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RESEARCH ARTICLE

Chlorhexidine – An Insight.

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Abstract

The effectiveness of mechanical plaque control is influenced by the 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 antimicrobial agents to replace or to be adjuncts to the mechanical approaches. Chemical plaque control agents can be used to augment mechanical cleaning methods both to prevent and to treat periodontal diseases. Chlorhexidine is a gold standard against which other antiplaque and antigingivitis agents are measured.It can be either bacteriostatic or bactericidal depending on the dose. It is available in different formulations.Thus the aim of the article was to provide a thorough review regarding the characteristics, the applications and problems associated with the use of chlorhexidine in dental field.

Introduction:-

The prevention of dental caries and periodontal diseases is targeted at the control of dental plaque. In this context, chemical agents could represent a valuable complement to mechanical plaque control. The effectiveness of mechanical plaque control is influenced by the 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 antimicrobial agents to replace or to be adjuncts to the mechanical approaches.Chemical plaque control agents can be used to augment mechanical cleaning methods both to prevent and to treat periodontal diseases.

Chlorhexidine with its almost 40 years of use by dental practitioners[1] is considered one of the most widely studied and efficacious componds . In dentistry , it is primarily as an antibacterial mouthwash that has been shown to significantlyreduce gingival inflammation ,plaque and gingival bleeding indices[2].

Nowadays , updated and complete reviews on chx dental uses are not available.

Thus the aim of the article was to provide a thorough review regarding the characteristics, the applications and problems associated with the use of chx in dental field.

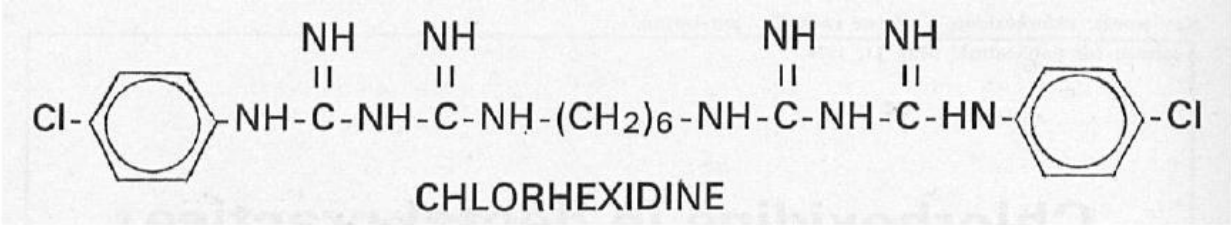
History:-

Chlorhexidine was developed by Imperial Chemical Industries in England during 1940's.It was marketed as a general antiseptic in the year 1950. In 1957 chlorhexidine was introduced for human use in Britain as an antiseptic for skin. Later it was widely used in medicine and surgery. Plaque inhibition first investigated by Schroeder in 1969[3]. A definitive study for caries inhibition by inhibition of dental plaque was done by Loe and Schiott 1972.[4]

Structure:-

It is a bisbiguanide antiseptic- a symmetrical molecule consisting of 4 chlorophenyl rings and 2 biguanide groups connected by a central hexamethylene bridge as shown in figure 1.
Chlorhexidine is available in three forms:
Digluconate [water soluble]

Acetate [water soluble]
Hydrochloride salts [poorly soluble in water]



Structure of Chlorhexidine[5] [**figure 1**]

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 it is a antiplaque andantigingivitis agent[6]. It can be bacteriostatic [0.02-0.06] or bactericidal [0.2-0.12] depending on the dose[7]. The Council on Dental Therapeutics of the American Dental Association [8] has accepted Chlorhexidine as an antimicrobial and antigingivitis agent. 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[9] . 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.

Spectrum Of Activity:-

The wide spectrum of activity emcompasses,
a. gram-positive bacteria
b. gram-negative bacteria
c. yeasts
d. some lipophilic viruses [10]

Pharmacodynamics:-

Antibacterial action of Chlorhexidine [By Woodcock 1988 ; Mechanism of action of chlorhexidine by Russel and chopra 1990 and Denton 1991]

Chlorhexidine's superior antibacterial effect (both bacteriostatic and bactericidal) can be explained in terms of its superior persistence at tooth and mucosal surfaces.

Bacteriostatic:-
at low concentration . By altering the osmotic balance of the bacteria cell, it promotes release of low molecular weight molecules[potassium and phoshorous]

Bactericidal:-
at high concentration. Chlorhexidine causes cell death by cytolysis: its ability to increase the permeability of bacteria cell membrane results in the release of the main intracellular components including potassium thereby altering the cells protein structure and causing the precipitation / coagulation of cytoplasmic proteins[11] .

