REVIEW ARTICLE

Periodontics

CHEMICAL PLAQUE CONTROL IN THE PREVENTION OF GINGIVAL & PERIODONTAL DISEASES

KEY WORDS: Periodontitis, Gingivitis, Dental plaque, Anti-plaque agents, Prevention.

Dr. Riddhi Awasthi PGT, Department of Periodontics & Oral Implantology, Kalinga Institute of Dental Sciences, KIIT Deemed To Be University, Bhubaneswar.

Dr. Dhirendra Kumar Singh* Professor, Department of Periodontics & Oral Implantology, Kalinga Institute of Dental Sciences, KIIT Deemed To Be University, Bhubaneswar. *Corresponding Author

ABSTRACT

Periodontal disease and chronic gingivitis, is certainly pandemic but is of such low morbidity that the case for prevention and indeed treatment is harder to aid. Nevertheless, for the most common dental diseases such as caries and periodontitis, there is a widespread demand for primary and tertiary prevention aimed at the individual or the population as a whole. The chemical anti-plaque agents constitutes one of the most successful prevention measures documented in dentistry for gingival and periodontal disease. Notably, this approach has benefited very large numbers of people and yet has been a cost effective exercise. The search for effective antiplaque agents has subsequently received much impetus over the last decade, with numerous reviews published on the subject. These review primarily debate the efficacy and side effects of a range of chemical agents used for the prevention of periodontal and gingival diseases.

INTRODUCTION:

Periodontal disease is an infection that involves the inflammatory process and the immune response. It can cause a breakdown of periodontal structures resulting in increased pocket depth, clinical attachment loss, and destruction of alveolar bone. Treatment of periodontal diseases has evolved appreciably in the last decade.[1] Greater emphasis has been placed on nonsurgical approaches to periodontal therapy. Nonsurgical periodontal therapy is used to delay repopulation of pathogenic microorganisms by controlling the supragingival bacterial plaque, and by disrupting or removing the subgingival gram-negative flora. The goal of this therapy is to return the tissues to a state of health that can be easily maintained by the patient through periodontal debridement procedures.[2]

In our efforts to control pathogenic microorganisms through periodontal debridement, we have learned that repopulation of the periodontal pocket of bacteria can occur after debridement within 60 days.[3] Additionally, certain bacteria can invade the soft tissues of the periodontal pocket, and other areas of the oral cavity, to provide a nidus for infection.[4] Therefore, in addition to mechanical therapy, it is sometimes necessary to administer chemical agents to suppress the bacterial load of inflammatory periodontal diseases. The use of chemical agents in the treatment of periodontal disease is an important adjunctive therapy.[5]

Chemical plaque control agents:

Over a period of more than three decades there has been quite intense interest in the use of chemical agents to control supragingival plaque and thereby gingivitis.[6] The number and variation of chemical agents evaluated are quite large but most have antiseptic or antimicrobial actions and success has been variable at the extreme. It is important to emphasize that formulations based on antimicrobial agents provide a considerably greater preventive than therapeutic action. The most effective agents inhibit the development of plaque and gingivitis but are limited or slow to affect established plaque and gingivitis.[7]

Terminology:

An **antiseptic** is a substance that prevents or inhibits the growth of microorganisms or kills microbes on contact. 1

An **antibiotic** is a substance that is synthesized by microorganisms that prevents or inhibits the growth of microorganisms by stopping reproduction of or by killing the bacteria.[3]

An **antimicrobial agent** is a chemical that has bacteriostatic or bactericidal effect in vitro that alone cannot be extrapolated to a proven efficacy in vivo against plaque.[9]

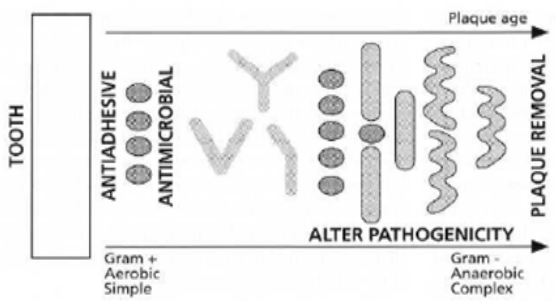

Figure 1: Bacterial succession plaque formation. There is increasing mass and bacterial complexity as plaque bacteria attach and proliferate. Ideal sites of action for chemicals which might influence plaque accumulation are shown.[10]

First generation antiplaque agents

Group	Example of Agents	Action	Used now/ Product
Antibiotics	Penicillin Vancomycin Kanamycin Niddamycin Spiromycin	Antimicrobial	No
Enzymes	Protease Lipase Nuclease Dextranase Mutanase	Plaque removal	No
	Glucose oxidase Amyloglucosidase	Antimicrobial	Yes Toothpaste
Bisbiguanide antiseptics	Chlorhexidine Alexidine Octenidine	Antimicrobial	Yes Mouthrinse Spray Gel Toothpaste Chewing gum Varnish
Quaternary NH_4 Compounds	Cetylpyridinium chloride Benzalconium chloride	Antimicrobial	Yes Mouthrinse
Phenols & essential oils	Thymol Hexylresorcinol, Ecalyptol	Antimicrobial	Yes Mouthrinse Toothpaste
	Triclosan	Anti-inflammatory	
Natural products	Sanguinarine	Antimicrobial	No

2nd generation Agents

These are retained longer in the oral cavity & tissues.

Group	Example of Agents	Action	Used now/ Product
Fluorides	Sodium fluoride Sodium monofluorophosphate Stannous fluoride, Amine fluoride	Antimicrobial	Yes Toothpaste Mouthrinse, Gel
Metal Salts	Tin, Zinc, Copper	Antimicrobial	Yes, Toothpaste Mouthrinse, Gel
Oxygenating agents	Hydrogen peroxide Sodium peroxyborate Sodium peroxycarbonate	Antimicrobial ? Plaque removal	Yes Mouthrinse
Detergents	Sodium lauryl sulfate	Antimicrobial ? Plaque removal	Yes Toothpaste Mouthrinse

3rd generation agents

They block binding of the micro-organisms to the tooth or to each other.

Group	Example of Agents	Action	Used now/ Product
Amine alcohols	Octapinol Delmopinol	Plaque matrix Inhibition	No Yes Toothpaste Mouthrinse[17]
Salicylanide	Salifluor	Antimicrobial & antiinflammatory	No

History of oral hygiene products

The terminology "oral hygiene products" is recent but there is evidence dating back at least 6000 years that formulations and recipes existed to benefit oral and dental health (for reviews see Fischman 1992, 1997).[2] This includes the written Ebers Papyrus 1500 BC containing recipes for tooth powders and mouthrinses dating back to 4000 BC. A considerable number of formulations can be attributed to the writer and scientist Hippocrates (circa 480 BC). By today's standards the early formulations appear strange if not disgusting but they were not always without logic. Thus, bodies or body parts of animals perceived to have good or continuously erupting teeth were used in the belief that they would impart health and strength to the teeth of the user. Hippocrates, for example, recommended the head of one hare and three whole mice, after taking out the intestines of two, mixing the powder derived from burning the animals with greasy wool, honey, anise seeds, myrrh and white wine. This early toothpaste was to be rubbed on the teeth frequently.

Mouthrinses similarly contained ingredients which would have had some salivary flow stimulating effect, breath odor masking and antimicrobial actions, albeit not necessarily formulated with all these activities in mind.[12] Alcohol-based mouthrinses were particularly popular with the Romans and included white wine and beer.[13] Urine, as a mouthrinse, appeared to be popular with many peoples and over many centuries.[14] There even appeared differences in opinion, with the Cant-abri and other peoples of Spain preferring stale urine, whereas Fauchard (1690-1761) in France recommended fresh urine.[13] The Arab nations were purported to prefer children's urine and the Romans to prefer Arab urine. Anecdotal reports suggest the use of urine as a mouthrinse to this very day with individuals rinsing with their own urine.[14] There could, indeed, be benefits to oral health from rinsing with urine by virtue of the urea content; however this has never been evaluated, and given today's Guidelines for Good Clinical Practice, it is unlikely that study protocols would receive ethical approval.

