

# CONSIDERATION OF THE THERAPEUTIC POTENTIAL OF IRRIGANTS IN ENDODONTIC THERAPY

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## RAZMATRANJE TERAPIJSKIH MOGUĆNOSTI IRIGANASA U ENDODONTSKOJ TERAPIJI

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### ABSTRACT

The main objective of endodontic treatment is to remove vital and necrotic remnants of pulp tissue and microorganisms and their toxic products from the root canal. During chemo-mechanical endodontic preparation, a smear layer is formed on the wall of the canals. Due to an inability to remove all tissue remnants and the smear layer from the root canal by mechanical instrumentation, it is necessary to use irrigation to ensure sufficient cleaning and disinfection of the largest part of the root canalicular system. The most commonly used irrigants are sodium hypochlorite (NaOCl), ethylenediaminetetraacetic acid (EDTA), citric acid and chlorhexidine (CHX). Recently, the irrigants QMix and MTAD have been introduced to the market. They are a mixture of different components having antimicrobial, organolytic and mineralytic effects on canal detritus and the smear layer. This review article investigates irrigants in terms of the nature of their effect, their efficiency, optimal concentration, and method of use, and the interactions between the irrigants most commonly used in endodontic therapy are discussed, with special emphasis on QMix and MTAD.

**Keywords:** endodontic treatment, smear layer, endodontic irrigants

### SAŽETAK

Osnovni cilj endodontske terapije je uklanjanje vitalnih i nekrotičnih ostataka pulpnog tkiva, mikroorganizama i njihovih toksičnih produkata iz kanala korena zuba. U toku hemo-mehaničke obrade kanala korena na zidovima se formira razmazni sloj. Zbog nemogućnosti da se mehaničkom obradom uklone svi ostaci tkiva i razmazni sloj iz kanala korena, neophodno je koristiti irigaciju, kako bi se obezbedilo čišćenje i dezinfekcija najvećeg dela kanalikularnog sistema korena. Najčešće upotrebljavana sredstva za ispiranje kanala korena su natrijum-hipohlorit (NaOCl), etilendiaminotetraacetatna kiselina (EDTA), limunska kiselina i hlorheksidin (CHX). U novije vreme na tržištu su se pojavili irigansi, kao što su QMix i MTAD. Predstavljaju mešavinu različitih komponenti koje ispoljavaju antimikrobno dejstvo, kao i organo- i mineralolitički efekat na kanalni detritus i razmazni sloj. U ovom preglednom članku razmatran je način dejstva, efikasnost, optimalna koncentracija, način upotrebe i međusobna interakcija najčešće korišćenih iriganasa u endodontskoj terapiji, sa posebnim osvrtom na QMix i MTAD.

**Ključne reči:** endodontski tretman, razmazni sloj, endodontski irigansi

### INTRODUCTION

The most common aetiological factors causing pulp and periapical diseases are microorganisms. The main objective of endodontic treatment is to remove vital and necrotic remnants of the pulp tissue, microorganisms and their toxic products from the root canal. Due to the anatomical complexity of the root canal system and the presence of numerous isthmi and intercanal communications and pulp-periodontal communications, a significant part

of the intracanal area remains inaccessible to the mechanical effects of endodontic instruments. The research of Peters et al. shows that regardless of the technique of preparation, approximately 35% of the canal surface remains mechanically uninstrumented (1).

During chemo-mechanical preparation of the root canal, a smear layer 1-2 microns thick is produced on the walls. This layer contains remnants of vital and/or necrotic





pulp tissue, micro-organisms and their toxins and dentin particles of different size (2). The presence of a smear layer on the canal walls may partially or totally block the dentinal tubules and prevent the effects of irrigants and intracanal medicaments, obstruct the adhesion of materials for definitive obturation and provide a potential route for micro leakage (2). It also presents a nutritious foundation for the growth and multiplication of microorganisms. All of these factors lead to the failure of endodontic therapy, which is the reason why the removal of the smear layer is recommended (2).

