Etidronic Acid as a Root Canal Irrigant: A Systematic Review of its Efficacy in Disinfection and Potential to Enhance Endodontic Treatment Outcomes

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ABSTRACT
Aim: This systematic review aims to critically evaluate the efficacy of 1-hydroxyethylidene-1,1-bisphosphonate (HEBP) as an antimicrobial irrigant in root canal disinfection protocols.
Materials and Methods: A comprehensive literature search was conducted across PubMed, Google Scholar, and ScienceDirect databases, encompassing studies from the past 15 years. The inclusion criteria were strictly limited to studies utilizing HEBP on extracted human teeth, while animal studies and non-English publications were excluded. The systematic review adhered to PRISMA guidelines, and the methodological quality of included studies was assessed using Cochrane risk of bias tools. Quality assessment parameters included sample size adequacy, presence of control groups, procedural standardization, robustness of statistical analyses, and overall risk of bias. This rigorous approach aimed to provide an evidence-based analysis of HEBP's effectiveness in root canal disinfection.
Results: The initial search yielded 141 studies, of which 126 were excluded following duplicate removal and full-text analysis. Fifteen studies met the stringent inclusion criteria and were subjected to detailed review. The systematic analysis revealed that HEBP, when used as a sole irrigant, did not demonstrate superiority over conventional irrigants such as sodium hypochlorite or ethylenediaminetetraacetic acid (EDTA). However, the combination of HEBP with sodium hypochlorite exhibited synergistic effects, resulting in enhanced antimicrobial efficacy.
Conclusion: The findings of this systematic review indicate that while HEBP as a standalone irrigant does not surpass the antimicrobial efficacy of established agents like sodium hypochlorite or EDTA, it demonstrates comparable disinfection capabilities. Notably, the synergistic potential of HEBP when combined with sodium hypochlorite warrants further investigation for potential clinical applications in root canal disinfection protocols.

1. Introduction

The process of endodontic therapy is designed to optimize the cleaning and shaping of the intricate root canal system. An effective way to achieve this is through the use of chemical irrigants. While EDTA and citric acid are commonly used, HEBP (1-hydroxyethylidene-1,1-bisphosphonate), also known as etidronate or etidronic acid, has emerged as a promising alternative. This is due to its superior efficacy, as it does not react with NaOCl. Additionally, HEBP is a non-toxic substance that has been systematically applied to treat bone diseases[1].

In a study conducted by De-Deus et al., the effectiveness of two different HEBP solutions was compared to that of 17% EDTA in promoting demineralization kinetics. The HEBP solutions, one with a 9% concentration and the other with 18%, were found to have significantly slower kinetics than EDTA. However, the soft chelating irrigation protocol using 18% HEBP was discovered to optimize the bonding quality of Resilon/Epiphany, with bond strength ranging from 3.1 to 6.1 MPa. This irrigant, like EDTA or citric acid, may efficiently eradicate any layer of smear formed whilst being safely combined with hypochlorite while maintaining its antibacterial action[2].

The application of NaOCl in combination with HEBP does not compromise the tissue-dissolving capacity of NaOCl. Additionally, this approach demonstrates comparable effectiveness to the traditional NaOCl-EDTA sequence in minimizing formation of smear layer whilst conducting automated biomechanical instrumentation. Therefore, the amalgamated solution of NaOCl and HEBP may serve as a solitary irrigant throughout and following instrumentation, rendering the utilization of a chelating agent for the final rinse unnecessary[3].

At present, the available research is insufficient to draw comparisons on the effectiveness of NaOCl/HEBP combination versus Enterococcus faecalis biofilms and the viability of microorganisms present in dentinal tubules that are infected, using in situ methods. The objective of this research is to analyze the efficacy of the sodium hypochlorite/etidronic acid combination in eradicating E. faecalis from root canal space infections, based on its antimicrobial activity.

2. Methods

This systematic review followed the recommendations of PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guideline (http://www.prisma-statement.org) and is registered in PROSPERO (CRD42022378149).

Eligibility Criteria: The study included all human teeth, except for bovine teeth, to assess the efficiency of HEBP, an irrigant, against microbial species that are unique to the root canal system. The comparison was made between HEBP, sodium hypochlorite, saline, and EDTA. The research aimed to determine the antimicrobial activity of HEBP in disinfecting the root canal system using in-vitro experiments. Ex vivo or animal dentition studies were not included in this analysis.