Throughout the centuries, most tooth powders, toothpastes and mouthrinses appear to have been formulated for cosmetic reasons including tooth cleaning and breath freshening rather than the control of dental and periodontal diseases.[15] Many formulations contain very abrasive ingredients and/or acidic substances. However, ingredients with antimicrobial properties were used, perhaps not intentionally, and included arsenic and herbal materials. Herbal extracts are, perhaps, increasingly being used in toothpastes and mouthrinses, although there are little data to support efficacy for gingivitis and none for caries. Many agents prescribed well into the twentieth century, usually as rinses, had the potential to cause local damage to tissues, if not systemic toxicity, including aromatic sulfuric acid, mercuric perchloride, carbolic acid and formaldehyde (Dilling & Hallam 1936).[4]

Perhaps the biggest change to toothpastes came with the chemo-parasitic theory of tooth decay of W. D. Miller in 1890. The theory that organic acids were produced by oral bacteria acting on fermentable carbohydrates in contact with enamel led to both the introduction of agents into toothpaste, which might influence this process, and the production of alkaline products.[7] Shortly after, and at the beginning of the twentieth century, various potassium and sodium salts were added to toothpaste as a therapy for periodontal disease.[18] The first half of the twentieth century saw numerous claims for toothpastes for oral health benefits, including tooth decay and periodontal disease. For example, with the early recognition that periodontal diseases were associated with microorganisms, emetin hydrochloride was added to toothpaste to treat possible amoebic infections. Perhaps with the exception of the well-known essential oil mouthrinse marketed at the end of the nineteenth century, the addition of antimicrobial and/or antiseptic agents to toothpastes and mouthrinses is a relatively recent practice by manufacturers. During the nineteenth and twentieth centuries, toothpastes also became less abrasive.[18] Interestingly, the importance of a level of abrasivity in toothpastes to the prevention of extrinsic dental stain became apparent when one manufacturer marketed a non-abrasive liquid dentifrice. The unsightly brown tooth staining that developed in many users resulted in the early removal of this product from the marketplace. More recently also, standards organizations, notably the British Standards Institute and the International Standards Organization, have laid down standards for toothpastes (BS 5136: 1981, ISO 11609: 1995) and a standard for mouthrinses is under development. Such standards are concerned with safety rather than efficacy. Throughout the ages, and until relatively recently, scientific evaluations of agents and formulations for gum health were not performed and claims for efficacy appear based on anecdotal reports at best. Indeed, given the nature of many ingredients and the recipes recommended in the past for oral hygiene benefits, it is unlikely that efficacy will ever be tested. In the 6000 years history of oral hygiene products, scientific evaluation must be seen as an extremely recent event — an observation which can, of course, be applied to almost all aspects of chemo-prevention and chemo-therapy of human diseases. Indeed, perhaps the first ever, double-blind, randomized cross-over design clinical trial in dentistry was just over 40 years ago (Cooke & Armitage 1960).[19]

Rationale for chemical supragingival plaque control

The epidemiological data and clinical research (Ash et al. 1964, Loe et al. 1965) directly associating plaque with gingivitis perhaps, unfortunately, led to a rather simplistic view that regular tooth cleaning would prevent gingivitis and thereby periodontal disease.[20] Theoretically correct, this concept did not appear to consider the multiplicity of factors which influence the ability of individuals to clean their teeth sufficiently well to prevent disease, not the least of which are those factors which affect individual compliance with advice and dexterity in performing such tasks. The need for research into those psychosocial factors which might influence attitude to and performance in oral hygiene, was stated in a workshop report on plaque control and oral hygiene practices (Frandsen 1986) but appears not to have been heeded to this day.[15] Moreover, and as described in other chapters, epidemiological data suggest that not all individuals are particularly susceptible to periodontal disease. The most severe disease is accounted for by a relatively small proportion of any population and then by only a proportion of sites in their dentition (Baelum et al. 1986).[10] Even accepting that a considerable proportion of middle-aged adults will have one or more sites in the dentition with moderate periodontal disease, this will be of the chronic adult type and a minimal threat to the longevity of their dentition (Papapanou 1994).[23] This requires that prevention, through improved oral hygiene practices, will be grossly overprescribed.

Given our knowledge concerning the microbiological specificity of periodontal disease and, more particularly host susceptibility to the disease, it is at present difficult, if not impossible, to predict probable future disease in the, as yet unaffected, host. At present, host susceptibility is described retrospectively in the already diseased individual but, even here, an explanation for their susceptibility, except for a few risk factors, cannot be made. These risk factors include smoking, diabetes and polymorph defects and possible stress (for review see Johnson 1994, Porter & Scully 1994).[24] Genetic markers for periodontal disease have been identified but, at present, appear to be applied retrospectively rather than prospectively (Kornman et al. 1997)[25] and the value to early onset disease has been questioned (Hodge et al. 2001).[26]

One definition of periodontal disease is chronic gingivitis with loss of attachment. This is a particularly useful definition since not only does it describe the pathogenic processes occurring but also alludes to the approach to prevent, treat or prevent re-occurrence of the disease. Therefore prevention through supragingival plaque control still remains the main-stay of controlling gingivitis and therefore the occurrence or re-occurrence of periodontitis (for review see Addy & Adriaens 1998).[22] As alluded to, the importance of oral hygiene to outcome and long-term success of therapy for periodontal disease is hampered by the often ineffectiveness of mechanical cleaning to specific sites using a toothbrush and the limited or lack of use of interdental cleaning by many individuals (for reviews see Axelsson 1994).[23] Despite the encouraging improvements in oral hygiene, gingivitis and, to some extent, periodontitis in developed countries, gingival inflammation is still highly prevalent (for reviews see Baehni & Bourgeois 1998).[24] Taken with the microbial etiology of both gingivitis and periodontitis, this supports the concept of employing agents to control plaque which require minimal compliance and skill in their use. This is the concept that underlies chemical supragingival plaque control, but as with oral hygiene instruction in mechanical methods, it will have to be vastly overprescribed if periodontal disease prevention is to be achieved in susceptible individuals. Chemical supragingival plaque control has thus been the subject of extensive research using scientific methodologies for approximately 40 years. The question to be addressed here is whether a chemical or chemicals

Antibiotics:

Despite evidence for efficacy in preventing caries and gingivitis or resolving gingivitis, the opinion today is that antibiotics should not be used either topically or systemically as preventive agents against these diseases. The risk to benefit ratio is high and even antibiotic use in the treatment of adult periodontitis is open to debate. Thus, antibiotics have their own specific side effects not all of which can be avoided by topical application. Perhaps of greatest importance is the development of bacterial resistance within human populations.[30]

Enzymes:

Enzymes fall into two groups.[28] Those in the first group are not truly antimicrobial agents but more plaque removal agents in that they have the potential to disrupt the early plaque matrix, thereby dislodging bacteria from the tooth surface. The second group of enzymes employed glucose oxidase and amyloglucosidase to enhance the host defense mechanism. The aim was to catalyze the conversion of endogenous and exogenous thiocyanate to hypothiocyanite via the salivary lactoperoxydase system. The hypothiocyanite produces inhibitory effects upon oral bacteria, particularly streptococci, to interfere with their metabolism.[29] This approach is a theoretical possibility and the chemical processes can be produced in the laboratory. Tooth paste products containing these enzymes and thiocyanate were produced but equivocal results for benefits to gingivitis were not obtained and there are no convincing long term studies or efficacy.[33]

Bisbiguanide Antiseptics:

Chlorhexidine is thus far the most studied and effective antiseptic for plaque inhibition and the prevention of gingivitis.[34] Consequent upon the original publication, Chlorhexidine, arguably perhaps, represents the nearest that research has come to identifying a chemical agent that could be used as a replacement for, rather than an adjunct to, mechanical oral hygiene practices. Other bisbiguanides such as alexidine and octenidine have less or similar activity, respectively, to Chlorhexidine but bring with them no improvement in local side effects and have less toxicity data available. Chlorhexidine has thus remained the only bisbiguanide used in a number of vehicles and available in commercial products.[34]

Quaternary Ammonium Compounds:

Benzylconium chloride and more particularly, cetylpy ridinium chloride are the most studied of this family of antiseptics. Cetylpyridinium chloride is used in a wide variety of antiseptic mouthrinse products usually at a concentration of 0.05%. At oral pH these antiseptics are monocationic and adsorb readily and quantitatively, to a greater extent, than Chlorhexidine to oral surfaces. There is limited information on quaternary ammonium compounds in tooth pastes and very few products are available.[35]

Phenols and Essential Oils:

Phenols and essential oils have been used in mouth rinses and lozenges for many years. The non ionic antimicrobial triclosan is usually considered to belong to the phenol group and has been widely used over many years in a number of medicated products including antiperspirants and soaps. Triclosan tooth pastes appear to provide greater gingivitis benefits in some studies than plaque reductions and this could be explained by a possible anti-inflammatory action for this agent. Mouth rinses containing triclosan and the co-polymer are available, with some evidence of adjunctive benefits to oral hygiene and gingival health when used along side normal tooth cleaning.[36]

Natural Products:

Herb and plant extracts have been used in oral hygiene products for many years if not centuries. Unfortunately, there are few data available and such tooth paste products provide no greater benefits to oral hygiene and gingival health than conventional fluoride tooth paste does. The plant extract sanguinarine has been used in a number of formulations. Zinc salts are also incorporated, which makes it difficult to evaluate the efficacy of sanguinarine alone. Very recently, sanguinarine containing mouth rinses have been shown to increase the likelihood of oral precancerous lesions almost ten fold even after cessation of mouth rinse use.[37]

Fluorides:

The caries preventive benefits for a number of fluoride salts arc well established but the fluoride ion has no effect against the development of plaque and gingivitis. Amine fluoride and stannous fluoride provide some plaque inhibitory activity, particularly when combined, however, the effects appear to be derived from the non-fluoride portion of the molecules.[38]

Metal Salts:

Antimicrobial actions including plaque inhibition by metal salts have been appreciated for many years, with most research interest centered on copper, tin and zinc. Polyvalent metal salts alone are effective plaque inhibitors at relatively high concentration when taste and toxicity problems may arise.[39] Stannous fluoride is an exception but is difficult to formulate into oral hygiene products because of stability problems, with hydrolysis occurring in the presence of water.

