bone destruction.

- **Chemically modified tetracyclines**

Golub et al. described first chemically modified tetracycline (4-dedimethylamino tetracycline CMT-1), which is devoid of antibacterial activity due to the removal of the dimethylamino group from the carbon-4 position of the "A" ring of the drug molecule, but which retains anticollagenase activity.

A series of 10 different chemically modified tetracyclines have since been identified.So far CMTs have not received FDA approval for human studies.

- **Hormone replacement therapy for post menopausal women**

Estrogen deficiency is associated with large increase in bone resorption, with osteoclast formation and activity and reduced osteoclast apoptosis. Treatment with estrogens clearly inhibit bone loss as well as bone turnover and increase bone mineral density. The discovery of the agents able to exert full or partial estrogen effects on various tissues led to the development of a new class of drug known as Selective Estrogen Receptor Modulators-SERMs.The mechanism by without SERMs inhibit bone resorption is likely to be the same as estrogens mechanism, by blocking production of cytokines that promote osteoclast differentiation and by promoting osteoclast apoptosis.

5. Modulation of cell signalling pathways in periodontal disease

In periodontal disease the most important pathways include (Mitogen activated Protein Kinase) MAPK pathway, (Nuclear Factor kappa B) NFkB pathway. Studies have shown that inhibition of these signalling pathways can lead to reduction in the synthesis of pro-inflammatory cytokines.

6. Other host modulatory therapies

Probiotics have demonstrated significant potential as therapeutic options for a variety of disease as they have been known to modulate cytokine secretion profiles, influence T-lymphocyte populations, protect against physiologic stress, and enhance intestinal epithelial cell function and antibody secretion.

Periodontal vaccines: George Hajishengallis reported that toll like receptors (TLRs)

may offer novel targets for host-modulation therapy in periodontitis since manipulation of TLR signalling may contribute to control of infection or regulation of inflammation and, moreover, synthetic or natural TLR agonists could serve as novel periodontal vaccine adjuvants. *Yokoyama et al. in 2007* also demonstrated that egg yolk antibody against *Porphyromonas gingivalis* (IgY-GP) proved to be an effective immunotherapeutic agent in the treatment of periodontitis. Similarly, Choi *et al*. reported that prior immunization of mice to *Fusobacterium nucleatum* modulated the host immune responses to *Porphyromonas gingivalis* at the humoral, cellular and molecular level.

Nutrients which include major extracellular antioxidants, like vitamin C, vitamin E, carotenoids, reduced glutathione and omega 3 fatty acids can also act as modulators of inflammation by scavenging free radicals as they are formed, sequestering transition metal ions and catalyzing formation of other molecules. Studies have also demonstrated that cranberry juice contains molecules (A-type cranberry proantho-cyanidins: AC-PACs) that inhibit MMPs, interleukin-6, interleukin-8, and prostaglandin E production by lipopolysa-ccharide-activated gingival fibroblasts and hence show potential of being used as a novel host-modulating agent to inhibit tissue destruction during periodontitis.

B. Locally administered HMT agents

In addition, a number of local host modulatory agents have been investigated in clinical trials for their potential use as adjuncts to surgical procedures, not only to improve on wound healing but also to stimulate regeneration of lost bone, periodontal ligament, and cementum, restoring the complete periodontal attachment apparatus.

- ***Enamel matrix proteins***

It is believed that during development of root and attachment apparatus, there is a secretory phase in which Hertwig's epithelial root sheaths secretes enamel-related matrix proteins.Enamel matrix derivative is now commercially available for the treatment of periodontal defects as Emdogain ® (Biora AB, Malmφ, Sweden) which has received FDA approval. The basic rationale behind using Emdogain is that it will act as a tissue-healing modulator that would mimic the events that occur during root development and help stimulate periodontal regeneration. Enamel matrix proteins (EMD) initiates periodontal regeneration through recruitment of cementoblasts to the root-surface and stimulates these to form root-cementum, which will thereafter secondarily lead to regeneration of periodontal fibers and alveolar bone.The above mentioned actions of EMD justify its role as a host modulating agent.