Due to an inability to completely remove the remains of the residual tissue and smear layer from the root canal by mechanical instrumentation, it is necessary to use irrigation, which ensures cleaning and disinfection of the largest part of the canalicular system (3, 4). An ideal irrigant should possess antibacterial and fungicidal effects; not irritate periapical tissue; be chemically stable; possess prolonged antimicrobial activity; be effective in the presence of blood, serum and protein derivatives from the tissue; remove completely the smear layer; possess a low surface tension and the ability to penetrate into the dentinal tubules and disinfect them; not interfere with reparative processes in the periodontal tissue; not overpaint the tooth; not have antigenic, toxic or carcinogenic effects on surrounding vital structures; not have a negative effect on the physical and chemical properties of the dentin; not interfere with the adhesion of materials for the definitive obturation, and be easily prepared and applied to the prepared canal (5).

Currently, there is no single irrigant that meets all of the previously mentioned requirements, so that in everyday clinical practice it is necessary to combine irrigants. The most commonly used irrigants for rinsing the root canal are sodium hypochlorite (NaOCl), ethylenediaminetetraacetic acid (EDTA), citric acid and chlorhexidine (CHX) (6), while recently, irrigants such as QMix and MTAD have been introduced to the market. Both are a mixture of different components designed to dissolve organic and mineral parts of the canal detritus and smear layer, as well as to have antimicrobial effects. The use of MTAD and QMix as final irrigants should simplify the procedure of irrigation, prevent interaction between different irrigants and should not be detrimental to the mechanical, physical and chemical properties of the root canal dentin.

Development of new irrigants, and their use in an appropriate manner, is imperative for successful endodontic treatment. Thanks to the existence of a number of research methods, such as electron microscopy (7, 8, 9, 10), in tests of cytotoxicity (11, 10, 12) and antibacterial efficacy (13, 14, 15, 16, 17, 18), today it is possible to evaluate the efficiency of irrigants used in endodontic therapy in a relatively simple way.

This review article presents a brief overview of current knowledge of the effect, efficiency, optimal concentration, method of use and interaction of the most commonly used irrigants in endodontic therapy, with special emphasis on QMix and MTAD.

## SODIUM HYPOCHLORITE (NaOCl)

Sodium hypochlorite is a solution originally used for bleaching and disinfection (19). Due to its strong antimicrobial effect and its ability to dissolve organic tissue, it is the irrigant that is most often used during endodontic therapy (6, 20, 21). Due to its effect on soft tissue, NaOCl should be used cautiously, without the risk of transferring the irrigant over the apex. In the case of transfer of the solution onto the periapical tissue, pain can occur, as well as oedema, bleeding and even paraesthesia (22, 23). The chemical reaction of NaOCl with organic tissue proceeds through three phases. First, saponification of NaOCl dissolves the fatty acids by converting them into glycerol and fatty acid salts. This is followed by neutralization of amino acids by NaOCl caused by the formation of water and salt, with the release of hydroxyl ions, which strongly reduces the pH. Finally, the chlorination reaction, when hypochlorous acid from NaOCl comes into contact with organic tissue, acting as a solvent, leads to the release of chlorine, which reacts with the amino groups of proteins to form chloramine, which interferes with cell metabolism (24). The antibacterial effect of chloramine is based on its inhibitory effect on bacterial enzymes, leading to oxidation of sulphhydryl groups (SH). Hypochlorous acid (HOCl-) and hypochlorite ions (OCl-) cause the degradation of amino acids and protein hydrolysis (24). NaOCl is a strong base with a pH of 11, which is the basis of its antimicrobial effect, and its mode of action is similar to that of calcium hydroxide.

For endodontic treatment NaOCl is used at concentrations ranging from 0.5% to 6%. In a wide search of the literature, no clear recommendation was found for the best concentration to be used in endodontic therapy. Higher concentrations of NaOCl dissolve organic tissue better (25), but they have a stronger toxic effect (26). The toxicity of this solution can be overcome by using a lower concentration with prolonged periods of irrigation, and by using larger amounts of irrigants, by which the same antimicrobial efficacy and effect on dissolving organic tissue are achieved as at high concentrations (24, 26-30). The effect of NaOCl may be enhanced by increasing the concentration, heating, using a prolonged period of irrigation and sonic or ultrasonic activation (27).

In the presence of soft and dentin tissue, chlorine is released, but a weakening of the effect of NaOCl occurs (31-33). Therefore, a continuous renewal of the solution is necessary to ensure efficient disinfection and dissolution of all organic content.

