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An Overview on a Promising Root Canal Irrigation Solution: QMix

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ABSTRACT

Due to the complex micro-anatomy of the root canal system, mechanical instrumentation leaves significant portions of the root canal walls untouched; therefore, complete elimination of bacteria from the root canal by cleaning with instrumentation alone is unlikely. It has long been postulated but not demonstrated, that any pulp tissue left in the root canals can serve as bacterial/fungal/viral (microorganism nutrients) nutrients. Furthermore, tissue remnants also impede the antimicrobial effects of root canal irrigants and medicaments and prevent intimate adaptation of the root canal filling to the dentin. Therefore, specific irrigation/disinfection procedures are necessary to remove tissue from the root canals and to kill microorganisms, respectively. The purpose of this paper was to review different aspects of a promising root canal irrigant; QMix. This is a relatively new root canal irrigant composed of traditional materials like chlorhexidine (CHX), ethylele diamine tetraacetic acid (EDTA), saline and a detergent. QMix is antibacterial, antifungal and has antibiofilm activities, it displays substantivity, smear layer removing ability; moreover, its effect on dentin and retention of fiber posts *etc.* has been reviewed. There have been strong reports that show the chemical design of QMix prevents precipitation of CHX when together with EDTA and mixing with sodium hypochlorite does not produce the orange-brown precipitate. Furthermore, the smear layer removal ability of QMix is comparable to that of 17% EDTA and the antibacterial activity of QMix was greater than 1% and 2% sodium hypochlorite (NaOCl) and 2% CHX.

Keywords: Antibacterial Agent; Biofilm; Bond Strength; *Candida albicans*; Chlorhexidine; Dentin Bonding Agent; Endodontics; *Enterococcus faecalis*; Smear Layer; Qmix

Introduction

Animal models and clinical studies have clarified the essential role of microorganisms in development and perpetuation of pulpal and periapical diseases [1-3]. Elimination of microorganisms from infected root canals is a complicated biological task. Numerous measures have been described to reduce or eliminate the numbers of root canal microorganisms, such as the use of various instrumentation techniques, variable irrigation regimens and intra-canal medicaments. As yet there are no concrete reports in the literature that mechanical instrumentation alone results in a bacteria-free root canal system. Considering the complex anatomy of root canal pulp space [4], this is not surprising. On the contrary, there is ample *in vitro* and clinical evidence that mechanical instrumentation leaves significant portions of the root canal walls untouched [5] and complete elimination of bacteria by instrumentation alone is unlikely [6]. It is assumed, but not demonstrated, that any pulp tissue left in the root canals can serve as nutrients for microorganisms (bacterial nutrient). Furthermore, tissue remnants also impede the antimicrobial effects of root canal irrigants and medicaments and prevent intimate adaptation of the root canal filling to the dentin. Therefore, specific irrigation/disinfection procedures are necessary to remove tissue from the root canals and to kill microorganisms, respectively [7]. QMix is a chlorhexidine (CHX)-based root canal irrigation that also contains ethylele diamine tetraacetic acid (EDTA), saline and a detergent [8, 9]. The focus of this review is to discuss, based on the available literature QMix.

Materials and Methods

Retrieval of literature

An English-limited Medline search was performed through the articles published from 2010 to 2019. The searched keywords included "QMix AND antibacterial", "QMix AND *Enterococcus faecalis*"," QMix AND *Candida albicans*", "QMix AND dentin bonding" and "QMix AND endotoxin", "QMix AND smear layer", "QMix AND dentin discoloration", "QMix AND push-out bond strength", "QMix AND biocompatibility", "QMix AND apical seal", "QMix AND interactions". Then, a hand search was done in the references of result articles to find the matching papers.

Results

A total of 93 articles were found which are summarized in order of their related keywords in the Table 1. Subsequently, references of result articles were looked at and matching papers were hand selected. Of 93 searched documents, only full-text articles were used [book chapters and abstracts were not used]. In addition, common search results between paired keywords were excluded. Therefore, of the 93 searched documents, 50 were included in the study.

Antibacterial activity

Using confocal laser scanning microscopy (CLSM), Ma *et al.* [8] demonstrated that QMix was equally effective in killing bacteria in dentin as 6% sodium hypochlorite (NaOCl); more than 40% and 60% of the bacteria were killed by both at 1 min and 3 min, respectively.

