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MTAD: Is it the right "solution"? – An overview

Introduction: A plethora of chemical irrigants exists that is used for the elimination of residual microbes and endotoxins in root canals accompanied by mechanical instrumentation. However, due to complex root canal systems, the mechanical instrumentation and established irrigants still reach their limits and pathogenic microorganisms remain. Therefore, new irrigants with a wider spectrum are required.

Materials/Methods: The aim of this article was to summarize and discuss the available information concerning the irrigant MTAD (mixture of tetracycline isomer, acid and detergent) introduced in 2003 with its wider spectrum regarding antibacterial properties and the ability to remove the smear layer. A literature search was performed from English-language papers published until September of 2018.

Results: This review of literature focused on particular advantages of MTAD such as the antimicrobial efficacy, the ability of removing the smear layer and the effect on dentine structure. Also disadvantages were found, regarding the effect of MTAD on the dentine degeneration and the sealing properties of root-end filling materials.

Conclusion: MTAD could represent an effective complementary irrigant, specifically in combination with NaOCl. Further research is required to establish MTAD as a potent irrigant against more bacterial species, not only against Enterococcus faecalis.

Keywords: endodontic final irrigant; E. faecalis; MTAD; smear layer

Introduction

The main aim of the root canal treatment is to disinfect the root canal system, which requires the elimination of microorganisms and microbial components by instrumentation, irrigation and obturation of the root canal as well as the prevention of its re-infection during and after root canal treatment [9].

Many chemical irrigants have been used for the elimination of residual microbes in root canal systems accompanied by mechanical instrumentation [8]. NaOCl has been demonstrated to be an effective disinfectant and is widely accepted as the gold-standard irrigation solution [8, 11]. An irrigant should be able to disinfect, penetrate the dentine and its dentinal tubules, offer long-term antibacterial effects (substantivity), remove the smear layer, neutralize the endotoxins derived from the bacterial lysis [40, 65]. At the same time, an irrigant needs to be non-antigenic, non-toxic and non-carcinogenic [65]. However, at present, no single irrigant combines all these ideal characteristics, not even NaOCl. Considering the limitations of the well-established irrigants in Endodontics, new irrigants have been introduced that could possibly fulfill the ideal requirements. MTAD as an antibacterial irrigation solution showed promising results in several studies and has the potential to be an effective endodontic irrigant [51].

Methods

A comprehensive English literature search by Medline and by hand search was performed with the clos-

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ing date of September 11, 2018. The "free text" search string [MTAD] AND [root canal treatment] was used for the survey by hand search in the internet and by Medline using PubMed. In addition, a reference survey of all the relevant papers, 82 articles in total, was conducted. No relevant articles were rejected for the present review of literature.

ELEMENT	CONTENT
Doxycycline	3 %
Citric acid	4,25 %
Polysorbate 80 (Tween 80)	0,5 %

Table 1 Composition of MTAD according to Torabinejad et al. [58]

Properties of MTAD

MTAD (Mixture of Tetracycline isomer, Acid, Detergent) is an irrigant introduced in 2003 by Mahmoud Torabinejad of Loma Linda University (California, U.S.A). MTAD is a mixture of doxycycline, citric acid and polysorbate 80 detergent [56] (Tab. 1).

The combination of a broad-spectrum antibiotic and the demineralizing agent citric acid as a chelating factor ensures inhibition of bacterial growth and removal of the smear layer. In addition, a polysorbate detergent decreases surface tension thus improving the likelihood of reaching bacteria in the ramifications of the main root canal [58]. MTAD is commercially available as a 2-part mixture (Bio pure MTAD; Dentsply, USA), consisting of powder and liquid (Fig. 1).

1. Antimicrobial activity

Doxycycline is the main component of MTAD. It does not show bactericidal properties, but it prevents the multiplication of susceptible bacteria [5]. This bacteriostatic property may be advantageous as there are no antigenic products (endotoxins) released due to the absence of bacterial cell lysis [58]. The antimicrobial effect of MTAD has been largely attributed to the presence of doxycycline. However, the substitution of doxycycline by chlorhexidine significantly reduces the efficacy of the irrigant [50].