Certain *in vitro* studies suggest that high concentrations of NaOCl have a stronger effect on *E. faecalis* and *C. albicans* (28, 29, 34). In contrast, *in vivo* studies showed that both low and high concentrations have the same efficacy in eliminating microorganisms from the root canal (35). NaOCl can inactivate bacterial endotoxin, but this effect is much less than its antibacterial effect (36, 37).



By reducing the concentration of the solution and the time of irrigation, the ability of NaOCl to penetrate into dentinal tubules and disinfect them decreases (38, 39). With the addition of surface active substances which reduce the surface tension, the depth of penetration of NaOCl into the tubules and the dissolution rate of the tissue are increased (4, 40).

Compared to its superior effect in terms of antimicrobial effects, NaOCl has a strong cytotoxic effect (41, 42).

As a result of collagen and glycosaminoglycan degradation, NaOCl may affect the hardness, flexural strength and elasticity of the root dentin (43-46).

To be effective on the organic and inorganic components of the smear layer during endodontic treatment, NaOCl irrigation followed by a final irrigation with EDTA is recommended. In case of contact between NaOCl and EDTA and their interaction, the loss of NaOCl's active component chlorine occurs, thereby reducing the antimicrobial efficacy of NaOCl (47), as well as the solubility of vital and/or necrotic tissue (48). This reducing effect may even be caused by low concentrations of EDTA (49, 50). The interaction between NaOCl and CHX is spotted, which leads to discoloration of dentin and creation of an orange-brown residue containing para-chloroaniline, which has a carcinogenic effect (51). The interaction between NaOCl and CHX and the formation of those residues depends on the concentration of irrigants (52). After root canal irrigation with NaOCl, the root canal should be rinsed with distilled water (49) to prevent or at least to reduce the interaction with other irrigants. Despite the positive properties of NaOCl, including its antimicrobial property, ability to dissolve organic tissues and lubricating effect, it also has some disadvantages, namely, its toxicity, its corrosive effect on endodontic instruments, particularly on those manufactured of nickel-titanium, and its lack of an effect on the inorganic component of the smear layer (13, 53, 54).

## CHLORHEXIDINE (CHX)

CHX is used in endodontic therapy for irrigation and intracanal medication, in the form of a solution or a gel, in variable concentrations from 0.2 to 2%. It is the most commonly used irrigant after the use of NaOCl and EDTA (6). CHX is recommended as an irrigant because of its low toxicity, broad spectrum of antimicrobial effect, and gradual and prolonged effect on microorganisms (28, 55).

CHX has wide antimicrobial effects, including effectiveness on G + and G- bacteria and fungi, especially on *E. faecalis* and *C. albicans* (56). CHX is a positively charged hydrophobic and lipophilic molecule that attaches to negatively charged phosphate groups on the cell wall (57), leading to changes in the osmotic balance of the cell (58, 59). The antimicrobial activity of CHX depends on the pH (optimum pH of approximately 5.5-7) (60) and on the concentration of the solution (14). Low concentrations of CHX

(0.2%) produce a bacteriostatic effect, while high concentrations (2%) are bactericidal, causing cell damage, coagulation of cytoplasm, and precipitation of proteins and nucleic acids (61). *In vivo* and *in vitro* studies indicate that CHX has an anti-microbial effect similar to that of NaOCl, and it produces a greater effect on *E. faecalis* and some fusiform bacterial strains present in the infected root canal (15, 28, 55, 62-64).

CHX has the property of substantivity. Due to the cation structure of its molecules it is attached to negatively charged surfaces in the oral cavity, and is continuously released and produces a prolonged antimicrobial activity. The use of CHX may achieve long-term antimicrobial activity for up to 12 weeks (65). Substantivity depends on the presence of the CHX molecule that interacts with dentin (66).

CHX has minimal or no effects on the reduction of lipopolysaccharides (LPS, endotoxin, a component of the outer membrane of G- bacteria), which play a significant role in the pathogenesis of apical periodontitis, causing pain that occurs in cases of infection in the root canal (67, 68).

Unlike NaOCl, CHX is not capable of dissolving organic tissue, it is relatively safe when used as an irrigant, and it does not cause allergic reactions (69, 70).

