ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 5, pp. 16980-16986, May, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Review Article

APPLICATIONS OF VARIOUS FORMS OF CHLORHEXIDINE IN DENTISTRY – A REVIEW

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DOI: http://dx.doi.org/10.24327/ijrsr.2017.0805.0257

ARTICLE INFO

Article History:

Received 06th February, 2017
Received in revised form 14th March, 2017
Accepted 23rd April, 2017
Published online 28th May, 2017

Key Words:

Chlorhexidine, Mouthwash, Local drug delivery, Root canal irrigant.

ABSTRACT

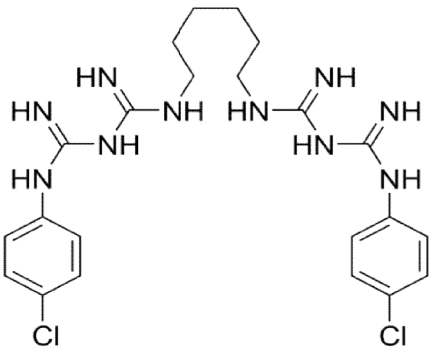
Chlorhexidine is a chemical antiseptic agent which is used extensively in the field of dentistry. It is effective against both gram positive and gram negative organisms. It has both bacteriostatic and bacteriocidal action in different concentrations. It is available in different forms such as mouth wash, spray, root canal irrigant, gel, lozenges, varnish, tooth brush disinfectant, chewing gum, intracanalmedicament, floss, mucoadhesive tablets, local drug delivery agent, chlorhexidine incorporated GIC, Chlorhexidine coated tooth picks. This article highlights the various forms of chlorhexidine and its applications in dentistry.

INTRODUCTION

Chlorhexidine (CHX) is a drug which is being used extensive in various fields of dentistry. The fact that chlorhexidine is effective against both gram positive and gram negative bacteria, intensifies its significance, but on comparative grounds, it is more active against gram positive organisms. It is a chemical antiseptic agent. Due to its extensive applications, numerous forms and combinations of chlorhexidine are available. The form of chlorhexidine used for a particular treatment is usually dependent upon; the site of application, duration of application, etc. The effectiveness of the drug in treatment is directly dependent on the selection of appropriate form, concentration and combination of drugs used during administration. Hence, an exquisite knowledge about the various forms, their concentration and method of administration is essential for proper treatment planning which has a positive impact on the outcome of the treatment. This article provides information of various forms of chlorhexidine available for dental use and their clinical applications.

Chlorhexidine

Chlorhexidine is N', N’’’’’-hexane-1, 6-diylbis [N-(4-chlorophenyl) (imidodicarbonimidicdiamide)]. It is both bacteriostatic and bactericidal in nature. The mechanism of action of chlorhexidine is mainly by membrane disruption [1]. Chlorhexidine is adsorbed onto the pellicle coated enamel surface which results in immediate bactericidal effect and prolonged bacteriostatic effect[2].



Studies suggest that, the level of streptococcus mutans reduction or plaque reduction by antimicrobial reduction does not essentially facilitate reduction in the rate of occurrence of dental caries [3]. Based on a multicenter, placebo controlled double blind randomized control trial; conducted in American population using 10% w/v Chlorhexidine gel to check the efficacy of Chlorhexidine in preventing dental caries, has shown net caries increment from baseline to 13 month follow up[4].

Available Forms of Chlorhexidine

Depending on the site of application, duration of application, pathology treated, various forms and combinations of chlorhexidine are available. They include:

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1. Mouthwash
2. ChlorhexidineSpray
3. Root canal Irrigant
4. Gel/Dentifrice
5. Lozenges
6. Varnish
7. Toothbrush disinfectant
8. Chewing gum
9. Intracanal medicament
10. Dental floss
11. Muco adhesive tablets
12. Glass Ionomer Cement containing chlorhexidine
13. Locally delivered chlorhexidine
14. Chlorhexidine Impregnated Toothpicks

Chlorhexidine Mouthwash

Mouthwashes have been used for centuries[5] with the objective of reducing the amount of microorganisms in the oral cavity[6]. Chlorhexidine based mouthwashes are more effective against S.aureus bacteria than other mouthwashes, hence they are widely used[7].