Based on the results of the *in vitro* study of Torabinejad et al., MTAD has a strong antimicrobial efficacy against *E. faecalis* compared to 5.25 % NaOCl and 17 % EDTA, without affecting the dentine structure of human teeth [38]. These results seem important as they demonstrate the efficacy of an irrigant to inhibit this bacterial strain, which has been shown to be resistant to many commonly used intracanal irrigants and dressings [38]. *E. faecalis* is present in many failed root canal treatments [15] and is the most commonly reported bacterial species present within the canals of non-healing cases and asymptomatic infected roots [42, 52, 54]. This bacterium has a high capability to form biofilms [28]. Furthermore, *E. faecalis* seems to be less sensitive than other bacteria to the exposure of NaOCl [44]. Thereby, the time of exposure and concentration of NaOCl play an important role to inhibit the growth of *E. faecalis*. The longer the time of exposure and the higher the concentration of NaOCl, the better the disinfection abilities of NaOCl regarding *E. faecalis*. These findings seem to correlate with the resistance of the *E. faecalis* to NaOCl [44].

Several in vitro studies have demonstrated the antibacterial action of MTAD against *E. faecalis*, both in biofilm and in the planktonic phase, when used as the only irrigant in root canals of human teeth [13, 38]. Specifically, an in vitro study stated that MTAD, as the only irrigant, had a wider range of microbial inhibition against *E. faecalis* when compared with 2 % CHX and 5.25 % NaOCl [13]. Furthermore, another study showed that MTAD with maximum antibacterial activity is more effective against *E. faecalis* than 3 % NaOCl, 2 % CHX and 0.12 % CHX [31].

Two research groups, Torabinejad et al. (surface disinfection) and Siren

Properties	NaOCl	EDTA	CHX	MTAD
Biocompatibility	-	+	+	+
Ability to dissolve pulp tissue	+	-	-	-
Antimicrobial activity	++	-	+	+
Ability to remove smear layer	-	+	-	+
Dentine degeneration	+	+/-	-	+/-
Inhibition of *E. faecalis*	+	-	+	+

Table 1 Properties of the irrigants in endodontics in comparison to MTAD (CHX = chlorhexidine; NaOCl = sodium hypochlorite; EDTA = Ethylenediaminetetraacetic acid)
(Tab. 1 and 2: M. Dede)

et al. (dentine block disinfection) documented that *E. faecalis* can be eliminated from the dentine by following a protocol using MTAD in combination with NaOCl [49, 58]. Different in vitro studies showed that MTAD as a final irrigant in human teeth was effective in completely inhibiting the growth of *E. faecalis* [1, 38, 49].

In an *in vivo* study with human primary teeth, 2.5 % NaOCl and BioPure MTAD, both irrigants were equally efficient against *E. faecalis* [60]. The aim of a present *in vivo* study was to evaluate the reduction in bacterial loading with the sterile paper point method using MTAD as an irrigating solution in pulpectomized primary teeth. The results showed that MTAD could serve as an alternative irrigant for pulpectomy of necrotic teeth compared to 1 % NaOCl [18].

Unfortunately, not many studies exist which examined the effectiveness of MTAD against other bacteria except for *E. faecalis*. According to Misuriya et al., the MTAD solution showed maximum antibacterial activity and was effective against *E. faecalis*, *F. nucleatum* and *P. anaerobicus*. In case of *C. albicans*, MTAD was less effective than 5 % NaOCl, 3 % NaOCl, 2 % CHX and 0.12 % CHX [31]. After mechanical treatment and irrigation of root canals with MTAD solution, *P. intermedia*, *P. gingivalis* and *T. forsythensis* were not found in an *in vitro* study with mixed infection in root canals [32]. Regarding the antifungal activity of MTAD against *C. albicans in vitro*, 1.3 % NaOCl and 2 % CHX were equally effective and significantly superior to MTAD and Tetraclean [35].

In 2004, Luciano Giardino patented an irrigant prototype, also antibiotic-based, called Tetraclean. It is similar to MTAD, although with differences in the components. It also contains citric acid and doxycycline, although the amount of doxycycline is reduced to a third (50 mg/5 ml vs. 150 mg/5 ml of MTAD). Additionally, Tetraclean contains Polypropylene glycol instead of Polysorbate 80 and the antiseptic cetrimide [22].

Finally, it is worth mentioning that MTAD and CHX have a residual antimicrobial activity with various lasting times. This effect duration of residual antimicrobial activity is better in MTAD [60]. The substantivity of MTAD *in vitro* was significantly greater than that of 2 % CHX and 2.6 % NaOCl. The substantivity of 100 % MTAD was significantly higher against bacterial biofilms than lower concentrations (10 % and 1 %) of MTAD [33, 34].