Using an experimental model, Stojicic *et al.* [9] showed that QMix and 1% NaOCl killed all *planktonic Enterococcus* (*E.*) *faecalis* bacteria in 5 sec. According to Wang *et al.* [10] in the presence of a smear layer, 10 min of exposure to QMix, 2% NaOCl+QMix and 6% NaOCl+QMix resulted in significantly more dead bacteria than 3 min of exposure to these same disinfecting solutions. Furthermore, 6% NaOCl+QMix showed the strongest antibacterial effect. A study on immature Beagle dogs teeth showed that root canal irrigation using QMix solution, with or without CHX gel dressing, or a triple antibiotic paste dressing, provides the same level of disinfection than irrigation with 5.25% sodium hypochlorite alone in only one session [11]. According to Aktemur Turker *et al.* [12] QMix was effective agent for rapid disinfection of gutta-percha cones as well-known irrigation solutions. In an *ex vivo* study, Liu *et al.* [13] investigated the antibacterial efficacy of QMix and other four final irrigation regimens in reducing *E. faecalis* within human root canals. Findings showed that the antimicrobial activity of QMix was comparable to that of EDTA/CHX and EDTA/cetrimide and more effective than that of EDTA/NaOCl against intracanal *E. faecalis*. Using agar diffusion test, Jose *et al.* [14] showed the superiority of QMix over other root canal irrigants against *E. faecalis*. Albino Souza *et al.* [15] evaluated the effectiveness of final decontamination protocols against *E. faecalis ex vivo*. According to their findings the greatest bacterial reduction was observed for 2% CHX, QMix and 6.5% grape seed extract, with no statistically significant difference between them.

In summary, it can be concluded that QMix possesses the acceptable antibacterial efficacy as a root canal irrigation solution.

Table 1. Results of searched articles according to each keywords combinations

Searched Keywords	Number of papers
QMix AND antibacterial	24
QMix AND *Enterococcus faecalis*	22
QMix AND *Candida albicans*	2
QMix AND dentin bonding	7
QMix AND endotoxin	3
QMix AND smear layer	33
QMix AND dentin discoloration	1
QMix AND push-out bond strength	16
QMix AND cytotoxicity	4
QMix AND apical seal	1
QMix AND interactions	5

Antifungal activity

Using agar diffusion test, Jose *et al.* [14] compared the efficacy of QMix, guava leaf extract, aloevera extract, 2.5% NaOCl and 2% CHX against *Candida albicans*. According to their findings QMix showed maximum inhibitory effect against *Candida albicans* followed by 2% CHX, then, 2.5% NaOCl, guava leaf extract and aloe vera extract.

In an *ex vivo* study, Kalyoncuoglu *et al.* [16] assessed the antifungal activity of QMix 2 in 1 (means that QMix is a single solution used as a final rinse for one-step smear layer removal and root canal disinfection), 5.25% NaOCl, 2% CHX, and 17% EDTA as a final rinse against *C. albicans*. Results showed that QMix 2 in 1, 5.25% NaOCl, and 2% CHX were equally effective and significantly superior to 17% EDTA in eradicating *C. albicans*.

In summary, the few conducted studies on the antifungal activity of QMix, confirmed its effectiveness against *C. albicans*.

Substantivity

CHX as well as tetracyclines have a unique feature within dental structures; as a medicament they exhibit antimicrobial substantivity [17, 18]. The positively charged ions released by CHX can adsorb into dentine and prevent microbial colonization

on the dentine surface for some time beyond the actual the period of time of application of the medicament [17, 18].

Zhang *et al.* [19] compared residual antimicrobial activities of five root canal irrigants as follows: 17% EDTA, 2% chlorhexidine, 0.2% cetrimide, MTAD (mixture of tetracycline, acid and detergent), and QMix, in a model with *E. faecalis* biofilm formation. According to their results, among the five irrigants, QMix had the strongest antibacterial activity. Residual antimicrobial activities of CHX were significantly higher at 12 h, 24 h and 36 h compared to untreated control. All five root canal irrigants were effective to some extent against *E. faecalis*, but QMix and CHX had the strongest, and CHX the longest (up to 36 h), antimicrobial activity.

In an *ex vivo* study on human teeth, Souza *et al.* [20] showed the substantivity of QMix for up to 120 days.

Using a human tooth model, Palazzi *et al.* [21] revealed that the substantivity of Tetraclean was significantly superior to QMix and Tetraclean NA in a 4 week period.

