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A Review On Chlorhexidine In Periodontal Therapy

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ABSTRACT

Plaque is the main etiological factor for periodontal diseases. In order to prevent occurrence and progression of periodontal disease, removal of plaque becomes important. Mechanical tooth cleaning aids such as toothbrushes, dental floss, interdental brushes are used for removal of plaque. However, in some cases, chemical agents are used as an adjunct to mechanical methods to facilitate plaque control and prevent gingivitis. Chlorhexidine (CHX) mouthwash is the most commonly used and is considered as gold standard chemical agent.It is available in different formulations. Thus, the aim of the article is to provide a thorough review regarding the characteristics, the applications and problems associated with the use of chlorhexidine in periodontics.

Key words: Plaque, periodontal disease, chemical plaque control, antiseptic, antimicrobial, chlorhexidine (CHX).

I.Introduction

The prevention of dental caries and periodontal diseases is targeted at the control of dental plaque. The effectiveness of mechanical plaque control is influenced by individual's manual ability and motivation. Because of the difficulty to ensure adequate removal of plaque by mechanical means, there is a great interest in the use of chemical plaque control agents as adjunct to mechanical approach.[1]

Chlorhexidine is a second-generation chemical plaque control agent which is the most studied and effective antimicrobial in oral use. It is a gold standard against which other antiplaque agents are measured. It is effective against Gram positive and negative bacteria as well as against facultative aerobes and anaerobes. It is primarily used as an antibacterial mouthwash that has been shown to significantly reduce plaque gingival inflammation, plaque and gingival bleeding indices.[2]

II.History[3]

Chlorhexidine was first discovered by the Imperial Chemical Industries Limited (Manchester UK) in 1950. Davis *et al.,* in 1954 found out that a biguanide with a chemical structure 1,6 bis-4 chloro-phenyldiguanidohexane had the greatest bacteriostatic and bactericidal properties. In 1957, Chlorhexidine gluconate was first commercially introduced in the United Kingdom as a disinfectant and topical anaesthetic. In the United States, it was first introduced in the 1970's as a disinfectant and topical antiseptic. Plaque inhibition was first investigated by Schroder in 1969. Loe and Schiott in 1970 performed the definitive study to demonstrate the anti-plaque property of CHX. The first study evaluating application of CHX mouthrinse with toothbrushing was carried out by Flotra*et al.,* 1972 in a group of soldiers. Since

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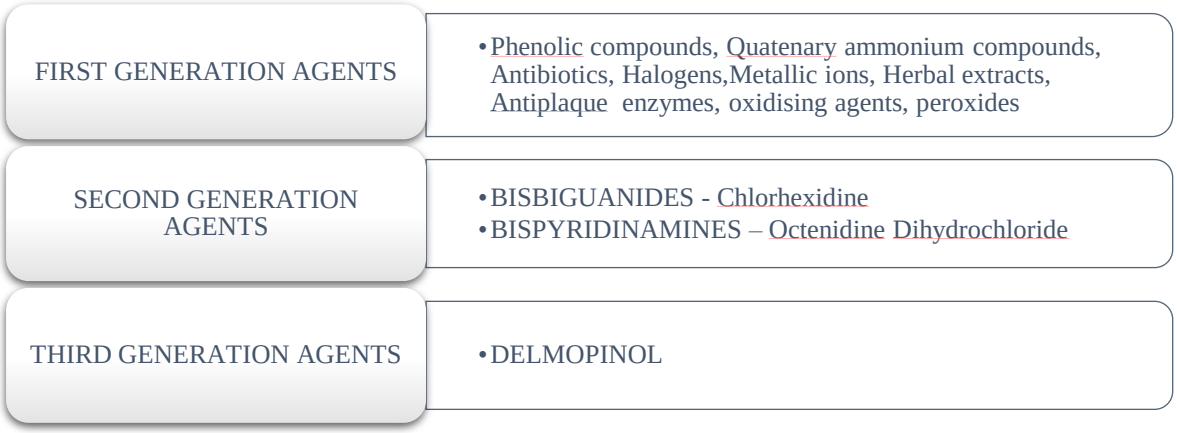
then,numerous studies have been done on CHX which have proved its antiplaque and anti-gingivitis efficiency.