2. Ability to remove smear layer

It is widely known and proven that the presence of organic tissue and smear layer reduces the effectiveness of antimicrobial protocols [23, 43]. The lack of increased antimicrobial efficacy may be due to the inability of NaOCl to remove the smear layer and to penetrate into dentinal tubules once the smear layer has been removed. Findings from studies of Torabinejad et al. have shown that the removal of the smear layer with a chelating solution (EDTA) with no antibacterial effect does not enhance the antibacterial effect of NaOCl. Otherwise, the combination of 1.3 % NaOCl as a root canal irrigant and MTAD as a final rinse was significantly more effective than the combination of 1.3 % NaOCl with 17 % EDTA [50, 58].

Using the scanning electronic microscope (SEM) Torabinejad et al. demonstrated that MTAD is a valid solution for the removal of the smear layer, which does not significantly change the structure of the dentinal tubules when used as a final irrigant in conjunction with 5.25 % NaOCl.

The changes in temperature at 4°C, 25°C, and 37°C play a specific role regarding the efficacy of MTAD for removing the smear layer. In a recent study, it was concluded that using 17 % EDTA and MTAD at 25°C and 37°C was more potent than using the solutions at 4°C temperature, even in the apical level of the root canal [12].

Using MTAD with ultrasonic agitation reduced the smear layer [26]. Based on the results of the SEM data in a recent study, 1.3 % NaOCl and MTAD combined with endosonic irrigation, acted synergistically to remove the smear layer and debris, while causing less erosion on the dentine surface [26]. In comparison to other solutions, MTAD has demonstrated improved results by removal of the smear layer on primary root dentine [7].

MTAD as a final rinse after the entire instrumentation with 3 % NaOCl provided the best cleaning ability in all parts of the root canal system and had good results particularly in cases of teeth with established infection in the apical part of the root canal [25]. In this study, the dentinal wall of the cervical, middle and apical thirds were observed at magnifications of up to ×1000 for the presence/absence of smear layer under SEM [25]. On the contrary, 2 studies summarized that the efficacy of 17 % EDTA as final rinse for the removal of the smear layer was better than MTAD [27, 61]. In addition, based on the outcomes and limitations of an *ex vivo* investigation, SmearClear (Sybron Endo; Orange, CA), a 17 % EDTA solution containing a cationic (cetrimide) and an anionic surfactant, was found most efficient in removing the smear layer in all regions of the root canal followed by MTAD [63].

Additionally, another present study demonstrated that chitosan (natural polysaccharide, derived from the deacetylation of chitin) was more effective in smear layer removal than MTAD, especially in the apical third of the root canal [67].

3. Effect on dentine structure

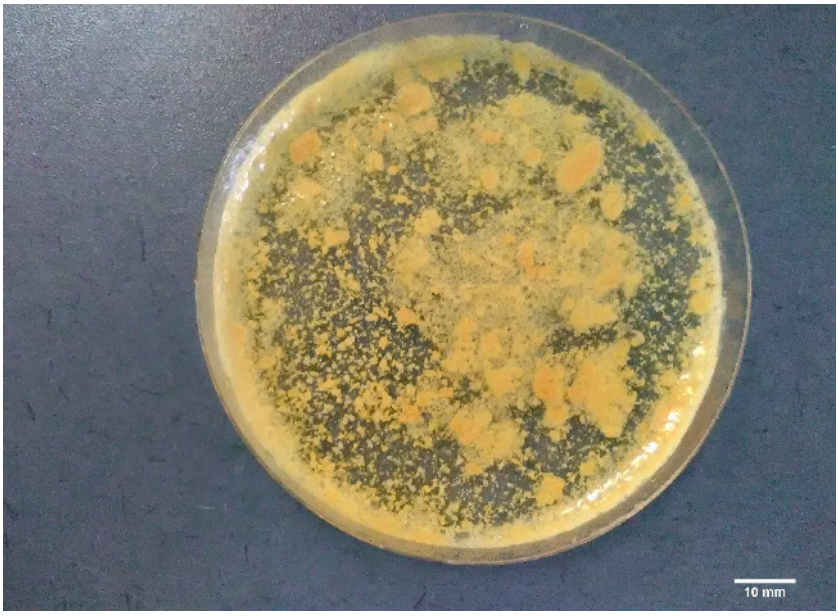
Chemicals used during endodontic treatment play an important role as they may lead to alterations of the root dentine and changes its chemical and physical properties. Pashley et al. stated that the tubular density affects the microhardness of the dentine surface – as the tubular density increases the dentine microhardness decreases, respectively [14, 41].

De Deus et al. and Sayin et al. examined the effect of endodontic irrigation solutions on root canal dentine surface and stated that there is a significant decrease of the microhardness in the dentine of the root canal after the application of EDTA [14, 48].