Anti - Bacterial Activity

Chlorhexidine mouthwashes are available in concentrations ranging from 0.12% to 0.2% in the market[8]. If 0.12% of chlorhexidine is used, then 15ml of mouth wash should be used and 15ml for 0.12% chlorhexidine. But lesser concentration are also used but not proved to be effective. A study conducted in children of age group 12-14 years of age shows that using chlorhexidine of concentration 0.12% showed the maximum reduction in Streptococcus mutans when compared with subjects using 0.02% and 0.06% concentrations[9]. 0.12% Chlorhexidine mouthwash is effective in eradicating S. mutans in periodontally healthy individuals, but a high rate of recurrence is observed after 3 – 6 months [10]. 0.2% Chlorhexidine showed highest substantivity in the oral cavity compared to 0.12% Chlorhexidine, 0.12% spray and swab impregnated with chlorhexidine[11] but no significant difference was observed in the anti plaque efficacy between these two concentrations of chlorhexidine mouthwash[12]. Addition of hydrogen peroxide to the chlorhexidinemouthrinse did not result in a further decrease in S. mutans levels [13]. Significant decrease in H_2S-producing bacteria was noted with these chlorhexidine rinses[14]. Intermittent rinsing with CHX may provide a preventive benefit in reducing levels of bacteria but only in subjects without alveolar bone loss[15].

Antifungal activity

Chlorhexidine can be used as antifungal agent. Studies showed that 0.2% Chlorhexidine showed better antifungal activity comparable to 0.25% laws one methyl ether mouthwash and 0.12% chlorhexidine[16].

Antiplaque agent

Chlorhexidine-sodium fluoride mouthrinse was more effective in reducing plaque accumulation and gingivitis[17]. CHX 0.05% alcoholic formulation is an effective antiplaque agent for long-term use with reduced subjective side effects such as extrinsic tooth staining, poor taste, taste disturbance, sensitivity changes in tongue, pain and irritation because of the alcohol content[18].

In the treatment of Alveolar Osteitis

Alveolar osteitis (dry socket) is the most common complication following the extraction of permanent teeth. To reduce alveolar osteitis after impacted third molar surgery, it was observed that use of postoperative chlorhexidine rinse was adequate for prevention of alveolar osteitits. The postoperative use of chlorhexidine is more feasible than both preoperative and postoperative use[19].

Adjuvant therapy in cleft lip patients

In cleft lip patients with multibracket appliances, CHX and fluoride application had a limited effect. However, no antibacterial adjuvant is more effective than CHX when combined with extensive prophylaxis [20].

Treatment of halitosis

Halitosis is also called oral malodour. It can be due to intra oral cause or extra oral cause. It is caused by sulphide production from bacteria present in dental plaque. Chlorhexidine has been used in the treatment of halitosis. Mouthrinses containing chlorhexidine, cetylpyridinium chloride and zinc-lactate is effective in the treatment of oral halitosis[21].

Role in Implant Surgeries:

Dental implant surgery produces bone debris that can be used in the "Simultaneous augmentation" technique. Although this debris is contaminated with oral bacteria, a stringent aspiration protocol has been shown to reduce the levels of contamination. Chlorhexidinemouthrinse is a well-proven antibacterial rinse that has been shown to reduce infectious complications associated with dental implants. A preoperative chlorhexidinemouthrinse should be utilised in conjunction with a stringent aspiration protocol to reduce further the bacterial contamination of bacterial debris[22].

ChlorhexidineSprays

The topical administration of Chlorhexidine associated to tooth brushing leads to a reduction in dental biofilm and gingival bleeding in children with special needs. Administration in spray form proved easier and was preferred by parents/caregivers [23].

Due to the side effects of Chlorhexidinedigluconate mouth rinsing, sprays have been proposed as an alternative method of CHX delivery to the oral cavity. CHX sprays are the most effective sprays in preventing plaque regrowth. CHX-containing sprays may represent an effective alternative to CHX rinses when mechanical oral hygiene has to be avoided in restricted areas [24].

The efficacy of CHX spray in the post-surgical control of dental plaque is similar to that of CHX mouthwash. Tooth staining, however, is significantly lower with sprays at sites not surgically involved [25].