Due to its broad antimicrobial spectrum, as well as an inability to dissolve organic tissue, it is proposed that CHX should be used as a final irrigant after irrigating with NaOCl and EDTA (71). The combination of NaOCl and CHX improves antimicrobial efficacy, and the use of CHX as a final irrigant extends its antimicrobial activity, due to its substantivity (72).

If contact occurs accidentally between CHX and NaOCl during irrigation, the formation of an orange-brown residue and the formation of a chemical smear layer occurs, which may exhibit cytotoxic potential (49, 51), block the dentinal tubules, impair adhesion of material for the definite obturation (73, 74), and cause a colour change of dentin (75-77). When CHX comes into contact with EDTA, the formation of a milky white precipitate occurs as a result of an acid-base reaction (49). To avoid or at least to reduce this formation, it is necessary to prevent mutual contact between the two irrigants by thorough rinsing of the root canal using distilled water (49).

## ETHYLENEDIAMINETETRAACETIC ACID (EDTA)

In addition to NaOCl, one of the most commonly used irrigants is EDTA (6). It is used for the dissolution of the inorganic part of the smear layer. Its mineralytic effect is expressed through its ability to bind divalent and trivalent metal ions, such as  $\text{Ca}^{2+}$  and  $\text{Fe}^{3+}$ . One molecule of EDTA binds a maximum of four calcium ions, which provides a relatively stable, water-soluble chelated complex. It is usually used in concentrations of 15-17%, at a pH of 7-8 (6, 71). A final root canal irrigation with 5 ml 17% EDTA for 3



minutes effectively removes the smear layer (7). Although a concentration of 17% is sufficient and commonly used to remove the smear layer, some studies have shown that lower concentrations of EDTA (15%, 10%, 5%, 1%), after initial irrigation with NaOCl, also effectively remove the smear layer (78).

In addition to the effect on the smear layer, EDTA can cause demineralization of dentin. With increasing concentrations, pH levels and the time of the exposure of dentin to EDTA, the degree of dentin demineralization increases. Application of 10 ml 17% EDTA for one min effectively removes the smear layer. If the exposure time is extended to 10 min, a severe erosion of the peritubular and intratubular dentin may occur (79). A study that examined the effect of EDTA and the combination of EDTA and NaOCl on dentin in elderly and young patients showed that it is necessary to avoid prolonged exposure of old dentin to the combination of those irrigants, to reduce the risk of excessive erosion and demineralization. Both irrigants led to an increased brittleness of already sclerotic root dentin, and consequently increased the incidence of cracks during the functional loading of the root (80).

Chelating agents significantly reduce the micro hardness and pressure resistance of dentin, and this effect is most pronounced when EDTA is used as an irrigant, either alone or in combination with 2.5% NaOCl (80).

Chelating agents also reduce the resistance of the root to fracture, and the use of 17% EDTA for 10 min and 1% NaOCl for one minute reduces the resistance to root fracture by approximately 1.5 times, while lower concentrations of EDTA (5%) and shorter exposure times (one minute) cause a smaller reduction in resistance (81).

As a result of the removal of the smear layer and demineralization of dentin, EDTA causes changes in the permeability of dentin by formation of certain precipitates and by partial or complete obturation of the root dentin tubules (82, 83). Therefore, complete removal of residual EDTA solution is necessary, using an application of either deionized/distilled water or saline solution.

## CITRIC ACID

Citric acid is a weak organic acid and is used to remove the inorganic part of the smear layer after initial rinsing of the canal (8). It is used at a concentration of 1-50%, but the most commonly used concentration is 10%.

The effect of H<sup>+</sup> ions from the citric acid leads to the release of ions from the surface of hydroxyapatite dentin crystals, forming soluble chelate complexes (84, 85). The effectiveness of citric acid may be improved by increasing the concentration (86), reducing the pH (87) and extending the time of use (88).

In comparison with EDTA, citric acid removes the smear layer in an inappropriate way (89) and has a more pronounced erosive effect on root dentin (90). In a study by De-Deus and his associates in which they exposed

dentin to 1% citric acid, 17% EDTA and 17% EDTAC, citric acid showed the strongest decalcification effect on root dentin (91).