In accordance with Torabinejad et al. 1 % NaOCl preceding MTAD can dissolve the organic portion of the

smear layer that covers the dentinal tubules after instrumentation. Due to the citric acid, MTAD is an acidic solution (pH 2.15) and is capable of removing inorganic substances. This allows MTAD to dissolve the inorganic portion of the smear layer, penetrating into dentinal tubules, and decalcifying them without affecting the structure of dentine [58]. An *in vitro* study by Pappen et al. concluded that the detergent of MTAD can additionally decrease the surface tension and increase the penetrating ability of MTAD, without affecting the structure of dentine, too. The samples were observed by confocal laser scanning microscopy (CLSM) after bacterial viability staining [40]. In an investigation of Machnick et al., there was no significant difference regarding the flexural strength and modulus of elasticity between the dentine bars exposed to saline or to MTAD [29]. Aranda et al. revealed significant dentine microhardness reduction promoted by (Biopure) MTAD and 17 % EDTA. Only the use of 17 % EDTA promoted dentinal tubules erosion *in vitro* [3].

The study of Machnick et al. compared the effect of MTAD and phosphoric acid on the bond strength to enamel and dentin using a conventional OptiBond Solo Plus dentine adhesive system. They reported that teeth treated with a MTAD protocol (20 min 1.3 % NaOCl/5 min MTAD) might not need any additional dentine conditioning before the application of the adhesive system [29]. Regarding the effect of MTAD on dentine bonding, some studies concluded that MTAD can significantly improve the resin-dentine bond stability due to its broad-spectrum matrix metalloproteinase-inhibitory effect [20, 29, 36]. Furthermore, studies stated that MTAD as *final rinse* influences the sealing properties of root-end filling materials negatively, like other chelator factors (EDTA) do as well. Leakage of root-end filling materials increased when 17 % EDTA or MTAD were used for irrigation [16, 37, 46]. A recent study concluded that the highest leakage rate was observed in the 17 % EDTA and MTAD groups when MTA, Portland cement, and Bioaggregate (BA) root-end filling materials were used [10]. Saghiri et al. showed in an *in vitro* study that MTAD as final irrigation lowered this push-out bond strength of MTA-dentine contact surfaces and thus affects it negatively [47].



(picture in laboratory, Faculty of Medicine Carl Gustav Carus, Dresden, Germany)

Figure 1 Viscosity of MTAD-fluid in a plate, a mixture of powder and liquid

4. Biocompatibility

Focusing on biocompatibility, MTAD as a final rinse for the removal of the smear layer did not cause postoperative discomfort after root canal treatment in 73 patients, according to a randomized clinical trial [59]. In this study, 1.3 % NaOCl and MTAD as endodontic irrigants were compared with irrigation using 5.25 % NaOCl and 17 % EDTA [59].

Regarding the cytotoxicity of MTAD, a study by Zhang et al. evaluated the viability of cultured fibroblasts after storage in MTAD and other standard irrigants. MTAD is less cytotoxic than eugenol, H_2O_2, Ca $(OH)_2$ paste, 5.25 % NaOCl, Peridex (CHX mouth rinse with additives) and 17 % EDTA, but more cytotoxic than 2.63 %, 1.31 % and 0.66 % NaOCl [66]. Bajrami et al. demonstrated that irrigating solutions should be used at lower concentrations to enhance cell viability. In this study incubation of rat ligamental fibroblasts in 0.1 ml/L concentrations of 3 % NaOCl and MTAD was only moderately cytotoxic, whereas 2 % CHX was highly deleterious to cell viability at this concentration. At 100 ml/L (high concentration) MTAD as well as 3 % NaOCl generated high levels of cytotoxicity to the fibroblasts [6]. Another present study also demonstrated that MTAD was less cytotoxic compared to NaOCl, CHX, QMix and EDTA [24]. This finding is in accordance with the results separately reported by Yasuda et al. and Zhang et al. that stated higher biocompatibility of MTAD in comparison with NaOCl 5.25 % and EDTA 17 % [64, 66].

Doxycycline (tetracycline) as a part of MTAD could cause permanent tooth discoloration when treatment occurs during teeth development. Tetracycline products should be avoided by young children with evolving teeth or by pregnant women, respectively [30]. NaOCl has been proven to react with MTAD thus triggering light brown discoloration by oxidizing the doxycycline component of MTAD [53, 55, 58]. This reaction may be affected by the release of doxycycline, which will be exposed to NaOCl if it is used as a final rinse after MTAD [58]. Clinically, this can be avoided by neutralizing the oxidizing action of NaOCl with a rinse of ascorbic acid before MTAD is applied into the root canal [55]. It is also worth noting that the chemical reaction be-

tween NaOCl and citric acid leads to the formation of white precipitates [2]. These interactions between NaOCl and MTAD require further investigations to validate the safety and usefulness of this combination [2].