Oxygenating Agents:

Oxygenating agents have been used as disinfectants in various disciplines of dentistry, including endodontics and Periodontics. Hydrogen peroxide has been employed for supragingival plaque control and more recently has become

important as bleach in tooth whitening.[40] Similarly, peroxyborate may be used in the treatment of acute ulcerative gingivitis.[41]

Detergents:
Detergents, such as sodium lauryl sulfate, are common ingredients in tooth paste and mouthrinse products. Sodium lauryl sulfate has moderate substantivity measured at between 5 and 7 hours and plaque inhibitory action similar to triclosan.[42]

Amine Alcohols:
This group of compounds does not truly fit into an antimicrobial or antiseptic category; indeed they exhibit minimal effects against microbes. Octopenol was first shown to be effective as an antiplaque agent but was withdrawn for toxicological reasons. Delmopinol followed and at 0.1% and 0.2% in mouth rinses was shown to be effective as a plaque inhibitor and antigingivitis agent in short term no oral hygiene and long term home use studies.[43] Side effects include tooth discoloration, transient numbness of the mucosa, particularly the tongue, and burning sensations in the mouth.

Acidified Sodium Chlorites:
Depending on the acid chosen and the conditions of the reaction between the acid and the sodium chlorite, a varied and complex range of reaction products can ensue. Under ideal conditions for antimicrobial benefits sodium chlorite is reacted with a proteic acid to produce chlorous acid, which then liberates a range of higher oxidant species but contains minimal mounts of chlorine dioxide.[40] These higher oxidant species have a broad range of antimicrobial action against bacteria, fungi, yeast and viruses.

Other Antiseptics:
A number of antiseptics / antimicrobial agents have been studied for plaque inhibition. Most have been found to have little or no effect in vivo; a few have been formulated in mouthrinse products including povidone iodine and hexetidine. Povidone iodine at 1% has a substantivity of only 60 minutes and lacks appreciable plaque inhibitory activity or action in acute infections such as acute ulcerative gingivitis for which it is recommended. Povidone iodine is largely without side effects but as a rinse has potential to affect thyroid function adversely. Hexetidine a saturated pyrimidine at 0.1% was shown to have limited plaque inhibitory action and no evidence for antiplaque activity when used as an adjunct for oral hygiene.

CHLORHEXIDINE:
Chlorhexidine is a bisbiguanide formulation with cationic properties. The molecule is symmetric with two 4, chlorophenyl rings and two biguanide groups connected by a central hexamethylene chain.

The drug was introduced by ICI (Maccles field, England) in 1940 (Hibitane) as a general disinfectant with a broad antibacterial spectrum against Gram + ve and Gram - ve pathogens (Davies et al. 1954). Since then Chlorhexidine has been extensively used in various medical fields such as gynecology, urology, ophthalmology, and in disinfection of operation fields and the treatment of burns, etc. The toxicity of the agent seems to be very low and the "records of side effects are remarkably clean" (Foulkes 1973).

The first use of Chlorhexidine in dental practice was in washing operation sites and in disinfecting root canals (Cawson & Curson 1959, Birch & Melville 1961, Atkinson & Hampson 1964, Birch et al. 1964). Subsequently, reports appeared in dental literature of the inhibition of the formation of deposits on human teeth and of the inhibition of caries in animals by Chlorhexidine (Renggli 1966, Regolati et al. 1969, Schroeder 1969). In 1970, & Schiott described a total inhibition of plaque formation and gingivitis by 0.2 % aqueous solutions of Chlorhexidine digluconate applied twice daily as mouth rinses. As dental plaque is generally accepted to be the predominant etiologic factor in gingivitis and periodontal disease and a prerequisite for the development of caries, these observations opened a new field of research on prevention of dental diseases.[18]

Availability:
Chlorhexidine is available in three forms, the digluconate, acetate and hydrochloride salts. Most studies and most oral formulations and products have used the digluconate salt, which is manufactured as a 20% V/V concentrate. Digluconate and acetate salts are water-soluble but hydrochloride is very sparingly soluble in water.[18]

Plaque inhibition by chlorhexidine was first investigated in 1969 (Schroeder 1969), but the definitive study was performed by Loe and Schiott (1970). This study showed that rinsing for 60 seconds twice per day with 10 ml of a 0.2% (20 mg dose) chlorhexidine gluconate solution in the absence of normal tooth cleaning, inhibited plaque regrowth and the development of gingivitis. Numerous studies followed, such that chlorhexidine was one of the most investigated compounds in dentistry.[16]

Chemistry of CHX:
Chlorhexidine is a bisbiguanide antiseptic, being a symmetrical molecule consisting of four chlorophenyl rings and two biguanide groups connected by a central hexamethylene bridge. CHX is a very strong base, and is most stable in the form of its salts. The salts originally employed were the acetate and hydrochloride, but both have a relatively poor water solubility. They were replaced by the digluconate in the late 1950's (Foulkes, 1973).[10]

The compound is a dicationic at pH levels above 3.5, with two positive charges on either side of a hexamethylene bridge (Albert & Sargeant 1962). Indeed, it is the dicationic nature of chlorhexidine, making it extremely interactive with anions, which is relevant to its efficacy, safety, local side effects and difficulties with formulation in products. Due to CHX's cationic properties it binds to the hydroxyapatite of the tooth enamel, to the pellicle on the tooth surfaces, and to salivary proteins. This absorbed CHX is gradually released from the teeth, as the concentration in the oral environment decreases. It is suspected to be released for up to 24 hours after absorption, thus preventing colonization of bacteria on the tooth surface (Yankell et al, 1979; Case, 1977).[8]

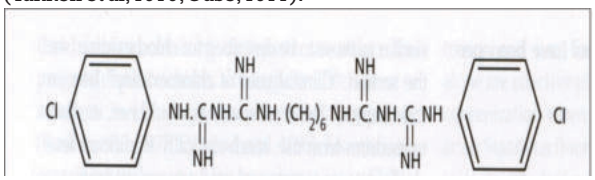

Figure 2: 1,6-di (4-chlorophenyldiguanido) hexane

Mechanism of action:
Chlorhexidine is a potent antibacterial substance but this alone does not explain its antiplaque action. The interaction of CHX with bacteria begins with cell wall adsorption, which is facilitated by the negative charge present on the wall surface. The amount adsorbed is concentration-dependent. The cell wall functions as a rigid outer coat which protects the more delicate cell membrane from disruptive forces. CHX adsorption to the wall will cause an alteration in electrophoretic mobility of the whole microorganism (Gjermo, 1974). However, experiments by Hugo and Longworth (1966) and Hennessey (1977) suggest that CHX does not form a complete monolayer over the bacterial surface, and the cell wall remains negatively charged. The cell membrane is the osmotic barrier which controls transport of metabolities in and out of the cell, and is the location of many enzymes. When CHX contacts the cell

membrane its integrity is disrupted causing leakage of the intracellular components. At low CHX concentration, small molecular weight substances will leak out, specifically potassium ions, then phosphorus. At higher CHX concentrations, precipitation of cytoplasmic contents will occur, most probably due to protein cross-linking, reducing any secondary release.Hennessey (1973) states that, CHX does not cause lysis of the cell. The lethal effect is related to extensive intracellular damage. Thus, CHX can exert a bacteriostatic action which becomes lethal as the concentration is raised, by causing cytoplasmic precipitation or coagulation.[4]

Adherence

CHX displays an affinity for oral surfaces, proteins, bacteria, and extracellular polysaccarides which are of bacterial origin (Davies, 1977; Bonesvoll et al, 1977; Hjeljordeta, 1973; Turesky etal, 1977).[8] In vivo experiments using ^{4}C-ring-labeled CHX have shown a correlation between clinical action and CHX retention in the oral cavity.[9] CHX is gradually released from retention sites and thus exerts a bacteriostatic effect over a prolonged period of time. Thus, CHX reacts specifically with both organic and inorganic surfaces. This may possibly enhance the antibacterial actions of the drug for control of caries and periodontal disease[6] (Loe, 1973; Gjermo, 1977; Schiott et al, 1972; Schiott et al., 1976; Briner etal, 1980.)