Chlorhexidine as Root Canal Irrigant

Use of an appropriate root canal irrigant is essential during endodontic treatment, due to the complex and unpredictable anatomy of the root canal system and limitations in the mechanical instrumentation techniques used to obtain a clean, bacteria-free canal. The use of root canal irrigating solutions exerting antimicrobial activity and

prolonged residual activity is desirable in order to control dentin infection and delay reinfection of the root canal. The major advantages of chlorhexidine over NaOCl are its lower cytotoxicity and lack of foul smell and bad taste. However, unlike NaOCl, it cannot dissolve organic substances and necrotic tissues present in the root canal system. In addition, like NaOCl, it is unable to kill all bacteria and cannot remove the smear layer.

The widely used endodontic irrigantchlorhexidine is a positively charged lipophilic/hydrophobic molecule that interacts with phospholipids and lipopolysaccharides on the bacterial cell membrane. 2% CHX is considered to be the final irrigating solution which can aid in achieving the maximum residual and antimicrobial activity and in eradication of E. faecalis[26].

Chlorhexidine Dentifrice/ Gel

Chlorhexidine gel will inhibit plaque growth to some degree, but not to the same extent, as a CHX mouthwash [27]. Studies show that chlorhexidine containing toothpaste with non-ionic surfactant like sodium lauryl sulfate will be able to maintain the antibacterial property and substantivity of chlorhexidine [28].

A systematic analysis conducted to analyze the efficacy of chlorhexidine containing dentifrices showed that regarding plaque score reduction, the majority of the experiments using a CHX dentifrice provided a significant positive effect. All studies assessing gingival bleeding as parameter for gingivitis observed a significant reduction in favor of CHX dentifrice over placebo dentifrice. Tooth surface discoloration was more pronounced with CHX dentifrice. So, it could be concluded that, brushing with a CHX dentifrice can be effective with regard to the control of plaque and gingivitis. Tooth surface discoloration was observed as side effect, which potentially can have a negative impact on patients' compliance [29].

In pediatric patients, CHX toothpastes did not make a significant contribution in the reduction of S. mutans count. A randomized, controlled clinical trial conducted to compare the effectiveness of 0.12% chlorhexidine gel and fluoride toothpaste to prevent early childhood caries showed no differences in percentages of MS-positive children between the CHX and control groups. But the authors concluded that the non- effectiveness of CHX in children was mainly due to low compliance [30].

Chlorhexidine Lozenges

Lozenges are medicated tablet intended to be dissolved slowly in the mouth. Lozenges are generally used for throat infection treatment. In dentistry, Chlorhexidine incorporated lozenges are used to control plaque microorganisms. According to the research of Koenig *et al*., the increased temperature has a beneficial effect on the activity of chlorhexidine applied as the mouth rinse. The temperature in mouth is in the range of 36.8°C, whereas during the infection increases up to 38.5°C. This is a factor which would increase the temperature of chlorhexidine applied in the form of lozenges [31]. The crucial parameter in the formulation of a tablet with chlorhexidine would be the concentration of the drug in the oral cavity during the application of the lozenge. In the case of antimicrobial substances, like chlorhexidine salts, the prolonged presence of the active substance in the minimal inhibition concentration (MIC) or the minimal bactericidal concentration (MBC) is of great importance [32]. Chlorhexidine lozenges have a role in plaque control also. Lozenges are a more convenient alternative to chlorhexidinemouthrinses and have superior results in plaque control [33].

Chlorhexidine Varnish

Friedman and Golomb [34] demonstrated that it was possible to obtain sustained (slow) release of chlorhexidine for several months in vitro. Balanyk and Sandham [35] developed a varnish vehicle that was safe in humans, compatible with chlorhexidine and able to release the chemotherapeutic agent over an extended period of time. This varnish released chlorhexidine into the oral environment at low but bactericidal levels for approximately two weeks. This sustained release chlorhexidine varnish was proven to be very successful at suppressing MS for prolonged periods and more effective than other chlorhexidine therapies. [36, 37] A single application of the chlorhexidine varnish to the teeth resulted in the elimination of detectable MS from the saliva of some individuals for many weeks. The chlorhexidine varnish, when applied before the placement of fixed orthodontic appliances, was able to significantly reduce the levels from baseline values for up to seven months. [38]

Chlorhexidine as Toothbrush disinfectant

The literature contains studies showing that the simple cleaning routine with a toothbrush could cause bacteremia. Thus, the toothbrush, which also aids in the removal of biofilm could indirectly lead to the installation of a disease by bacteremia that would follow the tooth brushing. Chlorhexidine can be used to disinfect the bristles. Studies showed chlorhexidine had greater effect in disinfecting the bristles of the toothbrush and can be used to prevent bacteremia [39].