In summary, substantivity of QMix was reported from 6 h to 120 days.

Antibiofilm activity

Wang *et al.* [10] compared the antibacterial effects of different disinfecting solutions (2% and 6% NaOCl, 2% CHX and QMix) on young and old *E. faecalis* biofilms in dentin canals using a novel dentin infection model and CLSM. According to their findings, significantly fewer bacteria were killed in the 3-week-old dentin biofilm than in the 7-day-old biofilm. Three min of exposure resulted in more dead bacteria than 1 min of exposure for both biofilms in all experimental groups. Six percent NaOCl and QMix were the most effective disinfecting solutions against the young biofilm, whereas against the 3-week-old biofilm, 6% NaOCl was the most effective followed by QMix. Using an experimental model, Stojicic *et al.* [9] showed that QMix killed up to 12 times more biofilm bacteria than 1% NaOCl. Bago Jurič [22] compared the disinfection effect of antimicrobial photodynamic therapy (PDT), Nd: YAG laser and QMix solution against *E. faecalis* biofilm. Findings showed that PDT and the QMix solution were equally effective, with the reduction rate of *E. faecalis* CFUs of 98.8% and 99.3% respectively. The Nd: YAG laser caused 96% reduction of *E. faecalis*. Zhang *et al.* [19] compared the antibacterial activity of five root canal irrigants [17% EDTA, 2% CHX, 0.2% cetrimide, mixture of doxycycline, citric acid & Tween-80 (MTAD), and QMix] in a model of *E. faecalis* biofilm formation. According to their findings, QMix showed the strongest efficacy. Balic *et al.* [23] assessed the antibacterial efficacy of photon-initiated photoacoustic streaming (PIPS) using an Er: YAG laser and sonic-activated irrigation combined with QMix irrigant or NaOCl against *E. faecalis* intracanal biofilm. Findings showed that the best antibacterial efficacy was recorded after sonic-activated irrigation with both NaOCl (99.999%) and QMix (99.999%) and after PIPS with QMix (99.999%), which were more effective than conventional irrigation with NaOCl (99.998%) and the PIPS with the NaOCl (99.966%). Furthermore, the PIPS with QMix solution provided the highest number of sterile samples.

In summary, it seems that the effectiveness of QMix against bacterial biofilms is comparable to that of NaOCl and other promising root canal irrigants and methods.

Effect on endotoxin

Endotoxin, a part of the cell-wall of all gram-negative bacteria, is composed of polysaccharides, lipids and proteins and is referred to as lipopolysaccharide (LPS), emphasizing its chemical structure [24]. Lipid A is the region of the endotoxin molecule responsible for its toxic effects [25].

Currently, a persisting concern in endodontics is the treatment of teeth with necrotic pulps and periapical pathosis because post-treatment disease persists more often than in cases without periapical disease [25, 26]. In teeth with chronic periapical lesions, there is a greater prevalence of gram-negative anaerobic bacteria disseminated throughout the root canal system (dentinal tubules, apical resorptive defects and cementum lacunae), including apical bacterial biofilm [25, 26]. Because these areas are not reached by instrumentation, the use of a root canal medicament is recommended to aid in the elimination of these bacteria and thus increase the potential for clinical success [25-27].

Using an *in vitro* model of *E. Coli* LPS, Grundling *et al.* [28] showed that QMix decreased LPS levels significantly when compared to the other groups (3% NaOCl, 2% CHX and 17% EDTA).

In summary, only one study analyzes the anti-endotoxin activity of QMix; interestingly this study shows that it may be effective against endotoxins. However, more studies in this area should be conducted.

Modulating effect of dentin

In an *in vitro* study, Morgental *et al.* [29] compared the antibacterial effect of QMix with that of conventional irrigation solutions in the presence or absence of dentin powder. Findings showed that dentin had a significant inhibitory effect on the antibacterial activity of QMix (10 sec and 1 min). However, after 6 h, regardless of the presence of dentin, QMix killed all bacteria.

In summary, considering the fact that there is only one study in this regard, it seems that the dentine has no inhibitory effect on the antibacterial activity of QMix. Naturally, more studies are required in this area.