The antiseptic binds strongly to bacterial cell membranes. At low concentration this results in increased permeability with leakage of intracellular components including potassium (Hugo & Longworth 1964, 1965).[11,12] At high concentration, chlorhexidine causes precipitation of bacterial cytoplasm and cell death (Hugo & Longworth 1966).[13] In the mouth chlorhexidine readily adsorbs to surfaces including pellicle-coated teeth. Once adsorbed, and unlike some other antiseptics, chlorhexidine shows a persistent bacteriostatic action lasting in excess of 12 hours (Schiott et al. 1970)[4], Radio-labelled chlorhexidine studies suggest a slow release of the antiseptic from, surfaces (Bonesvoli et al. 1974a,b) and this was suggested to produce a prolonged antibacterial milieu in the mouth (Gjermo et al. 1974). However, the methods could not determine the activity of the chlorhexidine, which was almost certainly attached to the salivary proteins and desquamating epithelial cells and therefore unavailable for action. Consistent with the original work and conclusions (Davies et al. 1970), a more recent study and review suggested that plaque inhibition is derived only from the chlorhexidine adsorbed to the tooth surface (Jenkins et al. 1988).[15] It is possible that the molecule attaches to pellicle by one cation leaving the other free to interact with bacteria attempting to colonize the tooth surface. This mechanism would, therefore, be similar to that associated with tooth staining. It would also explain why anionic substances such as sodium lauryl sulfate based toothpastes reduce the plaque inhibition of chlorhexidine if used shortly after rinses with the antiseptic (Barkvoll et al. 1989).[6] Indeed, a more recent study has demonstrated that plaque inhibition by chlorhexidine mouthrinses is reduced if toothpaste is used immediately before or immediately after the rinse (Owens et al. 1997). These inhibitory effects of chlorhexidine activity by substances such as toothpastes can be modeled using the chlorhexidine tea staining method, which shows reduced staining activity by the chlorhexidine solutions resulting from an interaction with toothpaste (Sheen et al. 2001). Plaque inhibition by chlorhexidine mouthrinses appears to be dose related (Cancro et al. 1973, 1974, Jenkins et al. 1994) such that similar effects to that seen with the more usual 10 ml, 0.2% solution (20 mg) can be achieved with high volumes of low concentration solutions (Cumming & Loe 1973, Lang & Ramseier-Grossman 1981). It is worth noting, however, that not inconsiderable plaque inhibition is obtained with doses as low as 1-5 mg twice daily (Jenkins et al. 1994). Also, and relevant to the probable mechanism of action, topically applying 0.2% solutions of chlorhexidine only to the tooth surface, including by the use of sprays, produces the same level of plaque inhibition as rinsing with the full 20 mg dose (Addy & Moran 1983, Francis et al. 1987a, Jenkins et al. 1988, Kalagaetal. 1989a).[5]

Based on knowledge derived from chlorhexidine, the most effective plaque inhibitory agents in the antiseptic or antimicrobial group are those showing persistence of action in the mouth measured in hours. Such persistence of action, sometimes termed substantivity (Kornman 1986), appears dependent on several factors:

1. Adsorption and prolonged retention on oral surfaces including, importantly, pellicle coated teeth.
2. Maintenance of antimicrobial activity once adsorbed primarily through a bactcriostatic action against the primary plaque forming bacteria.
3. Minimal or slow neutralization of antimicrobial activity within the oral environment or slow desorption from surfaces.

Effects on Microbial Ecology:

Changes in the microbial ecology of the oral cavity have been noted, involving comparisons between the effects of CHX on oral microorganisms and on plaque as a whole (Emilson et al, 1972; Schiott, 1973).[8]

Schott et al (1970) reported that over a 40-day period of time with daily treatment with a 10 ml rinse of 0.2% CHX solution, there was a 85-90% reduction in the total number of aerobes and anaerobes present in saliva.[15] They also noted a reduction in the population of bacterial colonies and colonization on the tooth surfaces. The formation of plaque was not observed during this test period in the CHX group. However, Schott concludes that "it appears unlikely that the inhibition of plaque formation is primarily the result of a reduction of the salivary flora."

Johnson and Kenney (1972) reported that "daily topical applications of 2% aqueous CHX gluconate in macaca monkeys allowed development of only minimal amounts of simple plaque, containing only epithelial cells and Gram positive cocci." They concluded that daily topical application of CHX significantly inhibits plaque accumulation and maintains a significant reduction in gingivitis hi animal studies.[6]

Emilson (1977) has summarized the effects of CHX on a broad range of oral microorganisms. Staphylococci, S. mutans, S. salivauus and E.coli are highly susceptible. Streptococcus sanguis is less susceptible, and there is evidence that the proportion of S. sanguis in plaque increases with long-term CHX use. An earlier study by Hamp and Emilson (1973) had shown that plaque in beagle dogs tends to be composed of CHX-resistant organisms after six months of twice-daily CHX treatment. Strains of Pseudomonas and Klebsiella require relatively high CHX concentrations for inhibition of growth, and with S. sanguis may be expected to predominate in plaque with long-term CHX therapy.[7]

Effect on Fungi:

Chlorhexidine has been reported to be effective against Candida albicans invitro (Arskaug et al 1972), and in vivo studies on the effect on denture stomatitis have confirmed its efficacy against fungal infections in man (Budtz-Jorgensen & Loe 1972, Olsen 1974). Furthermore, chlorhexidine has been successfully used to control oral Candida albicans infections in seriously ill (leukemia) children (Langslet et al. 1974).[11]

Toxicology, safety and side effects:

The cationic nature of chlorhexidine minimizes absorption through the skin and mucosa, including from the gastrointestinal tract. Systemic toxicity from topical application or ingestion is therefore not reported, nor is there evidence of teratogenicity in the animal model. Even in intravenous infusion in animals, chlorhexidine is well tolerated and has occurred accidentally in humans without serious consequences. Hypersensitivity reactions including anaphylaxis have been reported in fewer than 10 people in Japan and resulted from the application of non-proprietary chlorhexidine products to sites other than the mouth. There was insufficient information to confirm that the reactions were

actually due to chlorhexidine. Neurosensory deafness can occur if chlorhexidine is introduced into the middle ear and the antiseptic should not be placed in the outer ear in case the eardrum is perforated. The antiseptic has a broad antimicrobial action, including a wide range of Gram-positive and Gram-negative bacteria (Wade & Addy 1989). It is also effective against some fungi and yeasts including Candida, and some viruses including HBV and HIV. Bacterial resistance has not been reported with long-term, oral use, or evidence of supra-infection by fungi, yeasts or viruses. Long-term oral use resulted in a small shift in the flora towards the less sensitive organisms but this was rapidly reversible at the end of the 2-year study (Schiott et al. 1976).[12]

Effect of CHX oh blood cells:

Studies by Helgeland Heyden and Rolla (1977) have shown that CHX has a cytotoxic effect on epithelial and red blood cells while Goldschmidt Cogne and Taubman (1977) have demonstrated that brief contact between CHX and epithelial cells or flbroblasts causes cell injury and /or cell death. Astoe-Jorgensen et al (1974) reported that there will be delay in wound healing in case of exposure to CHX. It may reflect CHX damage to fibroblasts.[13]

Leukocytes are also adversely affected by CHX these cells have a putative role in protecting the host from periodontal pathogens. Page and Schroeder (1981) Wilton (1982) have reported that CHX causes membrane damage to neutrophils and macro phages with release of intercellular enzyme. CHX is cytotoxic to both neutrophils and red blood cells over a narrow concentration - range of 0.01 to 0.02% drug.[24]

At a concentration of 0.01% CHX acted as a potent activator of the neutrophils oxidative burst stimulating the cells to produce oxygen radicals such as super oxide. CHX ranging from 0.01 to 0.1% caused spontaneous degranulation of neutrophils. If neutrophils are pretreated with CHX and then activated by the chemoattractant tripeptide (FMLP1) [formyl methionyl leucyl phenylanine], CHX inhibited the induced generation and degranulation.[14]

If on the other hand neutrophils are activated with Phorbol myristate acetate (PMA) following CHX treatment, the antimicrobial agent enhanced both synthesis and degranulation. It appears that the responsiveness of CHX treated neutrophils to subsequent activators is dependent upon the nature of the activator.[14]

Effect of CHX on fibroblasts:

The drug CHX has been widely utilized as a wound antiseptic and oral antimicrobial rinse. There have been numerous reports on its safety as an oral rinse but its effect on wound healing has been contradictory. In a study, Jeffery. J. Pucher and Jon. C. Baniel utilized human fibroblasts derived from skin and oral tissue to test the effects of CHX on viability growth collagen gel contractions and total protein synthesis. Cells were exposed for an hour to 0.005% and 0.002% CHX and for 30 seconds to 0.12% CHX. The results indicated that a 0.002% concentration of the drug shows minimal cytotoxicity but is able to suppress cell division almost completely. Collagen gel contraction as a model of wound contraction was also severely affected by all of the concentration of CHX used. Total protein synthesis was suppressed by CHX in collagen gel culture. The data support the hypothesis that CHX is highly cytotoxic to cells in vitro but various others functions such as proliferation collagen gel contract-ion and protein synthesis are affected to different degrees by the drug.[15]

Side effects:

After more than 20 years of use, chlorhexidine has a remarkably clean record regarding side effects (Foulkes 1973, Loe 1973).[16] A series of toxicologic tests has shown that the molecule seems to be very stable and apparently follows the ordinary routes of excretion through the body in the several species tested. There is no evidence that chlorhexidine is permanently retained in the body (Winrow 1973, Magnusson & Heyden 1973).[17] It has been shown that chlorhexidine may penetrate the oral mucosa (Haugen & Johansen 1974), but the amounts are probably very small (Winrow 1973).[18]

In oral use as a mouthrinse, chlorhexidine has been reported to have a number of local side effects (Flotra et al. 1971).[19] These side effects are:

1. Brown discoloration of the teeth and some restorative materials and the dorsum of the tongue.

2. Taste perturbation where the salt taste appears to be preferentially affected (Lang et al. 1988) to leave food and drinks with a rather bland taste.