Chlorhexidine Chewing gum

Chlorhexidine is also available as a chewing gum.CHewX a commercially available chlorhexidine chewing gum was introduced in Switzerland. It contains 5mg chlrohexidinediacetate per pellet. Approximately 35% of chlorhexidine is released in 5 minutes and 68% is released after 15 minutes of chewing. Regular use of CHX-containing chewing gum appears useful to control dental plaque formation [40]. Maternal consumption of chlorhexidine containing chewing gums significantly reduced the mother-child transmission of salivary mutans streptococci [41].

Chlorhexidine as Intra Canal Medicament

Treatment of concomitant endodontic-periodontal lesions remains a challenge in clinical practice and requires effective endodontic and regenerative periodontal therapy. Among other factors, cross seeding and recolonization of flora may affect the outcome of periodontal therapy. Intracanal medicaments have been shown to exert antimicrobial activity on the external root surface, and local delivery of antimicrobials has been suggested to be a complementary approach in the management of periodontitis [42]. CHX based intracanal medicaments are effective in decreasing the viability of E. faecalis compared to conventional calcium hydroxide intra canal medicament [43]. Special devices have been designed to deliver chlorhexidine inside root canals in incremental manner. In these devices,

CHX is contained in a polymer sheath that, when placed in a liquid environment, gradually dissolves and releases the CHX. Although the applicability of such devices to the root canal of human teeth remains to be proven, their efficacy in the release of CHX has been shown both in agar plates and in bovine roots [44].

Chlorhexidine Impregnated Dental floss

Tooth brush cannot access the interdental areas effectively and hence interdental cleansing aid in the form of dental floss plays an important role in plaque control. Flossing with chlorhexidine suppresses S. mutans during the period of time. Brushing for seven days with chlorhexidine gel (1%) without a preceding intensive chlorhexidine treatment had virtually no effect on S. mutans in approximal areas and in saliva, but suppressed S. mutans in fissures and on smooth surfaces [45]. Long term studies are needed to validate the effect of chlorhexidine floss on dental caries prevention.

Mucoadhesive tablets containing Chlorhexidine

Mucoadhesive tablets are designed so that they can release chlorhexidine in a sustained manner. They contain chlorhexidine and able to adhere to the buccal mucosa to give local controlled release of drug. A mucoadhesive formulation was designed to swell and form a gel adhering to the mucosa and controlling the drug release into the oral cavity. Some batches of tablets were developed by direct compression, containing different amounts of hydroxyl propylmethylcellulose (HPMC) and carbomer; changing the amount ratio of these excipients in formulations, it is possible easily modulate the mucoadhesive effect and release of drug [46]. In vivo studies suggest that the palatal adhesive tablets containing herbal formulation may serve as an effective means of treatment for patients complaining of oral malodor[47]. The composition of mucoadhesive tablets include carboxymethyl (CMC), hydroxypropylmethyl (HPMC) and hydroxypropyl(HPC) cellulose, alone (3% w/w) or in binary mixtures (5% w/w). This mixture is able to guarantee both prolonged release and reduced transmucosal permeation [48]. A recent study concluded that, the presence of Cordiamyxa powdered mucilage may significantly affect the tablet characteristics and increasing in muco-adhesiveness may be achieved by using 20% w/w mucilage [49].

