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Review Article

Dentistry Section

Etidronate as A Weak Chelating Agent on Root Canal Dentin: An Update Review

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ABSTRACT

Successful root canal treatment depends on proper biomechanical cleaning and shaping of root canal system followed by three-dimensional obturation. Irrigation solutions and chelating agents are used during root canal treatment to assist in smear layer removal and enhanced bonding with sealer. Different chelating agents are used in combination with irrigation solutions such as Ethylenediaminetetraacetic Acid (EDTA), Citric Acid (CA), mixture of doxycycline, citric acid and a detergent {Tween 80 (MTAD)}, chitosan, maleic acid and etidronate. Etidronate is a weak biocompatible chelating agent effective in smear layer removal with less harmful erosive effects on root canal dentin, compared with other strong chelating agents like EDTA and citric acid. Etidronate can be mixed with Sodium Hypochlorite (NaOCl) without interfering with its antimicrobial or dissolving activity while EDTA retains its calcium-complex when it is mixed with NaOCl reducing its tissue dissolving capacity.

Keywords: Bisphosphonate, Chelation, Irrigation, Smear layer

INTRODUCTION

Successful root canal treatment depends on proper biomechanical cleaning and shaping of the root canal system, disinfection with complete debridement of intra-canal smear layer followed by three dimensional fluid tight seal obturation. Root canal instrumentation produces amorphous, irregular and granular layer, i.e, "smear layer" that contains inorganic debris, organic material like pulp tissue, necrotic debris, odontoblastic process, coagulated proteins, blood cells, nerve fibers, collagen, tissue fluid, microorganisms and their byproducts [1-3].

Presence of the smear layer contributes to microleakage as it provides shelter and nutrition to microbes, acts as a barrier between canal walls and the filling material, obliterates dentinal tubules thus, reducing dentinal permeability and prevents the penetration of disinfecting agents [2-4].

Proper mechanical bonding is obtained through penetration of obturating material to the adherent root canal system to create mechanical interlocking. To obtain effective adhesive bonding, the adherent should be properly cleaned, removing the smear layer and creating a rough surface [5].

Dentists used irrigation solutions and chelating agents to facilitate root canal instrumentation and remove the smear layer [6]. Such solutions can cause root canal deviation during biomechanical preparation [7]. These solutions alter the calcium phosphorus ratio (Ca/P) leading to an increase in the surface roughness and decrease in the microhardness facilitating the dentine cutting [8-11]. These changes affect the adhesion and sealing ability of root canal sealers and resin based cements to dentine [12,13].

To achieve better adhesion between filling material and root canal dentine any space between dentine wall and the obturating material should be eliminated, also the filling material should resist dislodgment forces [14,15].

Both tensile and shear forces play a role in the leakage at the dentin–sealer and gutta percha–sealer interface, so adhesion tests should measure both shear and tensile bond strength. Shear force is measured parallel to the interface among the surface and materials while tensile force is measured perpendicular to the interface [16,17].

Sodium hypochlorite solution (NaOCl) as an irrigation solution, has a microbicidal activity and tissue dissolving ability [18]. It decreases the dentine microhardness in all of its concentrations [19-21]. Its action allows removing the organic structure of smear layer only [22]. For complete removal of smear layer, NaOCl should be mixed with other chelating agents that can remove the inorganic phase of the smear layer. Chitosan, maleic acid, EDTA, citric acid, MTAD and etidronate which is also known as bisphosphonate, etidronic acid or HEBP (1-Hydroxyethylidene-1, 1-Bisphosphonate) have the ability to remove the inorganic phase of smear layer [23-26].

Ethylenediaminetetraacetic acid is a strong chelating agent that reacts with calcium ions in root canal dentine forming calcium chelates enhancing adaptation of filling material to root canal dentine [27]. On other hand, it results in excessive erosion of peritubular and intertubular dentine that decreases microhardness of root dentine and it also interacts with NaOCl decreasing its antimicrobial effect through reducing the free available chlorine [28-30].

Ethylenediaminetetraacetic acid, CA and MTAD when used as a final irrigant leaves the collagen matrix on root canal surface contributing to bacterial adherence and recontamination. Hence, NaOCl must be used as a final irrigant after chelating agent to remove the collagen matrix in a process called deproteination [22,31-34].