3. Oral mucosal erosion. A few cases of jjjg painful desquamations of the oral mucosa have been reported after chlorhexidine mouth rinses (Flotra et al. fi|| 1971a). The authors suggested that a precipitation of proteins in the mucin layer by the drug might have reduced the lubricating effect on the mucous membrane. This appears to be an idiosyncratic reaction and concentration dependent. Dilution of the 0.2% formulation to 0.1%, but rinsing with the whole volume to maintain dose, usually alleviates the problem. Erosions are rarely seen with 0.12% rinse products used at 15 ml volume.

4. Unilateral or bilateral parotid swelling. This is an extremely rare occurrence and an explanation is not available. The reports of virus infections (parotitis) in connection with chlorhexidine mouth rinses (Gjermo et al. 1970, Flotra et al. 1971a) are probably coincidental, but cannot be completely disregarded. Secretory IgA, which is known to possess antiviral activity, accumulates on the mucous membrane (Brandtzaeg 1972). A possible * precipitation of acidic proteins in the mucin layer coating mucous membrane of the oral cavity may thus interfere with the anti-virus mechanisms.

5. Enhanced supragingival calculus formation. This effect may be due to the precipitation of salivary proteins on to the tooth surface, thereby increasing pellicle thickness and/or precipitation of inorganic salts on to the pellicle layer. Certainly pellicle forming under the influence of chlorhexidine shows an early and highly calcified structure (Leach 1977).

6. The aqueous solution of chlorhexidine has a bitter taste which is difficult to mask completely and has been reported to interfere with the taste sensation for some hours after a mouth rinse (Loe & Schiott 1970, Gjermo et al. 1970, Flotra et al. 1971a). However, with dentifrices containing chlorhexidine no such complaints have been described (Gjermo & Rotla 1971, Eriksen et al. 1973).

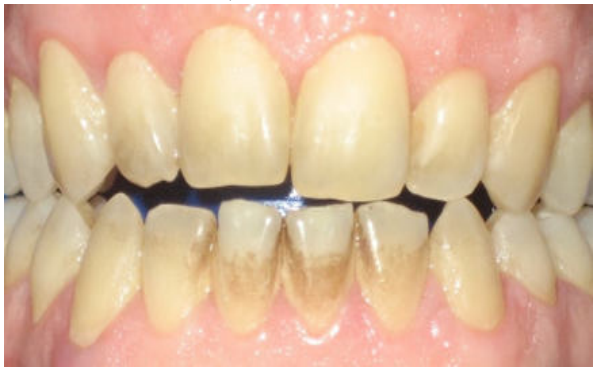

Figure 3: Brown discoloration of the teeth of an individual rinsing twice a day for 3 weeks with a 0.2% chlorhexidine mouthrinse.

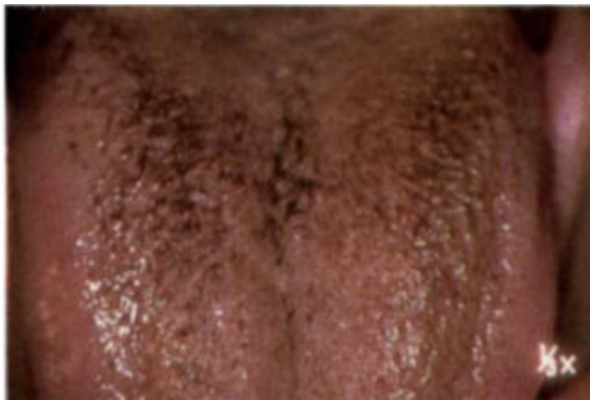

Figure 4: Brown discoloration of the tongue of an individual rinsing twice a day for 3 weeks with a 0.2% chlorhexidine mouthrinse.

Chlorhexidine staining:
The mechanisms proposed for chlorhexidine staining can be debated (Eriksen et al. 1985, Addy & Moran 1995, Watts & Addy 2001)[20] but have been proposed as:

1. Degradation of the chlorhexidine molecule to release parachloraniline
2. Catalysis of Maillard reactions
3. Protein denaturation with metal sulfide formation
4. Precipitation of anionic dietary chromogens.

1. Degradation of chlorhexidine to release parachloraniline appears not to occur on storage or as a result of metabolic processes. Also, alexidine, a related bis-biguanide, does not have parachloraniline groups, yet causes staining identical to that of chlorhexidine (Addy & Roberts 1981).

2. Non-enzymatic browning reactions (Maillard reactions) catalysed by chlorhexidine are a theoretical possibility (Nordbo^ 1979); however, evidence is indirect, circumstantial or inconclusive (Eriksen et al. 1985). The theory does not consider the fact that other antiseptics and metals such as tin, iron and copper also produce dental staining.

3. Protein denaturation produced by chlorhexidine with the interaction of exposed sulfide radicals with metal ions is also theoretically possible (Ellingsen et al. 1982, Nordbo et al. 1982) but there is no direct evidence to support this concept. Again, the theory does not take into account similar staining by other antiseptics and metal ions. Laboratory and clinical studies also could not reproduce this process (Addy et al. 1985, Addy & Moran 1985).

4. Precipitation of anionic dietary chromogens by cationic antiseptics, including chlorhexidine and polyvalent metal ions as an explanation for the phenomenon of staining by these substances, is supported by a number of well-controlled laboratory and clinical studies (Addy & Moran 1995, Watts & Addy 2001). Thus, the locally bound antiseptics or metal ions on mucosa or teeth can react with polyphenols in dietary substances to produce staining. Beverages such as tea, coffee and red wine are particularly chromogenic, but other foods and beverages will interact to produce various colored stains. These reactions between chlorhexidine and other cat ionic antiseptics and polyvalent metal ions with chromogenic beverages can be performed within the test tube. Interestingly, most of the precipitates formed between polyvalent metal ions and chromogens have the same color as their sulfide salts. It is for this reason that original theories considered that staining, seen in individuals exposed to these polyvalent metal ions, usually in the workplace, was due to metal sulfide formation. Again, laboratory and clinical experiments have failed to produce such interactions. It is perhaps the staining side effect that limits long-term use of chlorhexidine in preventive dentistry (Flotra et al, 1971) and occurs with all correctly formulated products including gels, toothpastes and sprays. Indeed, the staining side effect can be used to assess patient compliance in the use and activity of formulations. In the latter case laboratory and clinical studies on staining have revealed a proprietary chlorhexidine mouthrinse product to be inactive (Addy & Wade 1995, Renton-Harper et al. 1995). interestingly, this particular chlorhexidineproduct was reformulated in the UK *to* produce an active formulation (Addy et al. 1991), but the manufacturers maintained the original formulation within France when both laboratory and clinical studies confirmed markedly reduced potential of the product to cause staining in the laboratory, and plaque inhibition in the clinic (Addy & Wade 1995, Renton-Harper et al. 1995).

Chlorhexidine products:
Chlorhexidine has been formulated into a number of products.

Mouthrinses:
Aqueous alcohol solutions of 0.2% chlorhexidine were first made available for mouthrinse products for twice daily use in Europe in the 1970s. A 0.1% mouthrinse product also became available; however questions were raised over the activity of the 0.1% product and in some countries the efficacy of this product is less than would be expected from a 0.1% solution (Jenkins et al. 1989).[71] Later, in the US, a 0.12% mouthrinse was manufactured but to maintain the almost optimum 20 mg doses derived from 10 ml of 0.2% rinses, the product was recommended as a 15 ml rinse (18 mg dose), The studies revealed equal efficacy for 0.2% and 0.12% rinses when used at appropriate similar doses (Segreto et al. 1986).[12]

Figure 5: Chlorhexidene Gel

Sprays:
0.1% and 0.2% chlorhexidine in sprays are commercially available in some countries Studies with the 0.2% spray have revealed that small doses of approximately 1-2 mj delivered to all tooth surfaces produces similar plaque inhibition to a rinse with 0.2°/ mouth-rinses (Kalaga et al. 1989a). Sprays appear particularly useful for the physically and mentally handicapped groups, being well received by individuals

(Francis et al 1987a,b, Kalaga ctal. 1989).[14]

Toothpaste:
Chlorhexidine is difficult to formulate into toothpaste for reasons already given and early studies produced variable outcomes for benefits to plaque and gingivitis (Gjermo & Roila 1970, 1971, Johansen et al. 1972, 1975). More recently, a 1% chlorhexidine toothpaste with and without fluoride was found to be superior to the control product for the prevention of plaque and gingivitis in a 6-month home use study (Yates et al 1993). However, stain scores were markedly increased as was supragingival calculus formation, and the manufacturer did not produce a commercial product, for a short time a commercial product was available, having been shown to be efficacious for both plaque and gingivitis (Sanz et al. 1994). Although effective, chlorhexidine products based on toothpaste and sprays produce similar tooth staining to mouthrinses and gels; taste disturbance, mucosal erosion and parotid swellings tend to be less or have never been reported.[14]

Figure 6: Chlorhexidene Toothpaste

Varnishes:
Chlorhexidine varnishes have been used mainly for prophylaxis against root caries rather than an anti-plaque depot for chlorhexidine in the mouth.[15]

Varnish	Components	Experimental concentrations
chlorzoin	Chlorhexidine Sumatra benzoin Ethanol Polyurethane Methylene chloride	10% or 20% w/v
EC40	Chlorhexidine Sandarac Ethanol	10%,20%,25% 33%,40%(w/w)
cervitec	Chlorhexidine thymol ethanol or/ethyl acetate polyvinyl butyral	1% 1%

Varnish Recommended treatment regimen
chlorzoin A single application during 4 consecutive weeks \s recommended:
The dentition is cleaned, isolated and dried The therapeutic varnish is applied to all tooth surfaces by means Of a cotton pellet and dental floss and is dried for 15 s with a Gentle flow of air finally, the teeth are covered with a layer of polyurethane varnish and again dried for 15 sec EC **40*** A single application of about 10 to 15 mts is sufficient:

The dentition is cleaned, isolated and dried

The varnish is locally; applied by means of a syringe and is left in place for about 10 to 15 mts then, the varnish may be removed by the dentist or is **left** in place until the following tooth brush this treatment may be repeated 2x a year or more frequently

Cervitec 1 -3 applications within 10 to 14 days are recommended ; the dentition *k* cleaned, isolated and dried the varmsh is applied locally by means *o\'* a brush *and* dental floss and is left to dry during 15 to 30 s a treatment interval of 3 months is recommended

Chlorhexidine Local drug delivery:
The use of local delivery systems to treat various medical conditions - such as the skin patch to prevent seasickness, deliver HRT, or aid in smoking cessation - is now common. When treating periodontal disease, we are faced with the challenge of bacteria not only in the periodontal pocket, but also sometimes in the soft tissue walls and exposed dentin or cementum.