If 19% citric acid is used, it significantly reduces the micro hardness of dentin compared to 17% EDTA (92). Further, citric acid, like EDTA, has poor antimicrobial activity (16, 93, 94).

*In vitro* studies indicate some cytotoxicity of citric acid. However, 10% citric acid shows a significant biocompatibility compared to 17% EDTA and 17% EDTA-T (11). Using NaOCl and citric acid does not cause the formation of precipitates (49).

## MTAD

MTAD is the first irrigant on the market that can simultaneously perform disinfection of the canal system and remove the smear layer (17). It is a mixture of antibiotics (doxycycline, 3%), chelating agents (4.25% citric acid) and a detergent (Tween 80). It is sold under the name of the manufacturer, BioPure MTAD (Dentsply Tulsa Dental, Tulsa, OK, USA) and is prepared by mixing the liquid contained in the syringe with the powder contained in the bottle, immediately prior to its application. As a mixture, it has a shelf life of 48 h, which is considerably shorter than those of other irrigants used in endodontic practice (95). It does not possess the ability to dissolve organic tissue. It is recommended for use as the final irrigant after complete chemo-mechanical treatment of the root canal (17, 96--99). The irrigation protocol recommends the use of MTAD for 5 min, after an initial root canal irrigation with 1.3% NaOCl for 20 minutes (100).

In the available literature, there are no data on the exact mechanism of the effects of MTAD. The ability to remove the smear layer is attributed to the effect of citric acid and doxycycline, while its antibacterial effect is due to the effect of doxycycline, which is a tetracycline with a broad antibacterial spectrum, and exerts its bacteriostatic effect by inhibiting protein synthesis (101).

Despite the fact that MTAD has proven effectiveness against *E. faecalis* (17, 96, 97, 102), as well as effectiveness in the removal of the smear layer (103-105), in subsequent studies its antimicrobial efficiency has been challenged (106-108). When MTAD is applied after an initial irrigation with 1.3% NaOCl, its antimicrobial effect is reduced, probably due to oxidation of MTAD under the influence of NaOCl (109). The antibacterial efficiency of MTAD may be reduced due to the presence of dentin and serum albumins from the root canal (110). Its efficiency in eliminating *E. faecalis* biofilm is relatively low (100, 111, 112). *E. faecalis* biofilm is more difficult to remove and is more resistant to the effects of antimicrobials than planktonic bacteria (113). MTAD removes the smear layer more efficiently than EDTA, particularly in the apical third of the canal (114), where it causes less pronounced erosive changes to the dentin (104).



The low surface tension of MTAD (34.5 mJ / m<sup>2</sup>) (115) may provide a more complete contact of the irrigant with the dentin of the root canal, extending its ability to penetrate deeper into dentinal tubules, ensuring a more efficient removal of the smear layer, disinfecting canal walls and leading to better and easier diffusion of the components of intracanal medicaments.

MTAD has a lower cytotoxicity than most commonly used irrigants and intracanal medicaments in endodontic therapy, such as eugenol, hydrogen peroxide (3% solution), Ca(OH)<sub>2</sub> paste, NaOCl (5.25%) and EDTA, while its cytotoxic effect is greater than that of lower concentrations of NaOCl (2.63%, 1.31%, 0.66%) (116).

There is only one *in vivo* study showing that MTAD causes postoperative pain during endodontic therapy (117). Further studies are needed to confirm the efficacy of MTAD solution in *in vivo* conditions as well.

### QMix

QMix is a new irrigant recently introduced to the market. In addition to a detergent, CHX and EDTA are also included in its composition (114). It combines the advantages of EDTA, contains a surfactant plus CHX and has a slight effect on dentin. Based on the manufacturer's recommendation, it should be used as a final irrigant for a period of 60-90s, following a 6.15% NaOCl irrigation. If NaOCl is used during the chemo-mechanical preparation, it is necessary to rinse the canal with saline or distilled water before using QMix.

A large number of studies indicate that QMix has the same efficiency for removal of the smear layer as EDTA (18, 9), and it exhibits a lower erosive effect on dentin (118). Studies by Dai et al. (114) and Eliot et al. (9) indicated that QMix removes the smear layer more effectively than EDTA.

