

Chlorhexidine Gluconate – A Promising Endodontic Irrigant: A Review

S Neha¹, L Jyoti², C Manoj³, S Ajay⁴

(Dept. Of Endodontics and Conservative dentistry, Sharad Pawar dental college and hospital, Sawangi (Wardha) Maharashtra, India)

(Reader, Dept. Of Endodontics and Conservative dentistry, Sharad Pawar dental college and hospital, Sawangi (Wardha), Maharashtra, India)

(H.O.D & prof, Dept. Of Endodontics and Conservative dentistry, Sharad Pawar dental college and hospital, Sawangi (Wardha), Maharashtra, India)

(Asso.prof. Dept. Of Endodontics and Conservative dentistry, Sharad Pawar dental college and hospital, Sawangi (Wardha), Maharashtra, India)

Abstract: Local debridement in the diseased pulp space is the main step in root canal treatment to prevent the tooth from being a source of infection. In this review article, requirements for irrigating solutions, chlorhexidine as an endodontic irrigant, its mechanism of action, characteristics like substansivity, adhering property to dentin and new formulations which are chlorhexidine based are spelled out. Chemical and toxicological concerns related to their use are discussed, including different approaches to enhance local efficacy without increasing the caustic potential. Based on the actions and interactions of currently available solutions, a clinical irrigating regimen is proposed.

Keywords: Chlorhexidine, ChlorXtra, Chlor plus, QMiX, Substansivity

I. Introduction:

Bacteria have long been recognized as the primary etiological factor in the development of pulp and periapical lesions (1). Successful root canal therapy depends on thorough chemomechanical debridement of pulpal tissue, dentin debris, and infective microorganisms. Irrigation is defined as “to wash out a body cavity or wound with water or a medicated fluid” and aspiration as “the process of removing fluids or gases from the body with a suction device.” The objectives of irrigation in endodontics are mechanical, chemical, and biological. The mechanical and chemical objectives are as follows: (i) flush out debris, (ii) lubricate the canal, (iii) dissolve organic and inorganic tissue, and (iv) prevent the formation of a smear layer during instrumentation or dissolve it once it has formed. The biological function of the irrigants is related to their antimicrobial effect, more specifically: (i) they have a high efficacy against anaerobic and facultative microorganisms in their planktonic state and in biofilms, (ii) they have the ability to inactivate endotoxin, and (iii) they are nontoxic when they come in contact with vital tissues, are not caustic to periodontal tissues, and have little potential to cause an anaphylactic reaction.

II. Desired Actions Of Irrigating Solutions:

Historically, countless compounds in aqueous solution have been suggested as root canal irrigants, including inert substances such as sodium chloride (saline) or highly toxic and allergic biocides such as formaldehyde(2). In this review, however, the focus is on currently used irrigating solutions. Based on the above knowledge, it appears evident that root canal irrigants ideally should:

- Have a broad antimicrobial spectrum and high efficacy against anaerobic and facultative microorganisms organized in biofilms
 - Dissolve necrotic pulp tissue remnants
 - Inactivate endotoxin
 - Prevent the formation of a smear layer during instrumentation or dissolve the latter once it has formed
- Furthermore, as endodontic irrigants come in contact with vital tissues, they should be systemically nontoxic, noncaustic to periodontal tissues and have little potential to cause an anaphylactic reaction.

III. Chlorhexidine:

3.1 **HISTORY:** Chlorhexidine was developed in the late 1940s in the research laboratories of Imperial Chemical Industries Ltd. (Macclesfield, England). Initially, a series of polybisguanides was synthesized to obtain anti-viral substances. However, they had little anti-viral efficacy and were put aside, only to be re-discovered some years later as antibacterial agents. Chlorhexidine was the most potent of the tested

bisguanides.(3).Chlorhexidine is a strong base and is most stable in the form of its salts. The original salts were chlorhexidine acetate and hydrochloride, both of which are relatively poorly soluble in water (4). Hence, they have been replaced by chlorhexidine digluconate.

3.2 **MOLECULAR STRUCTURE:** CHX belongs to the polybiguanide antibacterial family, consisting of two symmetric 4-chlorophenyl rings and two biguanide groups connected by a central hexamethylene chain (Fig. 1). CHX is a strongly basic molecule and is stable as a salt. CHX digluconate salt is easily soluble in water (5).