Local drug delivery allows the use of concentrations of approximately 100 times higher that does systemic administration. Site-specific, controlled release delivery systems have allowed us to administer therapeutic levels of drug to the site of infection for prolonged periods of time. Agents are available that incorporate the active ingredient into an agent (fibers, gels, chips, collagen film, acrylic strips, and a polymer). The active ingredient is then released over a period of days.[16]

A locally delivered product must remain in the pocket long enough to be effective. Considering that the gingival crevicular fluid in a 5 mm pocket is replaced about 40 times per hour, a reservoir that can release the drug continuously to offset this fluid elimination is necessary.

The goal of locally delivered products should be to eliminate the pathogenic organisms or alter the inflammatory response, and thereby minimize tissue destruction.[16]

The three criteria for achieving these goals are;
The medication must reach the intended site of action;
It must remain at an adequate concentration; and
It must last for a sufficient amount of time.
Local delivery devices can be sustained-release devices or controlled delivery systems. A sustained release device provides drug delivery for less than 24 hours, and a controlled delivery system releases the drug for more than 24 hours.[17]

PerioChip®: 2.5 mg Chlorhexidine Gluconate:
PerioChip® (chlorhexidine gluconate) is a small, orange-brown, tombstone shaped chip

for insertion into periodontal pockets that was approved by FDA in 1998. Each PerioChip® weighs approximately 7.4 mg and contains 2.5 mg of chlorhexidine gluconate in a biodegradable matrix of hydrolyzed gelatin cross-linked with glutaraldehyde.[18]

PerioChip also contains glycerin and purified water.The purpose of this biodegradable delivery system is to reduce pocket depth in chronic periodontitis, as an adjunctive therapy to SRP. Studies with PerioChip showed reductions in the numbers of the putative periodontopathic organisms *Porphyromonas {Bacteroides) gingivalis, Prevotella {Bacteroides) intermedia, Bacteroides forsythus,* and *Campylobacter rectus{Wolinella recta)* after placement of the chip.

No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted. The product is inserted directly into periodontal pockets that are 5 mm or greater in depth, following SRP.

PerioChip releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 hours, and then releasing the remaining chlorhexidine in an almost linear fashion for 7-10 days.

This release profile may be explained as an initial burst effect, dependent on diffusion of chlorhexidine from the chip, followed by a further release of chlorhexidine as a result of enzymatic degradation.[19]

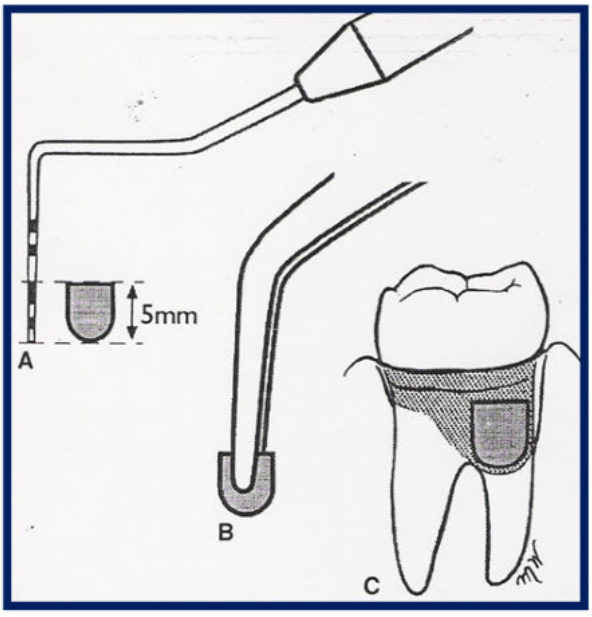

Figure 7: Chlorhexidiene Chip

(A) The chip is 5mm x 4mm rounded at one end.
(B) For insertion, the chip is grasped by cotton pliers on the square side.
(C) The chip is inserted to the very base of the pocket where the periodontal pathogens are concentrated.

Results of two large multicenter clinical studies in the U.S. indicates that the adjunctive use of PerioChip® with SRP results in significantly greater reduction of periodontal pockets than does SRP alone. Included in the double-blind, randomized, controlled clinical trials, were 447 adult clients with periodontitis who had at least 4 pockets with probing depth of 5 - 8 mm that bled on probing. Clients studied were in good general health. At the end of the nine-month study period, clients who received PerioChip in addition to SRP showed a .95 mm reduction in pocket depth compared to a .65 mm improvement with SRP alone. PerioChip should not be used in any client who is hypersensitive to chlorhexidine, and has not been studied for its effects on pregnant or lactating women, or on children. It is FDA pregnancy Category C. The use of PerioChip in an acutely abscessed periodontal pocket has not been studied and therefore is not recommended.[30]

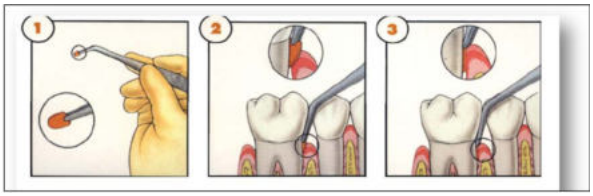

Figure 8: Perio Chip 1. Grasp PerioChip at flat end with forceps **2. Insert PerioChip curved end into the pocket, to its maximum depth** **3. Furthermaneuver PerioChip into position, if necessary.**

Placement is as follows: Remove the chip(s) from the refrigerator. The periodontal pocket should be isolated and the surrounding area dried before chip insertion. The PerioChip should be grasped by the square end using non-serrated forceps, so that the rounded end points into, and is inserted into, the periodontal pocket to its maximum depth. It should be placed at the base of the pocket. If necessary, the chip can be further maneuvered into position using the tips of the forceps or a flat instrument. The PerioChip does not need to be removed since it biodegrades completely.[21] According to clinical studies, it takes less than one minute to insert PerioChip into the periodontal pocket and no anesthesia is required. PerioChip stays in place, releasing chlorhexidine gluconate, and is fully bioabsorbable in 7 to 10 days. PerioChip may be inserted at the time of SRP and every three months thereafter as part of a periodontal maintenance program if pockets remain 5 mm or greater. Up to eight chips can be placed at each visit. Most oral pain or sensitivity occurred within the first week of the initial chip placement, was mild to moderate in nature, and resolved within days. These reactions were observed less frequently with subsequent chip placement at three and six months. In these studies and one additional study involving a total of 619 clients, there were no reports of visible staining or altered taste perception after the use of PerioChip. No serious adverse events were reported.[32]

The most frequently observed adverse events in the two pivotal trials (PerioChip versus placebo group) were toothache (51% versus 41%), upper respiratory tract infection (28% versus 26%), headache (27% versus 28%) and sinusitis (14% versus 13%), respectively. PerioChip treatment maintained probing attachment level compared with baseline or with SRP alone at nine months. Clients should avoid dental floss at the site of PerioChip insertion for 10 days after placement, because flossing might dislodge the chip. All other oral hygiene may be continued as usual, and dietary habits need not be modified. Dislodging of the PerioChip is uncommon; however, clients should be instructed to notify the dental hygienist or dentist promptly if it occurs. If the chip is dislodged seven days or more after placement, it should be considered that the client has received a full course of treatment. If dislodgement occurs more that 48 hrs after placement, the chip should not be replaced,but the client should be re inserted. If dislodgement occurs more than 48 hours after placement, the chip should not be replaced, but the client should be reevaluated at 3 months. A new PerioChip may be placed at that time if the pocket depth has not been reduced to less than 5 mm. Clients should also be advised that, although some mild to moderate sensitivity is normal during the first week after placement of PerioChip, they should notify the dental hygienist or dentist promptly if pain, swelling, or other problems occur. PerioChip must be stored in a refrigerator, 2°-8°C (36°^6°F), and has a shelf life of 2 years. Although some clinicians have reported placing this product in the freezer, this has not been studied and is not recommended.[12]