III.Generations of Chemical Plaque Control Agents

Kornman in 1986[3]



IV.Chemical Structure

Structurally, CHX molecule is an amphipathic molecule with both hydrophobic and hydrophilic groups. It is cationic at physiological pH. CHX is made up of two symmetrical chlorophenol rings and two biguanide groups, united by a central hydrophobic hexamethylene chain. In majority of mouth rinses, gels and varnishes digluconate salt is used because it is the most water and alcohol soluble. Because of its highly cationic nature, it is difficult to formulate it as dentifrices due to risk of inactivation of CHX molecule with other anionic ingredients.[2]

V.Characteristics

Chlorhexidine is an antimicrobial agent, Strong base and dicationic at pH levels above 3.5, with two positive charges. It prevents plaque accumulation, hence used as antiplaque and anti-gingivitis agent.[4] It can be bacteriostatic (0.02-0.06) or bactericidal (0.2-0.12) depending on the dose. The success of Chlorhexidine is due to the following characteristics:

Efficacy: Chlorhexidine is bactericidal against gram-positive and gram-negative bacteria and yeasts (such as those responsible for oral candidiasis).

Substantivity: Chlorhexidine binds with hard and soft tissues in the oral cavity and is slowly released over time in a concentration that is bactericidal. It depends on various factors such as concentration, pH, temperature and time of contact of the solution with oral structures.[5] The superior antiplaque effect of Chlorhexidine which makes it gold standard can be attributed to its substantivity.

Safety: Chlorhexidine seems to have a very low level of toxicity and shows no permanent retention in the body.

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VI.Mechanism of Action[6]

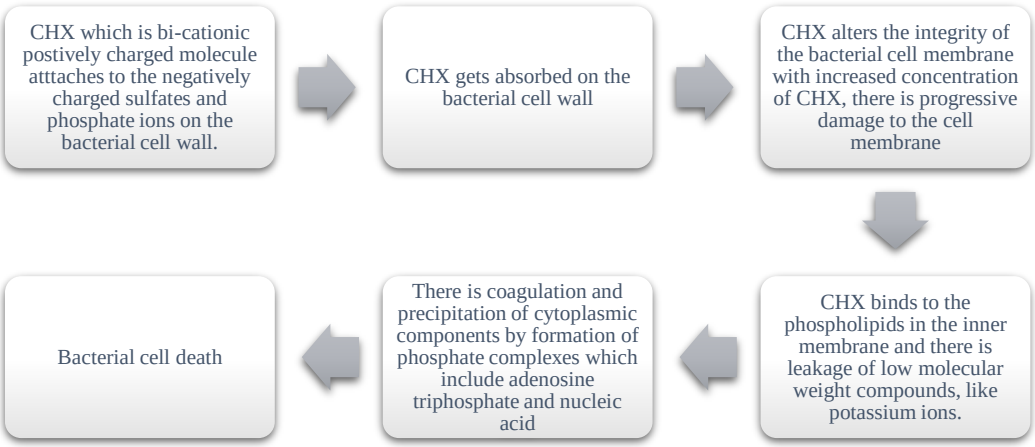

Fig 1: Mechanism of Action of CHX[3]

Pin cushion effect one charged end of the chlorhexidine (di-cationic) molecule binds to the tooth surface whereas the other remains available to initiate the interaction with the bacterial membrane as the microorganisms approaches the tooth surface.This prolongs chlorhexidine action.

VII.Spectrumof Activity[7]

The wide spectrum of activity encompasses gram-positive bacteria, gram-negative bacteria, yeasts and some lipophilic viruses.

VIII.Antiplaque Action of CHX

Rolla and Melsen[8] postulated that the desorbed CHX inhibited the plaque formation in the following ways: An influence on pellicle formation by blocking the acidic groups on the salivary glycoprotein, thus reducing the protein adsorption on the tooth surface, an influence on the adsorption of plaque onto the tooth surface by binding to the bacteria in sub-lethal

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amounts and an influence on the formation of plaque by precipitating the agglutination factors in saliva and displacing calcium from the plaque matrix.

IX.Synergistic effect of CHX with other agents

CHX with fluorine or thymol in varnish has shown to increase the anti-caries activity of varnish.[9]CHX with copper (Cu^{2+}) has been shown to be synergistic in inhibition of growth of *Streptococcus mutans, Actinomycesviscosus* and *Actinomycesnaeslundii.*[10]Low concentration CHX with copper (Cu^{2+}) in rinse reduces caries as well as development of gingivitis.CHX with Zn ions - 3to 30fold inhibition of *Porphyromonasgingivalis.*[11]

X.Various effects of CHX[1]

Several studies were carried out to assess the effects of Chlorhexidine on different cells. A study done by Astoe-Jorgensen *et al.,* (1974) reflected the damage done by CHX on fibroblasts which lead to delay in wound healing. The cytotoxic effect of CHX on epithelial and red blood cells was studied by Heyden and Rolla in 1977. Membrane damage to neutrophils and macrophages due to CHX results in the release of intercellular enzyme (Page and Schroeder 1981; Wilton 1982). The brief contact between CHX and epithelial cells or fibroblasts causes cell injury and/or cell death. The cytotoxic effects of CHX on fibroblasts, osteoblasts were also established (Goldschmidt and Taubman 1977; Cristina Trigo Cabral *et al.,* 2007; Flemingston*et al.,* 2008). The severe toxic effects on gingival fibroblasts and negative effect on wound healing by CHX was studied by Angelo Mariorri*et al.,* (1999).