3.3 **MECHANISM OF ACTION:** CHX is a wide-spectrum antimicrobial agent, active against Gram-positive and Gram-negative bacteria, and yeasts (6)... Due to its cationic nature, CHX is capable of electrostatically binding to the negatively charged surfaces of bacteria, damaging the outer layers of the cell wall and rendering it permeable (7) Depending on its concentration, CHX can have both bacteriostatic and bactericidal effects. At high concentrations, CHX acts as a detergent and by damaging the cell membrane, it causes precipitation of the cytoplasm and thereby exerts a bactericidal effect. At low sub-lethal concentrations, chlorhexidine is bacteriostatic, causing low molecular weight substances, i.e. potassium and phosphorous, to leak out without the cell being irreversibly damaged. It also can affect bacterial metabolism in several other ways such as abolishing the activity of the PTS sugar transport system and inhibiting acid production in some bacteria.(8)

3.4 **CHARACTERISTICS OF CHLORHEXIDINE:**

A. Antibacterial activity: CHX has a broad-spectrum antimicrobial activity, targeting both gram-positive and gram-negative microbes(9)(10)(11).In general, in vitro studies suggested that CHX and NaOCl have comparable antibacterial effect when used in similar concentration(11) (12) In addition, CHX appeared to be a promising agent to be used as a final irrigant(13). Antifungal: CHX is also an effective antifungal agent especially against *Candida albicans*.

B. Substantivity: Chlorhexidine remains in dentinal tubules for around 12 weeks.

C. pH : CHX has an optimal pH of around 5-7 (14)

D. Dentin, components (HA and collagen), microbial biomass, and inflammatory exudate in the root canal system may reduce or inhibit the antibacterial activity of CHX by altering the pH.

Despite its usefulness as a final irrigant, chlorhexidine cannot be advocated as the main irrigant in standard endodontic cases, because:

A. Chlorhexidine is unable to dissolve necrotic tissue remnants (15)

B. Medication and/or irrigation with CHX may delay the contamination of root-filled teeth by bacteria entering through the coronal restoration/tooth interface

C. Medication and/or irrigation with CHX will not increase leakage through the root-filled apical foramen

D. Combinations of NaOCl and CHX cause color changes and formation of a precipitate, which may interfere with the seal of the root filling

E. CHX can significantly improve the integrity of the hybrid layer and resin–dentin bond stability

F. Acceptable biocompatibility

G. 2% CHX is irritating to skin(37)

H. Heating a CHX solution of lesser concentration could increase its local efficiency in root canal system while keeping systemic toxicity low

I. Effect of CHX on bacterial biofilms is significantly less than NaOCl.

3.5 **SUBSTANTIVITY:** Due to the cationic nature of the CHX molecule, it can be adsorbed by anionic substrates such as the oral mucosa (16)(17) Chlorhexidine has the ability to bind to proteins such as albumin, which is present in serum or saliva, pellicle found on the tooth surface, salivary glycoproteins and mucous membranes. This reaction is reversible(18).CHX can also be adsorbed onto hydroxyapatite and teeth. Studies have shown that the uptake of CHX onto teeth also is reversible. This reversible reaction of uptake and release of CHX leads to substantive antimicrobial activity and is referred to as “substantivity” (19). This effect depends on the concentration of CHX. At low concentrations of 0.005–0.01%, a stable monolayer of CHX is adsorbed and formed on the tooth surface, which might change the physical and chemical properties of the surface and may prevent or reduce bacterial colonization. At higher concentrations (> 0.02%), a multilayer of CHX is formed on the surface, providing a reservoir of chlorhexidine, and this multilayer can rapidly release excess CHX into the environment as the concentration of the CHX in the surrounding environment decreases (20). The antibacterial substantivity of three concentrations of CHX solution (4%, 2%, and 0.2%) after 5 min of application has been evaluated. The results have revealed a direct relationship between the concentration of CHX and its substantivity (21).. In contrast, Lin et al. (22). attributed the substantivity of CHX to its ability to

adsorb onto the dentin during the first hour. They stated that it is only after the saturation point is reached after the first hour that the antimicrobial capability of CHX increases with time. Furthermore, Komorowski et al. (23) revealed that a 5-min application of CHX did not induce substantivity and that the dentin should be treated with CHX for 7 days. Overall, it seems that residual antimicrobial activity from CHX remains in the root canal system for up to 12 weeks (24)

3.6 DENTIN BONDING PROPERTY: During the last 2 decades, chemical and technical advances have contributed to increases in resin-dentin bond strength. However, the premature loss of bond strength is one of the problems that still affects adhesive restorations (25) and markedly reduces their durability (26) **Carrilho et al.** (27) evaluated the effect of CHX on resin-dentin bond stability *ex vivo*. The investigators found significantly better preservation of bond strength 6 months after CHX use and that the protease inhibitors in the storage medium had no effect on the bond strength. Analysis showed there was significantly less failure in the hybrid layer with CHX compared to controls after 6 months. The same authors also evaluated the effect of CHX on the preservation of the hybrid layer *in vivo*. Their findings showed that bond strength remained stable in the CHX-treated specimens, while bond strength decreased significantly in control teeth. Resin infiltrated dentin in CHX-treated specimens exhibited a collagen network with normal structural integrity. Conversely, progressive disintegration of the fibrillar network was identified in control specimens. They concluded that auto-degradation of collagen matrices can occur in resin-infiltrated dentin, but may be prevented by the application of a synthetic protease inhibitor such as CHX. Overall, because of its broad-spectrum MMP-inhibitory effect, CHX can significantly improve resin-dentin bond stability.