QMix effectively eliminates *E. faecalis*, eroding its biofilm more quickly than 1% NaOCl and 2% CHX and to the same extent as 2% NaOCl (18). The bactericidal effect of QMix on a one-day old bacterial biofilm is the same as the effect of 6% NaOCl and is more efficient than a lower concentration of NaOCl or 2% CHX (119, 120).

In studies in which the ability of QMix to penetrate dentinal tubules was tested, it was observed that QMix may present its antimicrobial activity at the same depth as 6% NaOCl, within three minutes (119-121). Exposure of dentin tubules to QMix for one minute is more effective than using 2% CHX for three minutes or using lower concentrations of NaOCl (120). When the smear layer is present, the bactericidal effect of QMix inside the dentinal tubules is greater after exposure to 6% NaOCl for ten minutes than after the combination of 6% NaOCl, 17% EDTA and 2% CHX (121).

In addition to efficient removal of the smear layer, QMix increases the humidity of dentin more than EDTA, which has a poorer wetting power (122); this is probably due to the effect of the detergent in the QMix.

**Table 1.** Characteristics of endodontic irrigants

NaOCl	<ul style="list-style-type: none"> <li>• effective antimicrobial agent</li> <li>• current irrigant of choice</li> <li>• organic tissue solvent</li> <li>• lubricates</li> <li>• toxic</li> <li>• corrosive effect</li> <li>• not substantive</li> <li>• removes only the organic part of the smear layer</li> </ul>
CHX	<ul style="list-style-type: none"> <li>• wide range of antimicrobial effects against G + and G- bacteria and fungi</li> <li>• substantivity in dentin for up to 12 weeks</li> <li>• dentin components, inflammatory exudate may inhibit the antibacterial activity</li> <li>• no ability to dissolve organic or inorganic tissue</li> <li>• biocompatibility</li> </ul>
EDTA	<ul style="list-style-type: none"> <li>• effectively removes the smear layer after the initial NaOCl irrigation</li> <li>• demineralization of dentin</li> </ul>
Citric acid	<ul style="list-style-type: none"> <li>• less removal of the smear layer compared with EDTA</li> <li>• stronger erosive effect on the root canal dentin compared to EDTA</li> </ul>
MTAD	<ul style="list-style-type: none"> <li>• antimicrobial properties</li> <li>• effective solution for removal of the smear layer when used along with NaOCl</li> <li>• less adverse effects on dentinal structure</li> <li>• good biocompatibility</li> <li>• no dissolution of organic tissue</li> <li>• high cost</li> <li>• reduced shelf life</li> </ul>
QMix	<ul style="list-style-type: none"> <li>• antibacterial efficacy</li> <li>• effective solution for removal of the smear layer when used along with NaOCl</li> <li>• ready for use, fast working</li> <li>• less demineralization of dentin compared to EDTA</li> </ul>

QMix has a lower cytotoxicity than 17% EDTA, 2% CHX and 3% NaOCl (123). Unlike NaOCl, QMix leads to cell death more slowly, without any cell lysis (124). Currently, there are no clinical studies investigating the efficacy of QMix as a final irrigant.

During the application of QMix there is no development of a white precipitate, which typically occurs using a mixture of EDTA and CHX, nor is there formation of an orange-brown residue resulting from combining NaOCl and CHX (18). This is due to its uniform chemical composition.

### CONCLUSION

In everyday clinical practice, the most frequently used irrigant is sodium hypochlorite, which despite its organo-litic and antibacterial properties, does not completely remove the smear layer. To completely remove the smear layer, it is necessary to combine NaOCl with EDTA or another chelating agent, which act on the inorganic mineral component of the smear layer. In everyday clinical practice, a final irrigation with CHX is recommended because of its property of substantivity and of providing a prolonged an-



timicrobial effect after completion of the biomechanical preparation of the root canal.

By eliminating some of the drawbacks of currently used irrigants, a new generation of irrigants, such as MTAD and QMix, have appeared, whose application is the subject of our interest. These irrigants, in addition to having an impact on the smear layer, possess the ability to disinfect root canals. Although incapable of dissolving organic tissue, their use as the final canal irrigant is recommended, but only after prior irrigation with NaOCl has been completed.

Future research should focus on finding an irrigant that has the ability to dissolve tissue, remove the smear layer and exert an antibacterial effect.

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