Information Sources: The data was gathered from various online databases such as PubMed, Google Scholar, ScienceDirect, and Wiley's online library, using specific MeSH terms that include root canal irrigants and root canal medicaments.

Search Strategy: A online database search was conducted using the US National Library of Medicine's PubMed-MEDLINE (1946-present) database and restricted to studies published in English between 2008 and 2022. The search strategy included MeSH terms and keywords, and a comprehensive search was conducted for the grey literature using Google Scholar, and a manual screening process was employed to examine the reference lists of the chosen studies.

Table 1: Depicts the online database search keywords.

Database	Search terms	Number of articles	Timeline	Language	Article type
PubMed	((HEBP) +(Antibacterial)) + (root canal treatment)	22	2008-2022	English	Clinical trials
Google scholar	HEBP + root canal treatment + Antibacteria	29	2008-2022	English	Clinical trials
ScienceDirect	HEBP + root canal treatment + Antibacteria	73	2008-2022	English	Clinical trials
Wiley Online Library	HEBP + root canal treatment + Antibacteria	15	2008-2022	English	Clinical trials

Study Selection Process: To conduct a comprehensive literature review, we utilized four online databases and performed a preliminary filtration process that involved screening titles and abstracts. We followed the set inclusion and exclusion criteria based on PICOS to narrow down the relevant

articles. Quality assessment was done using Cochrane Risk of bias tools. To maintain precision, three evaluators conducted separate screenings of every record and report. Ultimately, only articles that met the inclusion and exclusion criteria were considered for the review.[4]

Data collection process: The data was acquired by carrying out explorations on the Medical Subject Headings (MeSH) vocabulary. Two separate reviewers collected the data, which was then compiled into a table. The collected data comprised details about the author, year of publishing, specific tooth studied, group of microorganisms, comparative agents used, and the outcomes obtained.

Risk of bias in individual studies: Before using them as references, the articles underwent a thorough risk assessment to gauge their level of bias. Given that all the articles were experimental in-vitro studies, we used the Cochrane risk of bias tool for the assessment. A '+' symbol denoted low risk, while a '-' symbol indicated high risk of bias.[5]

Quality assessment **:** The evaluation of study quality was conducted based on the following criteria: 1) sample size, 2) control group, 3) procedure standardization, 4) statistical analysis, and 5) risk of bias.

3. Results

Study Selection: As per the PRISMA guidelines, the literature search flowchart is presented below. The initial search resulted in 141 articles, out of which 116 were removed due to duplication. Any study not meeting the inclusion criteria was excluded immediately, and one article was further eliminated as it was conducted on bovine teeth. Finally, 15 articles were found eligible for the systematic review.