3.7 ACTIVITY ON HEATING:

Heating 10% Ca(OH)₂ and 0.12% CHX to 46°C produced approximately a 1.8-log reduction of *E. faecalis* relative to saline at 37°C. suggest that delivering 10% Ca(OH)₂ or 0.12% CHX at 46°C would increase its antibacterial efficacy without the addition of more cytotoxic materials. Further studies are needed to test these devices for their effectiveness in maintaining the prescribed level of heat.(28)

3.8 NEW FORMULATIONS:

a) QMiX: QMiX (Dentsply Tulsa dental speciality, Jhonson City, TN) was introduced in 2011. QMiX is one of the new combination products introduced for root canal irrigation(29) Its manufacturer recommends that it be used at the end of instrumentation after NaOCl irrigation. QMiX contains EDTA, CHX, and a detergent and comes as a ready-to-use clear solution.

Protocol

QMiX should be used as a final rinse. If sodium hypochlorite was used throughout the cleaning and shaping, saline should be used to rinse out the NaOCl to prevent the formation of PCA, although no precipitate has been described when mixing QMiX and NaOCl.

Surface tension

According to Grossman (30), low surface tension is one of the ideal characteristics of an irrigant. Lower surface tension may help in better penetration of the irrigating solutions into the dentinal tubules and inaccessible areas of the root canal system (31). To be more effective in debris removal and to penetrate more readily into the root canal system, irrigants must be in contact with the dentin walls. The closeness of this contact is directly related to its surface tension(32). Irrigants with a low surface tension are more suitable as endodontic irrigants. QMiX incorporated a detergent in its formula to decrease the surface tension.

Smear layer removal

(33)QMiX removed the smear layer equally as well as EDTA (P =0.18). They concluded that the ability to remove the smear layer by QMiX was comparable to that of EDTA. Dai et al. (34).examined the ability of two versions of QMiX to remove canal wall smear layers and debris using an open-canal design. Within the limitations of the open-canal design, the two experimental QMiX versions are as effective as 17% EDTA in removing canal wall smear layers after the use of 5.25% NaOCl as the initial rinse.

b) CHLORPLUS & CHLORXTRA: (Vista Dental, Racine, WI) Several studies have analyzed the antibacterial properties and wettability of these new irrigants with contrasting results. Williamson et al. (35) created a monoculture biofilm of a clinical isolate of *E. Faecalis* and determined the susceptibility against four antimicrobial irrigants. Biofilms were subjected to 1-,3-, or 5-min exposures to one of the following irrigants: 6% sodium hypochlorite (NaOCl), 2% chlorhexidine gluconate (CHX), or one of two new products, □□6%

NaOCl with surface modifiers (Chlor- XTRA) or 2% CHX with surface modifiers (CHXPlus) (Vista Dental Products, Racine, WI). It was hypothesized that NaOCl and CHX would be equally effective and that the addition of surface modifiers would improve the bactericidal activity of the respective irrigants compared to the original formulations. Results indicate that 6% NaOCl and Chlor-XTRA were superior against *E. faecalis* biofilms compared to 2% CHX and CHX-Plus at all timepoints except 5 min. Similarly, Palazzi et al. (36) studied the new 5.25% sodium hypochlorite solutions modified with surfactants, Hypoclean A and Hypoclean B. Both had surface tension values that were significantly lower ($P < 0.01$) than Chlor-XTRA and 5.25% NaOCl. Because of their low surface tension and increased contact with dentinal walls, these new irrigants have the potential to penetrate more readily into the uninstrumented areas of the root canal system as well as allow a more rapid exchange with fresh solution, enabling greater antimicrobial effectiveness and enhanced pulp tissue dissolution ability.

3.9 CYTOTOXICITY: Ethical clearance for this study was provided by the Faculty of Medicine, Ege University, Animal Ethics Committee. The cytotoxic effects of the root canal irrigants on the subcutaneous tissue of rats were examined using the methods described previously (Yesilsoy et al. 1995, Turku n et al. 1998). The results were obtained at 28hrs, 48hrs and 2 weeks interval. They concluded that In the 2% chlorhexidine gluconate group, the inflammatory reaction values reached the highest value at 48 h with a significant difference between after 2 and after 48 h ($P < 0.05$). At 2 weeks, there was a significant moderation in the values in comparison to the 48 h results ($P < 0.05$).