Smear layer removing ability

Aranda-Garcia *et al.* [30] demonstrated that there was no significant difference between EDTA and QMix efficacy in removing smear layer. Dai *et al.* [31] showed that 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. Using an experimental model, Stojicic *et al.* [32] showed that QMix removed smear layer as well as EDTA. In a study on single-rooted teeth, Eliot *et al.* [33] showed that QMix was superior to EDTA in removing the smear layer. Elnaghy [34] showed that QMix was as effective as 17% EDTA in removing smear layer from the prepared post spaces. Kocak *et al.* [35] assessed the effect of diode laser on the smear layer removing ability of EDTA and QMix. Findings showed that in the EDTA group, the amount of smear layer was significantly higher at the apical thirds, and the differences among the three regions were statistically significant. In the QMix group, no difference was found between the coronal and middle thirds; however, the amount of smear layer was significantly higher at the apical thirds. Furthermore, laser had no effect on the improvement of smear layer removing ability. According to Vemuri *et al.* [36] QMix showed the highest smear layer removing ability from the apical third of the root canal compared to other root canal irrigation solutions. According to Ballal *et al.* [37] 7% Maleic acid (MA) had superior smear layer removal ability compared with QMix and 17% EDTA. Calcium levels showed greater decrease with QMix while phosphorus level decreased further with 7% MA and QMix, respectively. Arslan *et al.* [38] assessed the effect of different activation techniques (EndoActivator [EA] system, photon-initiated photoacoustic streaming [PIPS], and an Er: YAG laser with an endodontic fiber tip) on the smear layer removing ability of QMix. Results showed that the highest scores were found in the apical third of all groups. The QMix+Er:YAG group removed the smear layer more effectively than the nonactivated QMix group in the apical third. The QMix+EA group removed the smear layer significantly in all three segments of the teeth when compared with the nonactivated QMix group. The QMix+PIPS group showed significantly greater efficacy than the QMix group in the coronal third. Using SEM, Aksel *et al.* [39] reported that rinsing with QMix as final irrigant followed by NaOCl, as the initial irrigant, caused less dentin decalcification and erosion compared to EDTA. Using scanning electron microscopy (SEM), Prado *et al.* [40] evaluated the effects of different auxiliary irrigation devices on smear layer removing ability of QMix. Findings showed that QMix 1 min was effective for smear layer removal only when used with auxiliary devices, and QMix+passive ultrasonic irrigation yielded the best results, particularly for the apical third.

In summary, it can be concluded that smear layer removing ability of QMix is superior or at least equal to that of EDTA.

Tissue dissolving ability

Arslan *et al.* [41] showed that QMix 2 in 1 could not significantly dissolve pulp tissue in comparison with NaOCl. Moreover, as expected, QMix 2 in 1 showed similar tissue dissolving effect with CHX.

In summary, QMix has little to none tissue dissolving ability.

Effect on apical seal

Maximum sealing ability or adhesion of endodontic sealers can be achieved after effective removal of the smear layer. Endodontic irrigants assist in adequate removal of the smear layer, improving the retention mechanism [42].

Singh *et al.* [43] assessed the effect of two different root canal irrigation solutions (5.25% NaOCl followed by 17% EDTA and QMix) on the apical sealing ability of two different root canal sealers (MTA Fillapex and Adseal). Findings showed that irrigation with NaOCl+EDTA produced the least amount of apical leakage compared to QMix.

In summary, QMix may exert positive effect on the apical seal of root canal sealers. However, further more extensive studies are recommended.

Effect on dentin microhardness

According to Aranda-Garcia *et al.* [44] QMix promoted significant dentin microhardness reduction. Taneja *et al.* [45], experimented single-rooted mandibular premolars, and assessed the effect of different chelating agents on the calcium loss and its subsequent effect on the microhardness of the root dentin. Findings showed that irrigating the root canal with 5% NaOCl for 5 min and then with QMix for 5 min was superior to 2.5% NaOCl for 5 min and then 7% EDTA for 5 min and also superior to 5% NaOCl for 5 min + 2.25% Peracetic acid (PAA) for 5 min. According to Cecchin *et al.* [46], QMix significantly reduced the mechanical properties of dentin (flexural strength and ultimate tensile strength). Baldasso *et al.* [47] showed that QMix reduced dentin microhardness up to 500 µm depth.

In summary, it may be wise to conclude that QMix reduces the mechanical properties of dentin (including microhardness) significantly.