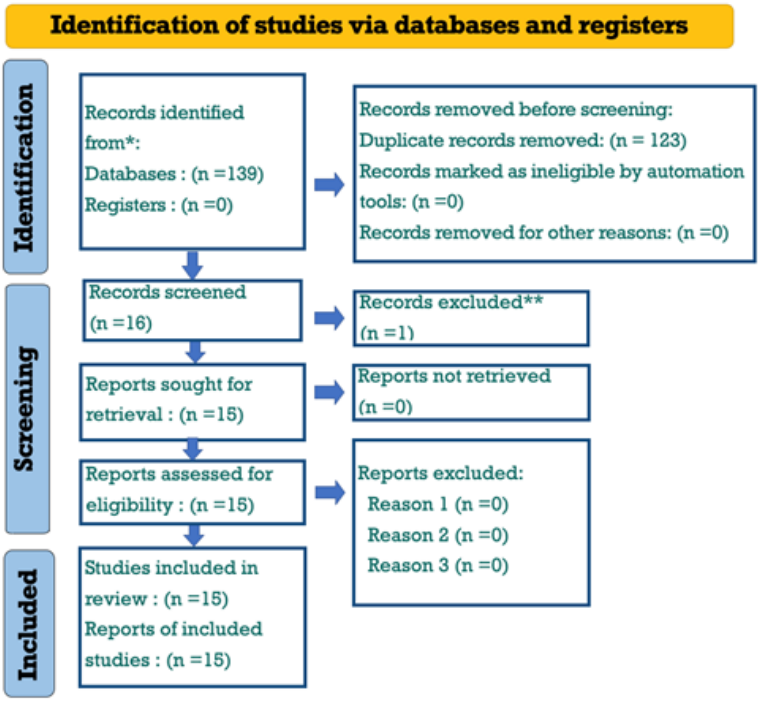

Fig. 1.PRISMA flow diagram

Study Characteristics: The analyzed studies consisted of experimental in-vitro evaluations performed on extracted human teeth. The samples were composed of teeth from primary and permanent dentitions, with a variable sample size ranging from 30 to 126 teeth. The efficacy of HEBP was assessed against several commonly employed irrigants, namely sodium hypochlorite (NaOCL), EDTA, and saline.

Table 2: Table representing authors, microorganisms, tooth type, irrigant concentration, and type of irrigants used along with results.

Author	Year of publication	Microorganism	Tooth	Groups	Result
Arias-Moliz et al 6	2014	E. faecalis	Molars	Chlorhexidine Peracetic acid Sodium hypochlorite	Sodium hypochlorite at a 2.5% concentration demonstrated high antimicrobial activity, with a cell death rate of 88.17% and a corresponding biovolume of 711 units. In contrast, 2% chlorhexidine exhibited lower effectiveness, resulting in 26.44% cell death and a biovolume of 61,578 units. Peracetic acid showed moderate efficacy, achieving a 50.45% cell death rate and a biovolume of 14,861 units. Notably, the combination of sodium hypochlorite and 1-hydroxyethylidene-1,1-bisphosphonate (HEBP) yielded a cell death rate of 86.32% and the lowest observed biovolume at 521 units, suggesting a synergistic effect in biofilm reduction and antimicrobial action.
Morago et al. 7	2019	E. faecalis	Mandibular premolars	Water 2.5%Sodium hypochlorite 2.5%Sodium hypochlorite/9% HEBP 2.5%Sodium hypochlorite/17% EDTA	Sodium hypochlorite (2.5% NaOCl) and its combination with HEBP showed similar effectiveness, with cell death rates around 70-72% and biovolumes of approximately 1400 units. The addition of 17% EDTA to 2.5% NaOCl enhanced its performance, achieving the highest cell death rate (79.86%) and the lowest biovolume (940.30 units). Water, serving as a control, demonstrated significantly lower antimicrobial activity with a cell death rate of 31.96% and the highest biovolume of 1517.73 units. These findings suggest that combining NaOCl with chelating agents like EDTA may improve its antimicrobial and biofilm removal capabilities.
Arias-Moliz1 et al 8	2016	E. faecalis	Maxillary and mandibular primary molars	1% Sodium hypochlorite 1% Sodium hypochlorite/9% HEBP 2.5%Sodium hypochlorite 2.5%Sodium hypochlorite/9% HEBP 9% HEBP	The study investigated the effects of sodium hypochlorite (NaOCl) at 1% and 2.5% concentrations, alone and combined with 9% 1-hydroxyethylidene-1,1-bisphosphonate (HEBP), on biofilm volumes with and without dentin powder. Generally, the presence of dentin powder increased total biovolume across treatments, with 1% NaOCl showing the most dramatic increase from 9.8×10^2 to 2.0×10^4 units. The combination of 2.5% NaOCl and 9% HEBP demonstrated unique behavior, with total biovolume decreasing from 5.2×10^2 to 2.2×10^2 units when dentin powder was added. HEBP alone at 9% concentration resulted in the highest biovolumes both with and without dentin powder. These findings suggest that higher concentrations of NaOCl combined with HEBP may be more effective in reducing biofilm volume, particularly in the presence of dentin powder, though statistical analysis would be required to confirm the significance of these observations.