Clinical uses of chlorhexidine:
Despite the excellent plaque inhibitory properties of chlorhexidine, widespread and prolonged use of the agent is limited by local side effects. Moreover, because of the cationic nature of the chlorhexidine and therefore its poor penetrability, the antiseptic is of limited value in the therapy of established oral conditions including gingivitis, and is much more valuable in the preventive mode. A number of clinical uses, some well researched, have been recommended for chlorhexidine (Gjermo 1974, Addy 1986, Addy & Renton-Harper 1996a, Addy & Moran 1997).[33]

As an adjunct to oral hygiene and professional prophylaxis:
Oral hygiene instruction is a key factor in the treatment plan for patients with periodontal disease and as part of the maintenance program following treatment. Adequate plaque control by periodontal patients is therefore essential to successful treatment and the prevention of re-occurrence of the disease. Chlorhexidine should therefore increase the improvement in gingival health through plaque control, particularly following a professional prophylaxis to remove existing supra and immediately subgingival plaque. There is, however, a potential disadvantage of using such an effective chemical plaque control agent at this stage of the periodontal treatment plan. Thus, following oral hygiene instruction, it is normal, usually by the use of indices, to quantify the improvement in plaque control by patients so instructed and, in particular, the improvement at specific sites which previously had been missed by individual patients. By virtue of the excellent plaque control effects of chlorhexidine, the

response to oral hygiene instruction cannot be accurately assessed since the antiseptic will overshadow any deficiencies in mechanical cleaning. Indeed, as the original research demonstrated, patients could maintain close to zero levels of plaque following a professional prophylaxis without using any form of me chanical oral hygiene (Loe & Schiott 1970).[24]

Postoral surgery including periodontal surgery or root planing:
Chlorhexidine may be used postoperatively since it offers the advantage of reducing the bacterial load in the oral cavity and preventing plaque formation at a time when mechanical cleaning may be difficult because of discomfort. In periodontal surgery, periodontal dressings have largely been replaced by the use of Chlorhexidine preparations, in particular mouthrinses, since healing is improved and discomfort reduced (Newman& Addy 1978,1982).[25] Regimens vary but chlorhexidine should be used immediately post treatment and for periods of time until the patient can reinstitute normal oral hygiene. Depending on the appointment schedule, chlorhexidine could be used throughout the treatment phase and for periods of weeks after completion of the treatment plan. If dressings are used, chlorhexidine is of limited value to the postoperative site since it does not penetrate beneath the periodontal dressings (Pluss et al. 1975). The idea of full mouth disinfection using chlorhexidine both supra and subgingivally has recently been assessed by one group of researchers (Quirynen et al. 1995). In the event, few adjunctive benefits could be shown and it appeared that the more dominant factor was the time over which the non-surgical treatment plan was completed. Thus, root planing performed totally within 24 hours was more effective than root planing completed over more conventional periods of several weeks (for review see Quirynen et al. 2001).[26]

Nonsurgical treatment for peri-implant mucositis:
Prevalence of peri-implants mucositis has been reported from 20% in compliant patients (enrolled in a periodontal maintenance program) to about 50% in non-compliant patients with sporadic maintenance schedules. The improvement of clinical outcomes around implants after mechanical debridement alone and with the adjunctive use of local antiseptic gels and mouthrinses, have been observed. Chlorhexidine (gel, irrigation, or rinse) has shown significant results when used as an adjunctive to non-surgical periodontal therapy. [46]

For patients with jaw fixation:
Oral hygiene is particularly difficult when jaws are immobilized by such methods as intermaxillary fixation. Chlorhexidine has been shown to reduce markedly the bacterial load, which tends to increase during jaw immobilization, and improve plaque control (Nash & Addy 1979).[22]

For oral hygiene and gingival health benefits in the mentally and physically
Handicapped: Chlorhexidine has been found particularly useful in institutionalized mentally and physically handicapped groups, improving both oral hygiene and gingival health (Storhaug 1977). Spray delivery of 0.2% solutions was found particularly useful and acceptable to patients and care workers (Francis et al 1987), Kalaga et al. 1989b).[33-34]

Medically compromised individuals predisposed to oral infections: A number of medical conditions predispose individuals to oral infections, notably candidiasis. Chlorhexidine is effective as an anticandidal agent but is most useful when combined with specific anticandidal drugs, such as nystatin or amphoteracin B (Simonetti et al. 1988).[25] Indications for chlorhexidine use combined with anticandidal drugs have been for the prevention of oral and systemic infections in the immuno compromised, including those with blood dyscrasias, those receiving chemotherapy and /or radiotherapy and notably bone marrow transplant patients (Firretti et al. 1987, 1988, Toth et al. 1990).[27] The value of chlorhexidine appears greatest when initiated before oral or systemic complications arise. A chlorhexidine spray was also found to produce symptomatic /psychological oral care benefits in the terminally ill (Jobbins et al. 1992).[28]

High-risk caries patients: Chlorhexidine rinses or gels can reduce considerably the streptococcus mutans counts in individuals who are caries prone. Additionally, and interestingly, chlorhexidine appears synergistic with fluoride and combining chlorhexidine and fluoride rinses appears beneficial to such at risk individuals (Dolles & Cjermo 1980, Lindquist et al. 1989).

Recurrent oral ulceration: Several studies have shown that chlorhexidine niouthrinses and chlorhexidine gels reduce the incidence, duration and severity of recurrent minor aphthous ulceration (Addy et al. 1974,1976, Hunter & Addy 1987).[34] The mechanism of action is unclear but may relate to a reduction in contamination of ulcers by oral bacteria, thereby reducing the natural history of the ulceration. Regimens have included three times daily use of chlorhexidine products for several weeks. Interestingly, one study showed that triclosan rinses reduce the incidence of recurrent mouth ulcers (Skaare et al. 1996).[36] There have been no controlled studies of chlorhexidine in the management of major aphthous ulceration or other oral erosive or ulcerative conditions, although anecdotally chlorhexidine appears ineffective. Again, this may reflect the low therapeutic potential of this and other antiseptics.

Removal and fixed orthodontic appliance wearers: Plaque control in the early stages of orthodontic appliance therapy may be compromise and chlorhexidine can be prescribed for the first 4-8 weeks. Additionally, Chlorhexidine has been shown to reduce the number and severity of traumatic ulcers during the first 4 weeks of fixed orthodontic therapy (Shaw et al. 1984).[34]

In denture stomatitis: Chlorhexidine has been recommended in the treatment of candidal associated infections. However, in practice even applying chlorhexidine gel to the fitting surfaces of denture produces, in many cases, slow and incomplete resolution of the condition. Again, chlorhexidine is less effective in the therapeutic mode and it is more advantageous to treat denture stomatitis with specific anti-candidal drugs and then employ chlorhexidine prevent recurrence.[38] The denture itself can be usefully sterilized from Candida by soaking in chlorhexidine solutions (Olsen et al. 1975a,b).[39]

Immediate preoperative chlorhexidine rinsing and irrigation: This technique can be used immediately prior to operative treatment, particularly when an ultrasonic polishing or high-speed instruments are to be used. Such preoperative rinsing markedly reduces the bacterial load and contamination of the operative area and operator and staff (Worral et al. 1987). Additionally, in susceptible patients, irrigation of chlorhexidine around the gingival margin reduces the incidence of bacteremia (MacFarlane et al. 1984).[40] However, this should be seen only as an adjunct to appropriate systemic antimicrobial prophylaxis.[41]

Subgingival irrigation:
Numerous antimicrobial agents have been used as subgingival irrigants in the management and treatment of periodontal diseases (Wennstrom 1992, 1997). Alone, irrigation with antimicrobial agents produces effects little different from using saline and of short duration, suggesting that the action is a washing-out effect. Irrigation combined with root planing appears to provide no adjunctive benefits.[42]

CONCLUSION:

- Many patients believe that visits to the dental office for periodontal care will eliminate the disease process. It is incumbent on the dentist to educate & inform the pt. To reinforce pt. Responsibility for the long term success of therapy & cure. Patient administered plaque control currently in the use is the most important preventive & therapeutic procedure.
- Reinforcement & encouragement should be given often to help pt's modify long standing habits, adopt new ones, and understand their plaque control is also important to the clinician.
- Chlorhexidine to date is the proven most effective antiplaque agent for which commercial products are available to the public. Chlorhexidine is free from systemic toxicity in oral use, and microbial resistance and supra-infection do not occur. Local side effects are reported which are mainly cosmetic problems. The antiplaque action of chlorhexidine appears dependent on prolonged persistence of antimicrobial action in the mouth (substantivity)[45] A number of vehicles for delivering chlorhexidine are available, but mouthrinses are most commonly recommended.