- ***Bone morphogenetic protein***

It guides modulation and differen tiation of mesenchymal cells into bone and bone marrow cells. Absorbable collagen sponge (ACS) containing recombinant human BMP-2 has been approved for clinical use in certain oral surgery procedures, including localized alveolar ridge augmentation, under the name INFUSE® Bone Graft (Medtronic, Minneapolis, MN, USA) and InductOS™ (Wyeth, Maidenhead, UK). These ACS release the protein over time in the location where it is implanted and provides a scaffold on which new bone can grow. As the graft site

heals, the ACS is absorbed and replaced by bone.

- ***Platelet derived growth factor***

FDA has approved Growth-factor Enhanced Matrix, GEM 21S ® (Osteohealth, Shirley, NY) which is a combination of a bioactive highly purified recombinant human PDGF-BB with an osteoconductive bone matrix. Platelet derived growth factor (PDGF), as a host modulating agent can increase chemotaxis of neutrophils and monocytes, stimulate fibroblasts proliferation and extracellular matrix synthesis, increase proliferation and differentiation of endothelial cells, stimulate proliferation of mesenchymal progenitor cells and differentiation of fibroblasts.

- ***Bisphosphonates***

Role and action of BPs have already being discussed above. Due to serious side-effects of systemically administered BPs leading to osteonecrosis of the jaws (ONJ) additional studies using topically administered bisphosphonates have been carried out which have reported a significant increase in the postoperative percentage of bone-defect fill, prevention of bone resorption as well as the boosting effect of locally delivered BPs on the osteoconductive and regenerative potential of bone grafts used in periodontal therapy.

- ***NSAIDs***

Role of NSAIDs as a host-modulating agent has also been discussed above. Since NSAIDs are lipophilic and are well absorbed into gingival tissues, its topical application is possible. NSAIDs that have been evaluated for topical administration include ketorolac tromethamine rinse and S-ketoprofen dentifrice, piroxicam and meclofenamic acid in inhibiting gingivitis and progression of periodontitis.

- ***Hypochlorous Acid and Taurine-N-Monochloramine***

It has been reported that hypochlorous acid (HOCl) and taurine-N-monochloramine (TauCl) which are the end-products of the neutrophilic respiratory burst, modulate the host inflammatory response by inhibiting the production of interleukin-6, prostaglandins, and other proinflammatory substances. Thus, HOCl and TauCl, playing a crucial role in the periodontal inflammatory process offer opportunities for the development of novel host-modulating therapies for the treatment of periodontitis.

- ***Cimetidine***

Cimetidine is a powerful H2-(Histamine) receptor antagonist, and hence eliminates histamine's inhibitory effects on immune response, thereby acting as a modulator of inflammation and immunity by inhibiting neutrophil chemotaxis and superoxide production, increasing cyclic adenosine monophosphate (cAMP) levels and down-regulating cytokines.

Conclusion

The adjunctive use of host modulatory therapy can enhance therapeutic responses, slow the progression of the disease, and allow for more predictable management of patients, particularly in those patients at increased risk caused by factors beyond the reach of conventional therapeutic approaches. The field of "perioceutics", or the use of pharmacological agents specifically

developed to better manage periodontitis, is emerging to aid in the management of these susceptible patients who develop periodontal disease. Host modulatory therapy, which can be used to bring down excessive levels of enzymes, cytokines, and prostanoids as well as modulate osteoclast function, is the key to addressing many of these risk factors that have adverse effects on the host response.[11]

Although, innumerable therapies are beginning to surface, a handful of these have true potential in clinical practice. We have ahead of us a Herculean task of identifying those strategies with the promise of clinical applicability and developing them to better suit all patients.

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AWARDS AND ACHIEVEMENTS

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