Author	Year of publication	Microorganism	Tooth	Groups	Result
Morago, et al. 9	2016	E. faecalis	Premolars	2.5% NaOCl, 2.5% NaOCl/9% HEBP	2.5% Sodium hypochlorite had a dead cell percentage of 76.11% without smear layer and with smear layer and dead cell percentage of 42.20% while 2.5 Sodium hypochlorite with 9% HEBP had a dead cell percentage of 68.86 % without smear layer and 69.75% in the presence of smear layer.
Ulusoy et al. 10	2017	Smear layer	Maxillary and mandibular single rooted tooth	0.5% peracetic acid 1% peracetic acid 2% peracetic acid 9% HEBP 18% HEBP 17% EDTA Saline	Peracetic acid at concentrations of 0.5%, 1%, and 2% showed varying effectiveness, with 2% generally performing better, especially in the lower third of the canal. 1-Hydroxyethylidene-1,1-bisphosphonate (HEBP) at 9% and 18% concentrations demonstrated superior smear layer removal across all canal thirds, with 18% HEBP slightly outperforming 9% HEBP. 17% Ethylenediaminetetraacetic acid (EDTA) exhibited good efficacy in the upper and middle thirds but was less effective in the lower third. Saline, serving as a control, showed the least effectiveness in smear layer removal across all canal sections.
Mankeliya1 et al. 11	2021	Smear layer	Premolars	10% EDTA With 5.25% NaOCl 10% citric acid & 5.25% NaOCl 18% etidronic & 5.25% NaOCl 7% maleic acid & 5.25% NaOCl	The mean scores for smear layer removal were: 1.355 ± 0.234 for 10% EDTA with NaOCl, 1.422 ± 0.332 for 10% citric acid with NaOCl, 1.2 ± 0.2108 for 18% etidronic acid with NaOCl, and 0.488 ± 0.353 for 7% maleic acid with NaOCl. These results suggest that 7% maleic acid in combination with 5.25% NaOCl was the most effective in removing the smear layer, demonstrating significantly lower scores compared to the other tested combinations.
Arias-Moliz et al 12	2014	E. faecalis		2.5% NaOCl 9% HEBP 2.5% NaOCl/9% HEBP Distilled water	Sodium hypochlorite (NaOCl) alone demonstrated high efficacy with 86.77% dead cells, while its combination with 1-hydroxyethylidene-1,1-bisphosphonate (HEBP) showed enhanced performance, resulting in 92.57% cell death. Interestingly, HEBP alone also exhibited potent antimicrobial activity with 88.73% dead cells, whereas distilled water, serving as a control, showed minimal effect with only 1.79% cell death.
Kfir et al. 13	2020	Smear layer	Anterior single rooted premolars	3 % NaOCl 17% EDTA Dual Rinse etidronic acid (HEDP) Saline solution	This study evaluated smear layer removal efficacy using a 5-point scoring system, where lower scores indicate better removal. For the NaOCl + EDTA group, smear layer removal was most effective in the coronal third (53% score 1), less effective in the mid-root (30% score 1), and least effective in the apical third (25% score 1). The Proper Next+ Dual Rinse group showed similar effectiveness in the coronal third (55% score 1), but demonstrated improved efficacy in the apical third (50% score 1) compared to the NaOCl + EDTA group. Both groups exhibited a trend of decreasing effectiveness from coronal to apical

Author	Year of publication	Microorganism	Tooth	Groups	Result
					regions, with the exception of the Proper Next+ Dual Rinse group's improved apical performance.
Lottanti et al. 14	2008	Smear layer	Premolar	NaOCl – Water NaOCl – EDTA NaOCl & EA– NaOCl & EA NaOCl – PA	The NaOCl-Water combination showed minimal effectiveness, with 97-100% smear layer coverage throughout the canal, while NaOCl-EDTA demonstrated superior performance, achieving complete smear layer removal in all thirds. The EA-NaOCl and NaOCl-PA protocols also exhibited high efficacy, with only 8% and 4% smear layer coverage in the lower and upper thirds, respectively, suggesting that chelating agents significantly enhance smear layer removal when combined with NaOCl.
Yadav et al. 15	2015	Calcium ions	Premolars	9% etidronic acid 18% etidronic acid SmearClear Biopure MTAD Normal saline	A comparative study evaluated the calcium ion removal efficacy of various chelating agents used in endodontic treatments. The results indicated that Smear Clear demonstrated the highest calcium ion removal capacity (20.04±0.2 µg/ml), followed by Biopure MTAD (18.15±0.3 µg/ml) and 18% etidronic acid (16.36±0.2 µg/ml). In contrast, 9% etidronic acid showed lower efficacy (13.32±0.5 µg/ml), while normal saline, serving as a control, exhibited minimal calcium ion removal (8.74±0.4 µg/ml).
Kuruvilla et al. 16	2015			17%EDTA - 18% etidronic acid 7% maleic acid	A qualitative assessment of smear layer removal in root canals was conducted using a three-tiered classification system. The first category represented optimal outcomes, characterized by the complete absence of smear layer and fully patent dentinal tubules. The second category indicated partial success, with the absence of smear layer in the root canal space but potential residual debris in dentinal tubules. The third category denoted ineffective smear layer removal, characterized by a non-homogeneous, heavy smear layer completely obliterating both the dentinal tubules and root canal space.
Yadav et al. 17	2017	Smear layer	Mandibular premolars	9% HEBP 18% HEBP SmearClear MTAD Normal saline	A comparative study evaluated the efficacy of various chelating agents in removing the smear layer across different regions of the root canal. SmearClear demonstrated the most consistent and effective smear layer removal throughout the canal (scores 1.20-1.50), followed closely by MTAD (scores 1.30-2.20), while etidronic acid at both 9% and 18% concentrations showed decreasing effectiveness from the upper to lower thirds (scores 1.50-3.20). Normal saline, serving as a control, exhibited minimal smear layer removal efficacy across all regions (scores 3.00-4.00), highlighting the importance of using specialized chelating agents in