Bisphosphonates (BPs) have a calcium chelating property and have similar structure as the natural pyrophosphate. It contains two phosphonate (PO_3) groups [35]. These two phosphonate groups attached to a central carbon that replaces oxygen in pyrophosphate. This three dimensional structure of pyrophosphate can chelate the divalent cations (Ca^{2+}). So, it has a strong remodelling bone affinity [36]. The bisphosphonates perform bone modulation at three levels: (A) At tissue level, it decreases bone resorption and number of new bone cells (multicellular units) that leads to decrease in bone turnover. Thus, positive bone balance in the body is maintained. (B) At cellular level, decrease in osteoclast recruitment, increased osteoclast apoptosis, decreased osteoclast adhesion, decrease in depth of resorption site, decrease in release of cytokines by the macrophages and increase in osteoblasts differentiation and number occurs. (C) At molecular level, it inhibits the mevalonate pathway which is an important cellular metabolic pathway present in all higher eukaryotes and many bacteria [35].

Bisphosphonates are administrated systemically in patients suffering from osteoclastic bone resorption, neoplastic diseases, osteoporosis, Paget's disease, multiple myeloma and breast/prostate cancer [37,38]. Recently, its use as a chelating agent during root canal treatment has been excessively increased instead of EDTA and CA [2,39].

1-Hydroxyethylidene-1, 1-Bisphosphonate is a weak biocompatible chelator [26,29]. It can be used in combination with NaOCl without interfering with its antimicrobial or dissolution activity and needs 300 seconds to completely remove the smear layer [30-34,40]. It is used in tooth paste to control calculus formation [36,41] as well as remove it. It is profound in removing calculus as it chelates calcium and magnesium in water without harming the dental enamel surface [42,43]. It is also used as an adjunct in household and personal care products such as soaps [2].

The aim of this article was to review and summarise the chelating and irrigating effect of etidronate (HEBP) as an alternative to EDTA and CA on root canal dentine.

DISCUSSION

With the help of currently available literature, this paper highlights the chelating and irrigating action of HEBP comparing it with other materials that are commonly used during root canal preparation. A total of 80 publications that included the titles and abstracts of articles in English language between 2006 to 2016 were searched and 73 papers were selected. The search words HEBP, EDTA, CA, maleic acid, chelation, irrigation and smear layer were used. The selected studies are listed in [Table/Fig-1].

Effects of chelating agents on root canal dentin

Erosive changes: One of the important goals of using chelating and irrigating agents during root canal mechanical preparation is to remove smear layer [6,44]. EDTA is a strong powerful chelating agent in removing smear layer but it has erosive effects on peritubular and intertubular dentin affecting its mechanical integrity that causes errors during canal instrumentation [45-47]. De-Deus G et al., when analysed the smear layer dissolution kinetics of 18% HEBP, 9% HEBP and 17% EDTA by using single tooth comparative model, found that EDTA is stronger in smear layer dissolution but it has erosive effects on dentin creating preparation errors than both concentrations of HEBP [40].

For smear layer removal, chemical chelating agents are used in combination with NaOCl [23,48]. However, this combination although removes smear layer but also alters physical and mechanical structure of dentin [9,49,50]. Chelating agents affect calcium ratio present in the hydroxyapatite crystals that affects dentin microhardness, permeability, bonding/sealing properties and solubility [13,28,50-53].

Altering Ca/P ratio: HEBP is a non-toxic biocompatible chelator used in combination with NaOCl without interfering with its disinfecting properties [29,30]. Peracetic acid decomposes into acetic acid and oxygen so, it could be used after instrumentation to dissolve smear layer and provides thorough disinfection of root canal that pretreated with NaOCl. Lottanti S et al., that suggested both HEBP and peracetic acid as potential replacement to EDTA [54]. While, Cobankara FK et al., found higher decrease in Ca levels of root dentin with application of 17% EDTA, 10% CA, 2.25% peracetic acid and 18% HEBP as chelating solutions on root dentin for five minute [2]. They reported peracetic acid showed lower Ca/P ratio and higher decrease in Ca level than other solutions. Thus, HEBP had soft and weak effect on Ca/P ratio.