The antibacterial action of chx is most likely the result of an immediate bactericidal action ,followed by a prolonged bacteriostatic action, due to its ability to attach to enamel surfaces.

Antiplaque Action Of Chx:-

Rolla and Melsen [12]postulated that the desorbed CHX inhibited the plaque formation in the following ways:
1. An influence on pellicle formation by blocking the acidic groups on the salivary glycoprotein, thus reducing the protein adsorption on the tooth surface.
2. An influence on the adsorption of plaque onto the tooth surface by binding to the bacteria in sub-lethal amounts
3. An influence on the formation of plaque by precipitating the agglutination factors in saliva and displacing calcium from the plaque matrix.

Pharmakokinetics:-

At the end of single rinse with chx mouthwash, around 30% of active ingredient remains on the oral mucosa and a negligible amount is swallowed[11].
Various formulations and their uses are shown in Table 1
Various effects of chlorhexidine are shown in Table 2.

Chlorhexidine Formulations:-

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[14]. 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[15]. 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 [16]. After single rinse with chlorhexidine, the saliva itself exhibits antibacterial activity for up to 5 hrs [17] whereas persistence at the oral mucosal surfaces has been shown to suppress salivary bacterial counts for over 12 hours [18]. In this regard, the dicationic nature of chlorhexidine must play a part; it can be envisaged as one charged end of chlorhexidine molecule binding to the tooth surface and the other remaining available to interact with bacterial membrane as microorganism approaches the tooth surface, a pin cushion effect [19] .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[20]. The concentration of 0.06% and sodium fluoride 0.2% and 0.055% of stannous fluoride was considered compatible with fluoride [21]. The chlorhexidine monofluorophosphate complexes was considered incompatible without fluoride [22].
Studies on mouthrinses shown in Table 3.

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 [25].

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 [26].

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 [27].

Varnishes:-

Chlorhexidine varnishes are used for prophylaxis against root caries [28].

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 [29].

Administration Schedule:-

Study suggested using 20mg of chx, twicw daily as the optimum dose[30].this quantity theoretically balancesthe efficacy of the compound against its local side effects, while at the same time making acceptable to the patient[31].
FDA suggests to use chx as an oral rinse, applying 10 to 15ml of product for about 30 seconds or as local applications of gel or spray preparation , twice daily , for a limited period of time [1 month or 2 weeks][31]

Perioperative Management:-

An aqueous solution of chx has been recommended:
In general surgery for the surgical antisepsis of the operator and the patient, before the procedure[32].
In gel and mouthwash form for plaque control during the perioperative period, before and after oral surgical procedures.[33]

Clinical Applications Of Chlorhexidine:-

- as an adjunct to oral hygiene and professional prophylaxis.
- post oral surgery in periodontal surgery or root planing.[34]
- patients with intermaxillary fixation and in patients who are under high risk of caries.[Nash and Addy 1979]
- physically and mentally handicapped chlorhexidine sprays can be used
- medically compromised patients who are predisposed to oral candidiasis[35]
- 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[35] [Halita is the name of a mouth rinse containing 0.05% of chlorhexidine, 0.05% cetyl pyridinium chloride and 0.14% of zinc lactate]
- for surgical skin preparation[36]
- 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 125 microgram per milliliter for 7 to 10 days[37]

Side Effects:-

- Brown discolouration of the teeth, restorative materials and yellow discoloration of tongue.[38]
- The mechanisms proposed for CHX staining can be debated {Eriksen et al. 1985, Addy & Moran 1995, Watts & Addy 2001} but have been proposed as:

1. Degradation of the chlorhexidine molecule to release parachloraniline.[(Addy and Roberts 1981)

Catalysis of Maillard reactions:-
Carbohydrates and proteins , which adhere to the enamel surface [acquired dental biofilm] undergo a series of condensation and polymerization reactions leading to the formation of brown pigmented substances known as melanoidins , giving the film a brownish colour[39].

Protein denaturation with metal sulfide formation. (Ellingsen et al 1982, Nordbo et al 1982):-
Chx causes protein denaturation and breaks down the disulphide bridges , forming highly reactive sulfhydryl groups. Proteins , carbohydrates , Fe^{+3} ions and polyphenol compounds , present in saliva and on oral surfaces , can react with these groups , forming organic ferric sulfides , which are of a yellow brownish colour and deposit on the hard and soft tissues of the oral cavity.