Some studies were performed focusing on the regenerative aspect of MTAD and other irrigating solutions. MTAD was used for the regeneration of immature permanent non-vital teeth in dogs [4]. EDTA showed significantly more growing tissue in the pulp and less inflammatory cells than MTAD. The use of collagen as a scaffold material and MTAD as a surface modifier did not improve the quality of the regenerative process [4]. Considering the cytotoxicity of different irrigants on the survival of stem cells of the human apical papilla, MTAD showed the highest cytotoxicity to stem cells compared to 17 % EDTA, QMix, 5.25 % NaOCl, 2 % CHX and sterile saline [17]. The table summarizes the properties of the different irrigants in comparison to MTAD (Tab. 2).

Discussion

Since its introduction by Torabinejad et al., MTAD has been in the focus of attention as an alternative root canal irrigant. Therefore, the publications of Torabinejad et al. should be taken into consideration carefully. The presence of doxycycline in MTAD suggests that MTAD may have some substantive antimicrobial action [58]. Doxycycline, as a hydroxyl derivative of tetracycline, is the most potent anticollagenase antibiotic among commercially available tetracyclines [22]. However, the exact antimicrobial action of MTAD has not been fully understood.

The initial studies of Torabinehad et al. conducted on MTAD showed good antimicrobial activity especially against *E. faecalis* [58, 38], but *E. faecalis* is not the only dominant bacteria. Findings of the study of Rôças et al. confirm the strong association between persistent intraradicular infection and posttreatment apical periodontitis [45]. Most cases harbored a mixed infection and an increasing concern arose that the cooperative behavior of a multi-species biofilm facilitates persistence after exposure to an antimicrobial agent [21, 45]. It has been indicated that MTAD is somewhat effective against bacterial biofilms. However, it cannot disrupt or dissolve biofilms completely [33]. Actually, not many studies examined the effect of MTAD against other bacteria species than *E. faecalis*. However, the difference of the studies in methodology and microbial sampling procedures play an important role, too. Most of the studies were based on the paper point sampling method for the analysis and quantification of bacteria, which is controversially discussed by scientists.

The bactericidal activity of MTAD as the only intracanal irrigant requires improvement. Attempts have been made to enhance the effectiveness of MTAD. In 2013, a new ingredient was added to MTAD. Nisin, an antibacterial peptide, was investigated in an *in vitro* study to show whether it increased the antibacterial and antibiofilm activities of MTAD against clinical isolates of *E. faecalis*. The results clarified that MTADN (Mixture of Tetracycline isomer, an Acid, an Detergent and Nicin) effectively inhibited both the growth of *E. faecalis* root canal isolates and the biofilm isolates [56, 57].

As another important aspect, MTAD showed improved results in combination with NaOCl in the removal of the smear layer during the root canal treatment when compared to EDTA and NaOCl, respectively [25, 38, 50]. Furthermore, recent studies for MTAD showed good disinfection results when used as a final rinse in combination with NaOCl and agitated with ultrasonic [25, 26]. However, regarding the clinical relevance, the cost of the material, the availability and the clinical feasibility as a 2-part mixture, MTAD seems to be disadvantageous compared to EDTA. Clinical studies are required to establish the solution as a more practicable material in clinical practice.

Biocompatibility and the effect of MTAD on bond strength to enamel and dentine are widely accepted, but discussed controversially [19, 51]. Regarding the effect of MTAD on stem cells as well as endodontic tissue regeneration, further research may potentially lead to unforeseen results. However, MTAD as a surface modifier did not improve the quality of the regenerative process in root canal [4, 17].

Conclusion

In conclusion, MTAD represents an effective final irrigant for the removal of the smear layer in combination with NaOCl. Promising data considering the antimicrobial activity of MTAD especially against *E. faecalis* exist, but further research is required to establish MTAD as a potent irrigant against other bacterial species and biofilms. Furthermore, the effects of MTAD on the sealing properties of root-end filling materials as well as its effect on dental stem cells in regenerative endodontics are still controversially discussed.

In general, MTAD seems to be a promising additional irrigant within an irrigation protocol. No solution exists that is able to ensure complete disinfection, yet. Therefore, the combination of irrigants along with proper instrumentation of the root canal has probably a much higher impact on the treatment outcome than one single irrigant.

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Conflicts of interest:
The authors declare that there is no conflict of interest within the meaning of the guidelines of the International Committee of Medical Journal Editors.

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