Author/year	Description of study	Subject used/ Methods of assessment	Results
De–Deus G et al., (2006) [28]	In vitro study Evaluation of the effect of EDTA, EDTAC and citric acid on the microhardness of root dentine.	n=16 Sixteen maxillary human canines. Low speed diamond saw. Epoxy resin cylinder.	With increased application time of chelating solutions, the microhardness decreased. EDTA was more effective in reducing dentine hardness than CA.
De–Deus G et al., (2008) [40]	In vitro study Longitudinal co-site optical microscopy study on the chelating ability of etidronate and EDTA using a comparative single–tooth model.	n=3 (Recently extracted three unerupted third molars). Co–site microscopy. Digital Image Analysis.	9% HEBP and 18% HEBP had significantly slower demineralisation kinetics than 17% EDTA. No difference was observed between the chelating abilities of HEBP and EDTA. No relation was found between the HEBP concentrations and their chelating ability.
Cobankara FK et al., (2011) [2]	In vitro study Effects of chelating agents on the mineral content of root canal dentin.	n=60 (Recently extracted Sixty human mandibular anterior teeth). Gates–Glidden no. 3,4,5 ICP-AES (Inductively Coupled Plasma-Atomic Emission Spectrometry).	Chelating agents have different effects on mineral contents of root dentin. Peracetic acid has the greatest decrease in P, K, Mg, Na, S and CA so it must be used with caution. Peracitic acid showed lower Ca/P ratio than EDTA, HEBP, CA. Highest Ca^{2+} ions decrease was with peracitic acid, CA and EDTA. HEBP showed the least decrease in Ca^{2+} ions than all solutions so it is a potential alternative to EDTA and CA.
Kandaswamy D et al., (2011) [58]	In vitro study Effects of various final irrigants on the shear bond strength of resin-based sealer to dentin.	n=40 (40 freshly extracted human maxillary first premolars). Low speed diamond saw. Plastic cylindrical ring. Handimet grinder. Polyethylene tubes.	When used as final irrigant. EDTA showed highest bond strength of AH-plus sealer to coronal root dentin followed by HEBP and MTAD.
Dineshkumar MK et al., (2012) [39]	In vitro study Effect of EDTA, MTAD™, and HEBP as a final rinse on the microhardness of root dentin.	n=40 40 human single rooted teeth decoronated at cementoenamel junction. Low speed diamond saw. Fine emery papers. 0.1 µm alumina suspension. Vickers microhardness test.	The highest microhardness was observed in HEBP-treated root dentin. There was an increased bond strength of resin-based sealers to root canal dentin by HEBP as compared to EDTA and MTAD. HEBP had a lesser impact on the mineral content of root dentin.
Tartari T et al., (2013) [71]	In vitro study A new weak chelator in endodontics: effects of different irrigation regimens with etidronate on root dentin microhardness.	n=72 Seventy two Single-rooted human teeth. low-speed diamond disk digital caliper PD-150 autopolymerising acrylic resin circular grinding machine polishing machine felt disc and extra-fine-grained diamond paste Knoop indenter of the microhardness tester FM-700 ultrasonic tub.	5% NaOCl, 17% EDTA, 10% CA, and 9 and 18% HEBP all reduced the microhardness of the root dentin lumen. The root thirds behaved similarly when subjected to the same irrigation regimen even with their structure difference.