Author	Year of publication	Microorganism	Tooth	Groups	Result
					endodontic treatments.
Giardino et al. 18	2019	E. faecalis	Single rooted teeth	NaOCl+EDTA NaOCl/Dual Rinse® HEDP	A comparative study evaluated the antimicrobial efficacy of two endodontic irrigation protocols: sodium hypochlorite combined with ethylenediaminetetraacetic acid (NaOCl+EDTA) versus sodium hypochlorite with 1-hydroxyethylidene-1,1-bisphosphonate (NaOCl+HEDP). The NaOCl+HEDP group demonstrated superior overall antimicrobial activity, with a bacterial survivability rate of 1.71% compared to 3.77% for the NaOCl+EDTA group. This enhanced efficacy of NaOCl+HEDP was consistent across different regions of the root canal, showing lower bacterial survivability in both the cervical (1.74% vs 4.79%) and middle thirds (1.89% vs 3.77%) compared to the NaOCl+EDTA group.
Espinoz et al. 19	2021	Smear layer	Central incisors	XP-EDTA XP-HEDP PUI-EDTA PUI-HEDP Control	A comparative study evaluated the efficacy of different irrigation protocols on smear layer removal across various root canal sections. The PUI-EDTA group demonstrated the most effective overall smear layer removal (0.4 ± 0.49), followed by XP-EDTA (1.2 ± 0.92), PUI-HEDP (0.68 ± 0.69), and XP-HEDP (1.5 ± 1.07). All treatment groups showed a consistent pattern of decreasing efficacy from the coronal to the apical third, with PUI-EDTA achieving complete smear layer removal in the coronal third (0 ± 0). The control group exhibited no smear layer removal (4 ± 0 in all thirds), highlighting the necessity of specialized irrigation protocols in endodontic treatments.
Erik et al. 20	2019	Smear layer	Premolars	Sterile saline • 17% EDTA • 9% HEBP • 18% HEBP • 1% NaOCl & 9% HEBP • 2% NaOCl & 18% HEBP	A comprehensive study evaluated the efficacy of various irrigation protocols on smear layer removal across different root canal sections. The 17% EDTA group showed effective removal in the coronal and middle thirds, with some persistence in the apical third. Both 9% and 18% HEBP groups demonstrated a gradual decrease in efficacy from coronal to apical regions, with 18% HEBP showing slightly better performance. The combination of 1% NaOCl with 9% HEBP exhibited improved smear layer removal compared to HEBP alone, particularly in the coronal and middle thirds. Notably, the 2% NaOCl with 18% HEBP group demonstrated the most consistent and effective smear layer removal across all thirds, with the highest number of score 1 ratings in the coronal third and minimal score 3 ratings overall.