Precipitation of anionic dietary chromogens:-
originating in the diet[food and drink like
tea , coffee ,red wine] which then interact with the cationic nature of Chx.[40]
Taste perturbation. Objective testing of the taste sensation has also confirmed a transient effect on the perception of sweet and salt taste (Gjermo et al 1974) with salt taste preferentially being affected (Lang et al 1988)
Mucosal erosion which is an idiosyncratic reaction and is dose dependent[38]

E.Enhanced supragingival calculus formation:-
This effect may be due to the precipitation of salivary proteins on to the tooth surfaces, thereby increasing the pellicle thickness and/or precipitation of inorganic salts on to the pellicle layer.[41]
Unilateral or bilateral parotid swelling : Although not a common adverse effect, this is seen as an extremely rare occurrence with no plaudible explanation. The reports of virus infections (parotitis) in connection with chlorhexidine mouth rinses (Gjermo et al 1970, Flotra et al 1971) [42] might probably be purely co-incidental, but cannot be completely disregarded.
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Overdose:-

There are no reported cases of systemic toxicity caused by topical application and /or accidental ingestion of chx in adults .There have been , however cases of accidental ingestion in infants , which resulted in signs and symptoms of acute intoxication , including gastralgia and vomiting .[43]

Antidiscoloration System [Ads]:-

Recent studies 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 [44] by interrupting the maillard reaction and interfering with the pigmentation reaction comes from the reduction of Fe III to Fe II thereby avoiding the reaction between Fe III and SH groups.

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 .

Metabolism of chlorhexidine :-
The chlorhexidine that is swallowed undergoes minimalmetabolic changes.[Winrow 1973] It has a half life of 4 days and it isexcreted in faeces.

Limitations :-

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).

Development of allergic reactions: Allergic reactions to chlorhexidine have been reported with certainty in fewer than 10 cases (Winrow 1973]

Precautions:-

After the use of chlorhexidine mouthwash the intake of tea, coffee and red wine must be avoided. The usage is restricted in cases of anterior composite restorations and glass ionomer restorations. There should be a 30 minute lapse between theusage of a dentifrice and chlorhexidine mouth wash[45]. It is so advised because the toothpastes contain detergents which are predominantly anionic agents. Chlorhexidine molecule being dicationic tends to bind with the anionic agents leading to a reduction in the substantivity of chlorhexidine mouthrinse.

Table 1:-Various formulations and their uses

Formulation	uses
4% CHLORHEXIDINE GLUCONATE	Skin cleanser
0.5% CHLORHEXIDINE IN 70% ISOPROPYL ALCOHOL	handrub
0.5% AQUEOS CHLORHEXIDINE FOR MUCOUS MEMBRANE	Mucous membrane
0.12-1%	gel
0.5% AQUEOS CHLORHEXIDINE FOR MUCOUS MEMBRANE	Tongue cleaning
0.12-0.2%	Oral rinses
0.12-0.2%	spray
1-2%	Chx chips
0.12 %chx with 1ppm of fluoride	toothpaste
20mg chx diacetate	Sugar free chewing gum

Table 2:- Various effects of chlorhexidine

Astoe-Jorgensen et al	1974	reflect CHX damage to fibroblasts	delay in wound healing
Heyden and Rolla	1977	that CHX has a cytotoxic effect on epithelial and red blood cells	delay in wound healing
Gabler WL etal	1987	CHX damages RBC and PMN	delay in wound healing
Page and Schroeder , Wilton	1981 1982	CHX causes membrane damage to neutrophils and macrophages with release of intercellular enzyme	delay in wound healing
Helgeland,Heyden,Rolla	1971	Human skin epithelial cells exhibited growth inhibition and differential staining	delay in wound healing
Goldschmidt and Taubman	1977	brief contact between CHX and epithelial cells or fibroblasts causes cell injury and /or cell death.	delay in wound healing
Cristina Trigo Cabral etal	2007	On osteoblasts,CHX has a higher cytotoxicity	delay in wound healing
Flemingson etal	2008	On gingival fibroblasts, Chx higher cytotoxicity	delay in wound healing
Wilken et al		have proved the in vitro cytotoxicity of Chlorhexidine on human gingival fibroblasts	delay in wound healing
Angelo J Mariorri etal	1999	severe toxic effects on gingival fibroblasts and negatively affect wound healing	delay in wound healing

Table 3:- Studies on mouthrinses

Russel AD 1986 [23]	Shown lower risk of developing gingivitis
Geossman et al 1986, Gunsolley JC 2006 [24]	Improved plaque index
Loe and schiott 1970	Complete plaque elimination
Vandana K L 2010	compared the ozonated water and 0.2% chlorhexidine in treatment of periodontitis and concluded that ozone is an alternative management strategy due to its powerful ability to inactivate microorganisms.

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