Tartari T et al., (2013) [60]	In vitro study Etidronate from medicine to endodontics: effects of different irrigation regimes on root dentin roughness.	n=45 Forty-five root halves of anterior teeth. low-speed diamond disk size 15 K-type file digital calliper PD-150 autopolymerising acrylic resin circular grinding machine silicon carbide abrasive papers digital roughness tester SJ 301.	5% NaOCl, 10% CA, 9 and 18% HEBP, 17% EDTA all altered the roughness of root dentin. The smallest changes in surface roughness were observed with 9% HEBP when applied for five min. HEBP is a weak chelating agent that attacks less dentin surface than EDTA. HEBP solutions need 300 seconds to completely remove the smear layer.
Ashraf H et al., (2014) [67]	Comparative in vitro study Smear layer removal in the apical third of root canals by two chelating agents and laser.	n=50 periapical radiographs Root canal instrumentation (HERO 642 rotary files) electric speed/torque controller device (X-SMART) Root sectioning and SEM evaluation.	The amount of smear layer removed by EDTA was greater than Er: YAG laser and 18% etidronate.
Kuruvilla A et al., (2015) [26]	An in vitro scanning electron microscopic study A comparative evaluation of smear layer removal by using EDTA, etidronic acid, and maleic acid as root canal irrigants.	n=30 Thirty freshly extracted single rooted human mandibular premolars. Buccal and proximal radiographs a diamond disk Gates-Glidden Standardised crown-down technique with sequentially sized K files.	EDTA, malic acid, etidronic acid removed smear layer effectively from coronal and middle third. Maleic acid showed better results than EDTA and etidronic acid at the apical third. There was no significant difference between etidronic acid and EDTA.
Yadav HK et al., (2015) [68]	An in vitro study Efficacy of etidronic acid, BioPure MTAD and Smear Clear in removing calcium ions from the root canal.	n=50 Fifty freshly extracted human mandibular premolars. slow speed, water-cooled diamond saw crown-down Root canal preparation ProTaper universal X-Smart endodontic motor.	Smear-Clear was most effective in removing Ca^{2+} ions from the root canal followed by BioPure MTAD, when compared with 18% HEBP, 9% HEBP, and normal saline.
Karale R et al., (2016) [73]	An in vitro study Effect of dentin on the antimicrobial efficacy of 3% sodium hypochlorite, 2% chlorhexidine, 17% EDTA, and 18% etidronic acid on *Candida albicans*.	n=25 Dentin powder was prepared by crushing and grinding radicular dentin of 25 mandibular premolars electronic grinder.	NaOCl and EDTA reduced number of *C. albicans* during root canal therapy. HEBP showed good antimicrobial efficacy and could be mixed with NaOCl without interfering with its properties. It showed less effect on dentin structure.

[Table/Fig-1]: List of various studies comparing the effect of HEBP with other chelating agents on root canal dentin.

Depth of demineralisation zone: Enhanced proper adhesion is influenced by smear layer removal that allows penetration of sealer into the dentinal tubules and in the depth of the demineralised zone of dentin which is created by chelating agent [55-57]. Garcia-Godoy F et al., reported that EDTA creates dentin demineralisation zone about 2-4 μm depth, while demineralisation zone created by HEBP was comparatively less. [57] Kandaswamy D et al., evaluated the effect of strong chelating agents 17% EDTA, MTAD and soft 18% HEBP as a final irrigating solution on the shear bond strength of AH-plus sealer to coronal dentin [58], and found that EDTA showed higher bond strength followed by HEBP while MTAD showed least shear bond strength although, it had better smear layer removal and greater depth of demineralisation in dentin (8 to 12 μm). De-Deus G et al., reported that EDTA had self-limiting action as it completely removes smear layer after 60 seconds when forming calcium chelate [40]. Violich D and Chandler N, reported that EDTA created dentin demineralisation zone of 20-30 μm in five minute. So, increasing time of application causes more demineralisation action resulting in peritubular and intertubular dentine erosion [1].

Dentin microhardness and surface roughness: The physicochemical properties of root dentin such as solubility, roughness microhardness, wettability, permeability and surface topography are influenced by irrigation solutions as these could be changed after use of chelating agents [8,10].

Dineshkumar MK et al., evaluated root dentin microhardness by using 17% EDTA, MTAD and soft 18% HEBP as a final rinse [39]. They found that HEBP treated root dentin showed the highest microhardness. Thus, it increased the bond strength of resin based sealer to root canal dentin than EDTA and MTAD. This could be due to the larger intertubular dentin area available for hybridisation and the partial depletion of surface Ca++ [40,59].

Tartari T et al., evaluated the effect of 2.5% NaOCl, 10% CA, 9% HEBP, 18% HEBP and 17% EDTA as final irrigation on dentin roughness and found that NaOCl treatment did not modify dentin surface roughness before or after use of chelating agents [60]. They reported greater increase in roughness with CA and HEBP than EDTA. Citric acid caused extensive demineralisation in dentinal tubules and peritubular dentin alongwith strong activity in smear layer removal. HEBP had an increased area of action owing to NaOCl ability to cause deproteination of dentinal canals [22,52]. On the contrary, De-Deus G et al., investigated the effect of 10% citric, 17% EDTA and 17% EDTAC (ethylenediaminetetraacetic acid plus Cetavlon) on root canal dentin microhardness and reported that CA was less effective in reducing dentin microhardness than EDTA [28].

There are many factors affecting the decalcifying effect of chelating and irrigating agent in smear layer removal and negotiation of calcified, fine and tortuous canal such as root length, diffusion in dentin, application time, the solution pH and its surface tension [9,29,46].