REFERENCES:

1) Könönen E, Gursoy M, Gursoy UK. Periodontitis: A Multifaceted Disease of Tooth-Supporting Tissues. J Clin Med. 2019 Jul 31;8(8):1135.
2) Shaddox LM, Walker CB. Treating chronic periodontitis: current status, challenges, and future directions. Clin Cosmet Investig Dent. 2010 Aug 11; 2: 79- 91.
3) Mombelli, A. Microbial colonization of the periodontal pocket and its significance for periodontal therapy. Periodontol 2000, 2018;76:85-96.
4) Costalonga M, Herzberg MC. The oral microbiome and the immunobiology of periodontal disease and caries. Immunol Lett. 2014 Dec;162(2 Pt A):22-38.
5) Krayer JW, Leite RS, Kirkwood KL. Non-surgical chemotherapeutic treatment strategies for the management of periodontal diseases. Dent Clin North Am. 2010 Jan;54(1):13-33.
6) Gunsolley JC. Clinical efficacy of antimicrobial mouthrinses. Journal of dentistry. 2010 Jun 1;38:S6-10.
7) Teles Ricardo Palmier, Teles Flavia Rocha Fonseca. Antimicrobial agents used in the control of periodontal biofilms: effective adjuncts to mechanical plaque control?. Braz. oral res. 2009 June; 23(Suppl 1):39-48.
8) Marsh PD. Dental plaque as a biofilm and a microbial community - implications for health and disease. BMC Oral Health. 2006 Jun 15;6 Suppl 1(Suppl 1):S14.
9) Fischman SL (1997) Oral hygiene products: How far have we come in 6000 years? Periodontol 2000 15:7-14.
10) Rao SS, Chava VK. Anti-plaque And Anti-gingivitis Agents In The Control Of Supragingival Plaque. Ann and Esse of Dent. Oct– Dec 2017;9(4)10-6.
11) Lemos CA Jr, Villoria GE. Reviewed evidence about the safety of the daily use of alcohol-based mouthrinses. Braz Oral Res. 2008;22 Suppl 1:24-31.
12) Loeffler JM. The golden fountain--is urine the miracle drug no one told you about? Pan Afr Med J. 2010 May 25;5:13. PMID: 21293740; PMCID: PMC3032615.
13) Gurudath G, Vijayakumar KV, Arun R. Oral Hygiene Practices: Ancient Historical Review. J Orofac Res 2012;2(4):225-227.
14) Lippert, Frank. (2013). An Introduction to Toothpaste - Its Purpose, History and Ingredients. Monographs in oral science. 23. 1-14.
15) Tschoppe P, Wolf O, Eichhorn M, Martus P, Kielbassa AM. Design of a randomized controlled double-blind crossover clinical trial to assess the effects of saliva substitutes on bovine enamel and dentin in situ. BMC Oral Health. 2011 Apr 9;11:13.
16) Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim). 2017 Apr-Jun;11(2):72-80.
17) Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim). 2017 Apr-Jun;11(2):72-80.
18) Ng E, Lim LP. An Overview of Different Interdental Cleaning Aids and Their Effectiveness. Dent J (Basel). 2019 Jun 1;7(2):56.
19) Baehni PC, Takeuchi Y. Anti-plaque agents in the prevention of biofilm-associated oral diseases. Oral Dis. 2003;9 Suppl 1:23-9.
20) Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century. Perspect Medicin Chem. 2014 Aug 28;6:25-64.
21) Tatikonda A, Debnath S, Chauhan VS, Chaurasia VR, Taranath M, Sharma AM. Effects of herbal and non-herbal toothpastes on plaque and gingivitis: A clinical comparative study. J Int Soc Prev Community Dent. 2014 Dec;4(Suppl 2):S126-9.
22) Najafi MH, Taheri M, Mokhtari MR, Forouzanfar A, Farazi F, Mirzaee M, Ebrahiminik Z, Mehrara R. Comparative study of 0.2% and 0.12% digluconate chlorhexidine mouth rinses on the level of dental staining and gingival indices. Dent Res J (Isfahan). 2012 May;9(3):305-8.
23) Sreenivasan, P., Haraszthy, V. and Zambon, J. (2013), Antimicrobial efficacy of 005% cetylpyridinium chloride mouthrinses. Lett Appl Microbiol, 56: 14-20.
24) Chandra Shekar BR, Nagarajappa R, Suma S, Thakur R. Herbal extracts in oral health care - A review of the current scenario and its future needs. Pharmacogn Rev. 2015 Jul-Dec;9(18):87-92.
25) Kirsch J, Hannig M, Winkel P, Basche S, Leis B, Pütz N, Kensche A, Hannig C. Influence of pure fluorides and stannous ions on the initial bacterial colonization in situ. Sci Rep. 2019 Dec 6;9(1):18499.
26) Rodríguez-Martínez, Jorge & Valiente, Manuel & Sánchez-Martín, Maria-Jesus. Tooth whitening: From the established treatments to novel approaches to prevent side effects. Journal of Esthetic and Restorative Dentistry. 2019:31.
27) Young RO (2016) Chlorine Dioxide (ClO_2) As a Non-Toxic Antimicrobial Agent for Virus, Bacteria and Yeast (Candida Albicans). Int J Vaccines Vaccin 2(6):00052.
28) Sajjan, Parappa & Laxminarayan, Nagesh & Kar, Prem & Sajjanar, Mangala. (2019). Chlorhexidine as an Antimicrobial Agent in Dentistry -A Review. Oral health and dental management. 15. 93-100.
29) Limoli DH, Jones CJ, Wozniak DJ. Bacterial Extracellular Polysaccharides in Biofilm Formation and Function. Microbiol Spectr. 2015 Jun; 3(3): 10. 1128/microbiolspec.MB-0011-2014.
30) Collares FM, Rodrigues SB, Leitune VC, Celeste RK, Borba de Araújo F, Samuel SM. Chlorhexidine application in adhesive procedures: a meta-regression analysis. J Adhes Dent. 2013 Feb;15(1):11-8.
31) Chhabra P, Chhabra P, Kakkar A, Kamboj M. Chlorhexidine- A Review. Int J Res Health Allied Sci 2018; 4(5):47-51.
32) Dundappa J, Kanteshwari K. Comparative evaluation of effects of chlorhexidine and tetracycline on neutrophil viability and functions in vitro. J Indian Soc Periodontol. 2012 Jul;16(3):342-9.
33) Liu JX, Werner J, Kirsch T, Zuckerman JD, Virk MS. Cytotoxicity evaluation of chlorhexidine gluconate on human fibroblasts, myoblasts, and osteoblasts. J Bone Jt Infect. 2018 Aug 10;3(4):165-172.
34) Magnusson, B. and Heyden, G. (1973), Autoradiographic studies of ^{14}C chlorhexidine given orally in mice. Journal of Periodontal Research, 8: 49-54.
35) Segreto, V.A., Collins, E.M., Beiswanger, B.B., de La Rosa, M., Isaacs, R.L., Lang, N.P., Mallatt, M.E. and Meckel, A.H. A comparison of mouthrinses containing two concentrations of chlorhexidine. Journal of Periodontal Research. 1986; 21: 23-32.
36) Francis, J.R., Addy, M. and Hunter, B. (1987), A Comparison of Three Delivery Methods of Chlorhexidine in Handicapped Children: II. Parent and House.Parent Preferences. Journal of Periodontology, 58: 456-459.
37) Lakhani, Nazam & Laxman, Vandana. (2016). Chlorhexidine – An Insight.. International Journal of Advanced Research. 4. 1321-1328.
38) Ruiz N, M.d.R., da Luz Raulino M., Goulart C, de Mello SF. Dental plaque control strategies for the elderly population: A scoping review. Int J Dent Hygiene. 2021:8.
39) Sahu B, Gathe B, Chandrakar J, Zade R, Khade A, Kamble RL. Efficacy of chlorhexidine chips as local drug delivery in non-surgical management of chronic periodontitis. Int Dent Med J Adv Res 2019;5:1-4.
40) Rajesh K.S, .Pooja M, Hedge S, Kumar A. "Effectiveness of Chlorhexidine Gel And Ozonated Oil In Treatment of Plaque Induced Gingivitis – A Randomized Controlled Clinical Study."IOSR Journal of Dental and Medical Sciences. 2020;19(1):67-75.
41) Jhinger N, Kapoor D, Jain R. Comparison of Periochip (chlorhexidine gluconate 2.5 mg) and Arestin (Minocycline hydrochloride 1 mg) in the management of chronic periodontitis. Indian J Dent. 2015 Jan-Mar;6(1):20-6.
42) Ma, L., Diao, X. Effect of chlorhexidine chip as an adjunct in non-surgical management of periodontal pockets: a meta-analysis. *BMC Oral Health.* 2020; 20:262.
43) Daltro Rosa CD, Luna Gomes JM, de Moraes, Araujo Lemos, da Fonte, de Oliveira Limirio, Piza Pellizzer. Use of chlorhexidine chip after scaling and root planning on periodontal disease: A systematic review and meta-analysis. The Saud Dent Jour,2021;33(1):1-10.
44) Oliveira, L.M., Pazinatto, J. and Zanatta, F.B. (2021), Are oral hygiene instructions with aid of plaque-disclosing methods effective in improving self-performed dental plaque control? A systematic review of randomized controlled trials. Int J Dent Hygiene, 19:239-254.
45) Vyas T, Bhatt G, Gaur A, Sharma C, Sharma A, Nagi R. Chemical plaque control-A brief review. Journal of Family Medicine and Primary Care. 2021 Apr 1; 10(4):1562.
46) Barootchi S, Ravidà A, Tavelli L, Wang HL. Nonsurgical treatment for peri-implant mucositis: A systematic review and meta-analysis.