Effect on push-out bond strength

According to Aranda-Garcia *et al.* [30] final rinse with QMix and EDTA solutions promoted similar push-out bond strength values. Elnaghy [48] evaluated the effect of QMix and other conventional endodontic irrigants on the micro-push-out bond strength of Biodentine (BD) and white MTA (WMTA) and found that QMix did not compromise the bond strength of not BD nor WMTA.

In summary, the effect of QMix on the push-out bond strength is controversial.

Effect on bond strength of posts

Elnaghy [34] assessed the effect of QMix and some other irrigants on the bond strength of glass fiber posts to root dentin and found that QMix and 17% EDTA/2% CHX demonstrated the highest mean bond strength values in all root levels amongst the groups. Uzunoglu *et al.* [49] assessed the effect of temperatures of QMix and EDTA on the bond-strength of AH-Plus. Findings demonstrated that, regardless of temperature, samples irrigated with QMix had higher push-out bond strength values than those irrigated with EDTA. Furthermore, samples irrigated with 37°C EDTA resulted in higher bond-strength values than those irrigated with 22°C EDTA. Using CLSM, Barreto *et al.* [50] assessed the effect of several root canal irrigants on the bond strength of fiber posts cemented with a new self-adhesive resin cement (RelyX U200). Findings showed that NaOCl enhanced bond strength, whereas, chelating agents such as EDTA and QMix caused a decrease in bond strength. Akman *et al.* [51] assessed the effect of post-space treatment with chelating agents on the push-out bond-strength of a glass fiber post-system (i-TFC). Results demonstrated that post-space could be treated with NaOCl and QMix in order to increase adhesion of i-TFC post-system to root dentine.

In summary, it could be concluded that irrigating the root canal with QMix enhances the bind strength of posts significantly.

Effect on dentin color

The combined use of NaOCl and CHX has been advocated to enhance their antimicrobial properties. In other words, a final rinse with CHX offers the advantage of substantivity (due to its affinity to dentin hydroxyl apatite) which prolongs the antimicrobial activity of CHX [52]. However, the disadvantage is that the when NaOCl is mixed with CHX, an orange-brown particle para-chloro anillin (PCA) is formed which results in the precipitation of a chemical smear layer that covers the dentinal tubules; thus, interfering with the seal of the root filling [52]. In addition, this precipitate changes the color of the tooth and is cytotoxic [53, 54]. According to Arslan *et al.* [55] the presence of orange-brown precipitate was shown in root canals irrigated with CHX and QMix after NaOCl irrigation. However, CHX had significantly higher scores of the cytotoxic precipitate than QMix. This result might have been due to the concentration of chlorhexidine in QMix being so low that it could not be detected.

In summary, irrigating the canal with QMix as well as CHX followed by NaOCl, results in the formation of an orange-brown precipitate (para-chloro-anillin), which is cytotoxic and may change the color of tooth.

Cytotoxicity

Using MTT (Mosmann's tetrazolium toxicity) and alamar Blue assays, Alkahtani *et al.* [56] showed that QMix exposure resulted in a significantly higher percentage of cell viability than NaOCl. Furthermore, SEM analysis demonstrated minimal morphological changes associated with cells that were exposed to the QMix solution, with little shrinkage and fragmentation of the cell wall. The live/dead analysis showed that the number of live cells after exposure to QMix was similar to that of the untreated control. Another study using MTT assay assessd the toxicity of some root canal irrigants at three time intervals (1, 5, 10 min) and showed that toxicity of QMix was lower that NaOCl and higher that CHX, EDTA and MTAD [57]. Another interesting study assessed the cytotoxic effect of various irrigating solutions on stem cells from the human apical papilla after different periods of exposure. Findings showed the cytotoxicity in an ascending order as follows: MTAD>EDTA>QMix=NaOCl> CHX>sterile saline (control group) [58].

In summary, it can be concluded that cytocompatibility of QMix is better than other root canal irrigants.

Interaction with other irrigants

Arslan *et al.* [55] compared CHX and QMix in terms of orange-brown precipitate generation in root canals. Findings showed that CHX had significantly higher scores than QMix in terms of orange-brown precipitate formed in the root canals. According to the 1h nuclear magnetic resonance (NMR) spectra, para-chloroaniline was present in the mixture of CHX and NaOCl. However, the mixture of QMix and NaOCl resulted in the formation of para-chloroaniline formation at so low level that could not be detected.

In summary, it seems that using QMix instead of CHX in the irrigation protocol of the root canal system prevents the formation of para-chloro anillin.

Conflict of Interest: 'None declared'.

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