XI.CHX delivery systems

The CHX formulations are available in various formulations such as mouth rinses, gels, sprays, toothpastes and chewing gums.

Mouthrinses: Chlorhexidine mouth rinses are available in the form of 0.2% and 0.12%. There is equal efficacy for 0.2%and 0.12% rinses when used at appropriate similar doses. The time of rinsing is 30 or 60 seconds depending on the adsorption rate of antiseptics to the oral surfaces (50% of chlorhexidine binds to receptors within 15 seconds) but this does vary from individual to individual. After rinsing with 10 ml of 0.2% aqueous solution of chlorhexidine for 1 min, approximately 30% of the drug is retained back in the oral cavity. After single rinse with chlorhexidine, the saliva itself exhibits antibacterial activity for up to 5 hrs, whereas persistence at the oral mucosal surfaces has been shown to suppress salivary bacterial counts for over 12 hours. In this regard, the dicationic nature of chlorhexidine must play a part; it can beenvisaged as one charged end of chlorhexidine molecule binding to the tooth surface and theother remaining available to interact with bacterial membrane as microorganism approaches the tooth surface, a pin cushion effect.The ideal regimen is twice daily (morning and night) which will have a substantivity for 12 hours. The addition of fluoride to chlorhexidine is considered questionable. The concentration of 0.06% and sodium fluoride 0.2% and 0.055% of stannous fluoride was considered compatible with fluoride.

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Thechlorhexidinemonofluorophosphate complexes was considered incompatible without fluoride.[12]

Gel: The different available concentrations of chlorhexidine gel are 1%, 0.2%, 0.12%. They are delivered in trays and toothbrushes. Chlorhexidine gel, that is applied once a day has therapeutic effects, like reducing oral malodour and also reduces chlorhexidine staining.[13]

Toothpastes: 0.12% of chlorhexidine with 1 ppm of fluoridehas antiplaque effects similar to chlorhexidine mouthwash. However, there were difficulties in incorporating chlorhexidine into gels and toothpastes.1% chlorhexidine used as slurries and rinsed twice per day for one-minute causes significant reduction in the plaque and gingival scores but also causes stains. Chlorhexidine in dentifrices gained little attention due to its possible interaction with anionic ingredients contained in toothpaste and competition for oral retention sites. [14]

Sprays: 0.1% and0.2% sprays have similar plaque inhibition properties of 0.2% mouthwash. It is well received by physically and mentally handicapped patients. [15]

Sugar free chewing gum: Chlorhexidine remains unbound in this form. It contains 20mg of chlorhexidine diacetate. It is advised to chew 2 pieces twice per day for 10 minutes. This procedure is said to cause less stains. It is a good method of using chlorhexidinefor a long period of time.[16]

XII.Clinical Applications of Chlorhexidine[1]

As an adjunct to oral hygiene and professional prophylaxis, post oral surgery in periodontal surgery or root planing, patients with intermaxillary fixation and in patients who are under high risk of caries.[nash and addy 1979], in physically and mentally handicapped chlorhexidine sprays can be used, medically compromised patients who are predisposed to oral candidiasis, used to limit the bacteremia and operatory contamination by oral bacteria and as an adjunct to antibiotic prophylaxis, sub gingival irrigation, final irrigation before root canal obturation, management of denture stomatitis,

Hypersensitivity, tooth decay, recurrent oral ulceration [addy 1974 ,1976], patients undergoing orthodontic treatment. [shaw et al 1984] Oral malodour , for surgical skin preparation, as a local drug delivery system in the form of a bio-degradable chip to be used in the subgingival environment [periochip-2.5mg of chlorhexidine is found to have an average drug concentration greater than 125microgram per millilitre for 7 to 10 days]

XIII.Side effects

CHX staining (Maillard reaction), taste disturbances (dysgeusia), oral mucosal erosion, increased calculus formation, unilateral or bilateral parotid swelling.

IX.Anti-Discolouration system (ADS)

Recent studies in Italy have investigated the possibility of reducing and / eliminating pigmentation associated with the use of CHX based products by adding antioxidants such as essential oils, peroxyborate, polyvinypyrolidine, sodium metabisulphite or ascorbic acid by interrupting the Maillard reaction.It interferes with the pigmentation reaction by reducing Fe III to Fe II and thereby avoiding the reaction between Fe III and SH groups.[17]One of the major problems related to these agents is the possibility to hamper the activity of CHX. Paucity of the studies does not allow a definitive conclusion. To date efficacy of antiseptic solutions containing 0.2% CHX with sodium metabisulphite or ascorbic acid ADS has only been studied in three studies.