Table 3: Risk of Bias Assessment Chart

Author	Experimental method (selection bias)	Blinding outcome (Performance bias)	Incomplete outcome data(attrition bias)	Detection method (Detection bias)	Selective reporting (reporting bias)	Other risk of bias
Arias-Moliz et al 2014. [6]	+	?	+	+	?	?
Morago et al 2019. [7]	+	?	+	+	?	?
Arias-Moliz et al 2016. [8]	+	?	+	+	?	?
Morago, et al 2016. [9]	+	?	+	+	?	?
Ulusoy et et al 2017. [10]	+	?	+	+	?	?
Mankeliya et al 2021. [11]	+	?	+	+	?	?
Arias-Moliz et al 2014. [12]	+	?	+	+	?	?
Kfir et al 2020. [13]	+	?	+	+	?	?
Lottanti et al 2008. [14]	+	?	+	+	?	?
Yadav et al 2015. [15]	+	?	+	+	?	?
Kuruvilla et al 2015. [16]	+	?	+	+	?	?
Yadav et al 2017. [17]	+	?	+	+	?	?
Giardino et al 2019. [18]	+	?	+	+	?	?
Espinoz et al 2021. [19]	+	?	+	+	?	?
Erik et al 2019. [20]	+	?	+	+	?	?

4. Discussion

The efficacy of various irrigation protocols in endodontic treatment has been a subject of extensive research, with particular attention given to the role of etidronate (HEBP) as an alternative chelating agent. This review synthesizes findings from multiple studies, elucidating the potential advantages of HEBP, especially when used in combination with sodium hypochlorite (NaOCl), in root canal therapy.

Arias-Moliz et al. conducted a comprehensive study comparing the antimicrobial efficacy of various irrigation solutions against Enterococcus faecalis biofilms. Their findings demonstrated that a mixture of 2.5% NaOCl and 9% HEBP exhibited comparable antimicrobial efficacy to 2.5% NaOCl alone, with both solutions achieving significantly higher dead cell percentages (88.17% and 86.32%, respectively) compared to chlorhexidine (26.44%) and peracetic acid (50.45%). This synergistic effect is particularly noteworthy, as HEBP does not compromise the antimicrobial activity of NaOCl, a property that distinguishes it from other chelating agents such as EDTA[6]. The influence of the smear layer on antimicrobial activity was elucidated by Morago et al. Their research revealed that while the

smear layer significantly hindered the effectiveness of NaOCl alone, the combination of NaOCl and HEBP maintained potent antimicrobial activity against E. faecalis in infected dentin tubules. This finding underscores the potential of NaOCl/HEBP mixtures in overcoming the barrier effect of the smear layer during root canal disinfection, a crucial factor in achieving thorough disinfection of the root canal system[7]. Further investigating the clinical relevance of these findings, Arias-Moliz et al. examined the influence of dentin powder on the bactericidal effects of various NaOCl concentrations with and without HEBP. Their results indicated that higher concentrations of NaOCl (2.5%) combined with HEBP were less affected by the presence of dentin powder, maintaining antimicrobial efficacy. This suggests that NaOCl/HEBP mixtures may be more resilient to the organic matter encountered during clinical root canal treatment, potentially leading to more predictable outcomes in complex cases[8].

Several studies have demonstrated promising results for HEBP in terms of smear layer removal. Ulusoy et al. found that 9% and 18% HEBP were more effective in removing the smear layer in the apical third compared to other chelating agents[10]. This is particularly significant given the challenges associated with achieving thorough cleaning in the apical region of the root canal. Mankeliya et al. compared various chelating agents and found 7% maleic acid to be the most effective in the apical third, followed by 10% citric acid, which outperformed both EDTA and HEBP11. These findings highlight the importance of considering multiple factors when selecting an irrigation protocol. The combination of NaOCl and HEBP has shown particular promise in simultaneous disinfection and smear layer removal. Morago et al. reported that NaOCl/HEBP was as effective as NaOCl+EDTA in reducing bacterial biovolume and removing the smear layer, with NaOCl/HEBP exhibiting the highest efficacy. The percentage of dentine tubules free of smear layer was 90.41% ± 7.33 for NaOCl/HEBP and 76.54% ± 15.30 for NaOCl+EDTA9. This dual action could potentially streamline the irrigation protocol, reducing treatment time and complexity without compromising efficacy.