GlassIonomer cement with chlorhexidine

Glass ionomer cements (GICs) are widely used dental materials first introduced to dentistry in 1972 by Wilson and Kent [50] to improve the anti-bacterial properties of GICs, anti-bacterial materials such as cetylpyridinium chloride, cetrimide and benzalkoniumchlorhexidine (CHX) were used. Amongst the anti-bacterial applications CHX is accepted to be the gold standard in dentistry. To increase the anti-bacterial properties of GICs different formulations are under development. Amongst them formulations that include both fluoride and CHX are promising. However, it is also important to determine the biocompatibility properties of new formulations [51]. It was observed that adding CHX at concentrations of 1% and 2% increased significantly the setting time of the glass ionomer cement. The tensile bond strength of the material also decreased significantly after adding CHX at a concentration of 2%. Addition of CHX promoted formation of an inhibition halo in both bacterial strains for all concentrations [52]. Recently, a series of GICs functionalized with chlorhexidine-hexametaphosphate nanoparticles were created for the first time. These released chlorhexidine in a dose-dependent manner. These materials may find application in the development of a new generation of antimicrobial dental nanomaterials [53]. Experiments show that resin modified GIC incorporated with chlorhexidine revealed significantly lower bacterial vitality than conventional GIC [54].

Locally Delivered Chlorhexidine

Locally delivered antimicrobials offer several advantages than systemic antimicrobials. Locally delivered drugs does not produce systemic toxicity because these drugs are not absorbed into the systemic circulation. Resistance is not developed against locally delivered drugs and high concentration is maintained for longer period. Chlorhexidine can be used as local drug delivery agent [55].

The safety and efficacy of a degradable, subgingivally placed drug delivery system containing 2.5 mg chlorhexidine (CHX) were evaluated in a randomized, blinded, multi-centerstudy of 118 patients with moderate periodontitis. A split-mouth design was used to compare the treatment outcomes of scaling and root planing (SRP) alone with the combined use of SRP and the CHX in pockets with probing depths of 5 to 8 mm. Clinical and safety measurements including probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) as well as gingivitis, plaque, and staining indices were recorded at baseline, and at 1, 3, and 6 months. The reduction in CAL at the treated sites was greater than at the SRP sites, although the difference was statistically significant at the 6-month visit only. An analysis of patients with initial probing depths of 7 to 8 mm (n = 56) revealed a significantly greater reduction in PD and CAL in those pockets treated with CHX compared to SRP at both 3 and 6 months. The mean differences between test and control sites at 6 months were 0.71 mm and 0.56 mm PD and CAL respectively [56].

Chlorhexidine can be delivered with vehicles like Polyethylmethacrylic strips. Evidence to date has demonstrated the potential value of acrylic strips to deliver antimicrobial compounds into periodontal pockets. Polyethylmethacrylic strips of suitable dimensions containing 10 to 50% chlorhexidine acetate are being used in the non- surgical management of chronic periodontitis [57].

The strips appear to have potential for prolonged drug delivery to periodontal pockets. Antimicrobial acrylic strips appear useful treatments for chronic periodontitis, but should be used primarily as an adjunct to conventional root planing [58].

Chlorhexidine Impregnated Toothpicks

A method of treating oral and systemic diseases includes impregnating or coating a toothpick with active therapeutic agents and rubbing the toothpick against mouth tissue to release the active therapeutic agents onto the tissue for penetration through the tissue. The amount of therapeutic agents available to be transferred from the toothpick to the oral tissues will vary dependant on whether the agents are impregnated within wood or coated on plastic or other materials. The concentration of therapeutic agents can be either increased or decreased in order to reduce or increase the

duration of effect of treatment or the amount of the application [59]. 2% CHX impregnated toothpick use did not show any significant difference in S. mutans count in the saliva of patients cultured in blood agar [60]. 2% chlorhexidine- and non-impregnated toothpicks had a similar effect on sound and demineralized enamel and on demineralized dentine [61].

CONCLUSION

Chlorhexidine as a therapeutic agent has wide applications in dentistry. Various forms of Chlorhexidine used in dental treatment were highlighted in the article. Side effects of chlorhexidine, though minor needs to be controlled to widen the usage of chlorhexidine in different treatment modalities. More research work is needed to explore other potential forms of chlorhexidine in dental practice.

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How to cite this article:

Jaiganesh Ramamurthy and Arvind Venkatesh.2017, Applications of Various Forms of Chlorhexidine in Dentistry-A Review. *Int J Recent Sci Res.* 8(5), pp. 16980-16986. DOI: http://dx.doi.org/10.24327/ijrsr.2017.0805.0257

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