Tartari T et al., reported similar increase in surface roughness behaviour of the three root canal thirds with 17% EDTA and 10% CA while same results obtained with 9% and 18% HEBP only for both coronal and middle root canal thirds but it reduced in apical third due to area sclerotic dentin and reduced number of deproteination canals created by NaOCl decreasing the area of action available for HEBP [60]. Sclerotic dentine has been reported to increase with age and has a refractive index similar to rest of the dentine [61,62].

Rotary nickel-titanium (NiTi) files produced higher amount of smear layer compared to hand instruments [42,63]. Schlingemann R and Schafer E conveyed that debridement of the apical third of the canals was less than the coronal and middle thirds [43]. Khabbaz MG and Arvaniti IS reported a significant difference in presence of smear layer between apical and middle thirds of the canals [64]. Subsequently, smear layer removal in the apical region remains unpredictable [65-66]. Ashraf H et al., reported significantly higher smear layer removal from apical third with 17% EDTA followed by Er: YAG laser and the least with 18% HEBP [67]. Laser also improved the action of EDTA while HEBP needed 300 seconds to completely remove smear layer.

The application time of irrigating and chelating solution have been reported to vary from 30 seconds to 10 minutes [46]. However, Yadav HK et al., compared the effect of 9% HEBP, 18% HEBP, Smear-Clear, BioPure MTAD, 17% EDTA in calcium ions removal from the root canal and reported that one minute EDTA irrigation was effective in smear layer removal than 10 minutes application as excessive peritubular and intertubular dentinal erosion occurred with greater application time [68].

The use of 17% EDTA for more than one minute causes harmful consequences as excessive erosion, enlarged dentinal tubules openings with deterioration of dentin surface. Malic acid at higher concentration than 7% causes damage to the intertubular dentin [46,54] in accordance with findings by De-Deus G et al., which were suggestive of decreased dentin microhardness with increased time of chelating agent application [28].

Ethylenediaminetetraacetic acid and maleic acid, when used in association with NaOCl, reduced the expected properties of NaOCl. Etidronic acid can be used in combination with NaOCl without any loss of its actions [69,70]. Similar findings have been reported by Kuruvilla A et al., [26].

The demineralisation process continues until the chelating agent forms complexes with calcium. The pH of EDTA is around 7.3 and for citric acid is 0.8-1.9 while it is neutral for HEBP. The HEBP has constant calcium-binding capacity so its chelation effects depend on its concentration. The amount of calcium ions eluted from root canal with 20% HEBP found to be similar to that with 17% EDTA or 10% CA [9,29,46]. Tartari T et al., reported that HEBP is a weak calcium-complex agent that causes less changes in dentin than other chelating agents [71]. Yadav HK et al., reported similar chelating capacity with 18% HEBP and 17% EDTA, so they recommend use of 7-10% HEBP as a less aggressive calcium-complex agent to prevent erosive dentinal changes [68].

Candida albicans is the most common yeast species isolated from the infected root canal as it can survive, penetrate and adhere to dentin walls even in high alkalinity [72]. Karale R et al., investigated the antimicrobial effect of 3% NaOCl, 2% CHX (chlorohexidine), 17% EDTA and 18% HEBP on *Candida albicans* and they found that EDTA showed the most effective antifungal activity after NaOCl but it caused reduction in tissue dissolving capacity of NaOCl, while HEBP showed effective antimicrobial effect without interfering with antimicrobial properties of NaOCl or CHX [73].

CONCLUSION

Increased time of chelating agent application will lead to increased Ca^{2+} ions removal, greater depth of demineralisation zone, more dentin surface roughness with decreased dentin microhardness, larger erosive effects and decreased bond strength between resin sealer and dentin wall. The strong chelating solution will lead to increased decrease in dentin microhardness and erosion of peritubular and intertubular dentin affecting the shear bond strength. Studies reported that EDTA, CA, maleic acid, MTAD, peracetic acid are stronger chelating agents than HEBP and must be used with caution whereas, the use of weak HEBP as chelating agent has optimal effects on Ca/P ratio, dentin surface roughness and microhardness with no erosive effects on dentin wall as compared to the other agents. HEBP can be used in association with NaOCl, without its interference in its action. Few studies reported that there is no correlation between HEBP concentration and its effect. So, more studies are required to investigate the actions and effects of HEBP in different concentrations on root canal dentin to further evaluate its usefulness as an irrigating and chelating agent in dental procedures.

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