X.Limitations[1]

Teratogenic effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at CHX gluconate doses up to 300 mg/kg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to the fetus (Foulkes 1973). Adequate and well-controlled studies in pregnant women have, however, not been attempted.

Neurosensory deafness: This can occur if CHX is introduced into the middle ear. The antiseptic should not be placed in the outer ear in case the ear drum is perforated.

Nursing mothers: It is not known whether CHX is excreted in human milk. Because many drugs are excreted in human milk, caution might be indicated when CHX is administered to a nursing woman.

Bacterial resistance: Resistance has not been reported even in long-term oral use. There is no evidence of superinfection by fungi, yeasts or viruses. Long-term oral use resulted in a small shift in the flora towards less sensitive organisms but the effect was rapidly reversible after discontinuation of use (Schiott et al 1976).

XI.Conclusion

Chemical plaque control measures are widely used for controlling plaque formation and preventing the development of gingival inflammation. CHX is effective antimicrobial agent with plaque inhibitory effects. It is available in various forms. It is indicated as an adjunct to mechanical methods in cases where plaque removal is not adequate. However, due to its side effects such as staining and taste alterations, patient compliance is affected. Tooth staining can be minimized with use of CHX just before sleeping. Staining is less with use of ADS, but its effect on efficacy of CHX is controversial. Further studies are required to prove effectiveness of CHX with ADS.

References

1. Lakhani N, Vandana KL. Chlorhexidine An-Insight. Int J Adv Res. 2016;4(7):1321-8.
2. Gunsolley JC.Clinical efficacy of antimicrobial mouthrinses. J Dent 2010;38:S6-10.
3. NitinSaroch. Periobasics: A Textbook of Periodontics and Implantology. 2nd Ed.Sushrut. India. 655- 660(2019).
4. Corbet EF, Tam JO, Zee KY, Wong MC, Lo EC, Mombelli AW. Therapeutic effects of supervised Chlorhexidinemouthrinses on untreated gingivitis. Oral Dis. 1997; 3:9– 18.

5. BonesvollP,Gjermo P. A comparison between chlorhexidine and some quaternary ammonium compounds with regard to retention,salivary concentration and plaque inhibiting effect in human mouth after mouth rinses. Arch Oral boil. 1978; 23: 289-294.
6. Jenkins S, Addy M Wade W.The mechanism of action of Chlorhexidine.A study of plaque growth on enamel inserts in vivo . J ClinPeriodontol. 1988;15: 415- 24.
7. Denton GW. Chlorhexidine. In: Disinfection, Sterilization and Preservation. 4th Ed. Lea and Febier, Philadelphia, 274-289 (1991).
8. Rölla G, Melsen B. On the mechanism of the plaque inhibition by chlorhexidine. J Dent Res. 1975; 54:57-62.
9. Brailsford SR, Fiske J, Gilbert S, Clark D, Beighton D. The effects of the combination of chlorhexidine/thymol-and fluorine-containing varnishes on the severity of root caries lesions in frail institutionalised frail elderly people. J Dent. 2002;30(7):319-24.
10. Drake DR, Grigsby W, Cardenzana A, Dunkerson D. Synergistic growth-inhibitory effects of chlorhexidine and copper combinations on *Streptococcus mutans, Actinomyces viscous and Actinomycesnaeslundii.* J Dent Res. 1993;72(2):524-8.
11. Cronan CA, Potempa J, Travis J, Mayo JA. Inhibition of *Porphyromonasgingivalis*proteinases by chlorhexidine synergistic effect of Zn(II). Oral MicrobiolImmunol. 2006;21(4):212-7.
12. Barkvoll, Marinho. Home use oral hygiene products: mouthrinses, J ClinPeriodontol. 2008;48 (1):42-53.
13. AddyM,Moran JM. Clinical indications for the use of chemical adjuncts to plaque control. Periodontol 2000.1997;15:52-54.
14. Dolles, Gjermo. The effects of a chlorhexidine toothpaste on the development of plaque,gingivitis and tooth staining. J ClinPeriodontol. 1993; 20:59-62.
15. Kalaga A, Addy M, Hunter B. The use of a 0.2% chlorhexidine spray as an adjunct to oral hygiene and gingival health in physically and mentally handicapped adults. J Periodontol. 1989; 60: 381– 385.
16. . Matthijs S, Adriaens P A. Chlorhexidine varnishes: a review. J Periodontol. 2002; 29:1-8.
17. KurtogluS ,Caksen H, Poyrazoglu MH. Neonatal poisonings in middle Anatolia of Turkey: an analysis of 72 cases. J ToxicolSci 2000; 25:115-9.