3.10 ALLERGIC REACTIONS: One case of anaphylactic shock after application of 0.6% CHX to intact skin, which presented as a rash following a minor accident, has been reported in the dermatological literature (37). Further allergic reactions such as anaphylaxis, contact dermatitis, and urticaria have been reported following direct contact to mucosal tissue or open wounds.

IV. Table Showing Studies On Chlorhexidine Gluconate As Irrigating Solution With Various Other Materials (Ref: 38 – 50)

YEAR	AUTHOR	CHX COMPARED WITH	STUDY	RESULTS
2001	B. P. F. A. Gomes	Sodium hypochlorite	antimicrobial activity of several concentrations of sodium hypochlorite and chlorhexidine gluconate in the elimination of <i>Enterococcus faecalis</i>	Chlorhexidine in the liquid form at all concentrations tested (0.2%, 1% and 2%) and NaOCl (5.25%) were the most effective irrigants. However, the time required by 0.2% chlorhexidine liquid and 2% chlorhexidine gel to promote negative cultures was only 30 s and 1 min, respectively.
2002	Portenier I et al	Iodine Potassium Iodide	Inactivation of Antibacterial activity against <i>E.faecalis</i> in presence of dentin	CHX & IPI both show reduced antimicrobial activity in presence of dentin
2003	S. Haenni et al	Calcium hydroxide	Chemical & antimicrobial activity of $Ca(OH)_2$ mixed with CHX	Mixture does not improve the properties
2003	B.P.F.A Gomes et al	Calcium hydroxide	Effectiveness against <i>E.faecalis</i> in bovine root dentin	CHX completely inhibits <i>E.faecalis</i> at 1,2,7&15 days. $Ca(OH)_2$ allowed growth at all times.
2003	D.Evans M et al	Calcium hydroxide	Efficiency as intracanal medication in bovine dentin	Combination of CHX & $Ca(OH)_2$ was significantly more effective than $Ca(OH)_2$ alone.
2006	R. Dunavant T et al	6% NaOCl 1%NaOCl Smear clear	Comparative evaluation against <i>E.feacalis</i> Biofilms	6% & 1% NaOCl was more efficient in eliminating <i>E.faecalis</i>

		REDA MTAD		than other solutions tested
2006	Portenier I. Et al	MTAD	Killing of E.faecalis by MTAD &CHX Digluconate with or without cetrimide in presence or absence of dentin	Presence of cetrimide reduced the time required for killing.
2007	Luciana M. Et al	Sodium hypochlorite	Antimicrobial activity of sodium hypochlorite & CHX by two different tests	0.12% CHX was ineffective in eliminating E.faecalis. while 0.5% & 1% CHX , 1% & 5% NaOCl were equally effective
2008	Bui. T et al	Sodium hypochlorite	Interaction between NaOCl & CHX gluconate & effects on dentin was evaluated	The NaOCl/CHX precipitate tends to occlude the dentinal tubules.
2009	Evangelos G et al	Calcium hydroxide	Effect of 2% CHX mixed with Ca(OH) ₂ as an intracanal medication on sealing ability of permanent Root Canal Filling.	The antimicrobial activity of the combination is increased and it did not affect the sealing ability of root canal obturation.
2010	Gonzales L. Et al	Calcium hydroxide	Influence of dentine on pH of 2% CHX &Ca(OH) ₂	Ca(OH) ₂ always showed higher pH values than CHX
2011	Agrawal V. Et al	5.25% NaOCl 17%EDTA Biopure MTAD	Evaluation of effect of endodontic solutions on flexural strength & hardness of White MTA	EDTA & MTAD significantly reduced hardness & flexural strength while CHX & NaOCl did not
2013	Morgental D. Et al	6% NaOCl 1% NaOCl QMIX 17% EDTA	Antibacterial effect of new conventional Endodontic Irrigants in presence of dentin	After 6 hrs both concentrations of NaOCl, QMiX & CHX killed all bacterias irrespective of the presence of dentin.

(whereas, CHX- Chlorhexidine; NaOCl- Sodium hypochlorite; MTAD- Mixture of tetracycline, acid and detergent; EDTA-Ethylene Diamine Tetra Acetic Acid;Ca(OH)₂- Calcium hydroxide)

V. Conclusion:

Chlorhexidine has long been suggested as the root canal irrigant because of its substansivity & antimicrobial effect via prolonged binding to hydroxyapatite. With all its properties and new formulations, chlorhexidine gluconate is proving to be a promising root canal irrigating solution in endodontics. Further studies should aim at improving the characteristics of chlorhexidine gluconate and formulating better advancements so that Chlorhexidine fullfills as many ideal requirements as possible.

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