Recent innovations in HEBP formulations have shown further improvements. Giardino et al. demonstrated that a new formulation combining NaOCl and HEBP powder (DualRinse) achieved significantly lower residual bacterial viability (1.71%) compared to the conventional NaOCl+EDTA irrigation protocol (3.77%)[18]. This finding suggests that novel HEBP-based formulations may offer enhanced antimicrobial efficacy in clinical practice, potentially leading to improved treatment outcomes. It is important to note that the efficacy of HEBP may vary depending on the irrigation technique employed. Espinoza et al. found that passive ultrasonic irrigation with EDTA (PUI-EDTA) was superior in smear layer removal compared to XP-endo Finisher with either EDTA or HEBP[19]. This highlights the need to consider both the chelating agent and the activation method when optimizing irrigation protocols, emphasizing the complex nature of effective root canal irrigation. Erik et al. investigated the efficacy of various etidronate treatments in smear layer removal. Their findings indicated that a combination of 2% NaOCl and 18% HEBP exhibited significantly better smear layer removal scores compared to other treatment groups, particularly in the apical third[20]. This concentration-dependent efficacy underscores the importance of optimizing HEBP concentrations for maximal effectiveness in clinical applications.

The collective evidence from these studies suggests that HEBP, particularly when combined with NaOCl, offers a promising alternative to traditional chelating agents in endodontic irrigation. The ability of HEBP to maintain the antimicrobial efficacy of NaOCl while simultaneously aiding in smear layer removal presents a significant advantage in clinical practice. Furthermore, the resilience of NaOCl/HEBP mixtures to the presence of organic matter and their effectiveness in the challenging apical third of the root canal system make them particularly suitable for clinical application. These findings have important implications for endodontic practice. The use of NaOCl/HEBP mixtures could potentially simplify irrigation protocols, reducing the number of steps required and possibly shortening treatment time. This could lead to more efficient and effective root canal treatments, potentially improving outcomes for patients. The dual action of disinfection and smear layer removal in a single

solution could streamline the irrigation process, potentially reducing the risk of reinfection and improving the seal of root canal fillings.

However, it is crucial to acknowledge the limitations of the current body of research. Many of these studies were conducted in vitro, and while they provide valuable insights, their direct clinical applicability may be limited. Further randomized controlled clinical trials are needed to validate these laboratory findings and to establish optimal concentrations and protocols for the use of HEBP in various clinical scenarios. Future research directions should focus on long-term clinical outcomes of HEBP-based irrigation protocols, potential interactions with different obturation materials, and the development of novel HEBP formulations or delivery systems to further enhance its efficacy. Additionally, investigations into the potential cytotoxicity and biocompatibility of HEBP at various concentrations would be valuable in ensuring its safety for clinical use. As research in this area continues to evolve, it is likely that HEBP-based irrigation protocols will play an increasingly important role in modern endodontic therapy. The potential benefits of simplified protocols, improved antimicrobial efficacy, and effective smear layer removal make HEBP a promising agent for advancing the field of endodontics. However, as with any emerging technology or technique in healthcare, careful consideration of the evidence and judicious application in clinical practice are essential to ensure optimal patient outcomes.

5. Conclusion

The body of evidence reviewed in this study underscores the potential of etidronate (HEBP) as a promising alternative chelating agent in endodontic irrigation protocols. The synergistic effects observed when HEBP is combined with sodium hypochlorite (NaOCl) offer a multifaceted approach to root canal treatment, addressing both antimicrobial efficacy and smear layer removal simultaneously. While these findings are encouraging, it is imperative to acknowledge the limitations of the current research. The predominance of in vitro studies necessitates cautious interpretation when extrapolating to clinical scenarios. Future research should prioritize randomized controlled clinical trials to validate these laboratory findings and establish optimal concentrations and protocols for various clinical presentations.

In conclusion, HEBP-based irrigation protocols show considerable promise in advancing endodontic therapy. The potential for simplified protocols, enhanced antimicrobial efficacy, and effective smear layer removal positions HEBP as a valuable tool in modern endodontics. However, as with any emerging technique in healthcare, the judicious application of HEBP-based protocols should be guided by ongoing research and clinical experience. As our understanding of HEBP's properties and interactions within the root canal system continues to evolve, it is likely to play an increasingly significant role in shaping the future of endodontic treatment strategies.

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Reporting guidelines: This study has been reported as per the PRISMA reporting guidelines

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