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Review Article

Role of vehicles on antimicrobial efficacy of calcium hydroxide

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ABSTRACT

Adequate disinfection of the root canal system plays a crucial role in ensuring the enduring success of endodontic therapy. While chemomechanical preparation is a major part of disinfection protocol, intracanal medicaments, such as calcium hydroxide ($Ca(OH)_2$), help in eliminating the microbial flora that remains even after chemomechanical preparation. Enhancing the action of these antimicrobial agents will improve disinfection. Various vehicles have been studied that augment the action of intracanal medicaments and debate about their supremacy has been ongoing. Aqueous, viscous, and oily tensioactive agents serve their functions and have their own limitations. This review was undertaken to comprehensively analyze the effect of various vehicles on the antimicrobial activity of $Ca(OH)_2$. In conclusion, aqueous, viscous, and oily vehicles have different advantages, and the type of vehicle utilized depends on the clinical situation at hand.

Keywords: Antimicrobial efficacy, Calcium hydroxide, Dentinal penetration, Intracanal medicament, Tensioactive agents, Vehicles

INTRODUCTION

The removal of microorganisms present within an infected root canal is necessary for a successful endodontic treatment outcome, and this is efficiently achieved by chemomechanical preparation. However, the lateral canals, isthmuses, apical deltas, and various anatomical variations cannot be thoroughly cleaned of microorganisms with this approach.[1] These sites can harbor microorganisms that can congregate inside the root canal and proliferate, and this can be detrimental toward the prognosis of endodontic therapy, mandating the need for the use of intracanal medicament between appointments to lower the endodontic microbiota and favor periapical tissue healing.

In the irrigation regime, sodium hypochlorite, when used as a primary root canal irrigant, shows penetration through the dentinal tubules up to 300 nm in a time, concentration, and temperature-dependent manner, making it effective in reaching up to 1000 nm depth.[1,2] Furthermore, the literature indicates that bacteria have the ability to infiltrate the dentinal tubules to a maximum depth of 1100 nm. This infiltration serves as a bacterial reservoir and has the potential to cause reinfection.[3] To completely eliminate such reservoirs for microorganisms that cannot be eliminated by the use of irrigants, intracanal medicaments are advocated to be used that can penetrate up to the desired depth for the complete elimination of bacteria.[4]

Various intracanal medicaments such as calcium hydroxide ($Ca(OH)_2$), chlorhexidine, and triple antibiotic paste have been effective as intracanal dressing, and among these $Ca(OH)_2$ has shown the most promising results.[5] Its high pH destroys the bacterial cell membranes and protein structures.[6] The medicament must have prolonged contact with dentin and efficient penetration within the dentinal tubules to be more effective. This is influenced by the contact angle of the medicament with the dentinal wall and vehicles used to carry these medicaments to the affected area.[7,8]

Furthermore, when employed as a root canal medicament, the Ca(OH)2 powder is utilized alongside various substances, including glycerin, propylene glycol (PG), olive oil, iodoform plus saline solution, camphorated parachlorophenol (CMPC), CMPC plus glycerin, methylcellulose, metacresylacetate, distilled water, saline, anesthetic solutions, Ringer's solution, and camphorated monochlorophenol cresatin, to ensure optimal wetting of the canal wall.[9]

The goal of the present review was to comprehensively analyze the available literature about the various vehicles and how they affect the antimicrobial ability of $Ca(OH)_2$.

METHODOLOGY

This review was done using multiple search platforms, including Google, PubMed, and ResearchGate, were utilized to conduct this review. The search was conducted using various keywords such as antimicrobial efficacy, $Ca(OH)_2$, dentinal penetration, intracanal medicament, tensioactive agents, and vehicles. The articles included in this review consisted of original research, full-text articles, *in vitro* studies, and reviews. However, articles written in languages other than English, case studies, and case reports were excluded from the study.

REVIEW

A layer of polysaccharides, proteins, and microbial organisms is called a biofilm. This layer offers a matrix that shields microbes from the human immune system and antimicrobial agents.[10] Since endodontic infection is biofilm-mediated, elimination or noticeable reduction of the endodontic biofilm is crucial for successful root canal therapy. The present study reviewed articles where $Ca(OH)_2$ was studied as an intracanal medicament due to its known antimicrobial efficacy and subsequent popularity in clinical use. The release of hydroxyl ions into a liquid environment is what causes the bactericidal effect of $Ca(OH)_2$. $Ca(OH)_2$ destroys bacterial DNA, denatures proteins, and damages the cytoplasmic membrane.[11]

$Ca(OH)_2$'s low ability to disinfect the root canal system was revealed by Sathorn *et al.*,[12] in their systematic assessment of the antibacterial action of the drug. To increase the antibacterial and cleaning effects of saturated $Ca(OH)_2$ solution, Barbosa *et al.*,[13] recommended the use of a tensioactive substance. The biological activity of $Ca(OH)_2$, which is governed by the ionic dissociation in Ca^{2+} and OH^- ions, is most significantly influenced by the vehicle, according to Rameezuddin.[14] As a vehicle for intracanal medicine, a number of compounds have been suggested. Empiricism underlies most recommendations. The combination of $Ca(OH)_2$ and chlorhexidine (CHX) has demonstrated enhanced antibacterial properties when compared to $Ca(OH)_2$ alone.[15,16]

The ionic dissociation of $Ca(OH)_2$ results in the formation of hydroxyl ions, which slowly alter the pH of the dentin. The rate of ionic dissociation and diffusion can be influenced by various other factors, such as the solubility of the vehicle employed, disparities in viscosity, acid-base characteristics, the permeability of dentin, and the extent of existing calcification.[17] It is most likely that protein denaturation, DNA damage, and cytoplasmic membrane damage are what cause hydroxyl ions to kill bacteria.[18] Various factors, such as the type of microorganism, its location within the root canal system, the presence or absence of a smear layer, and the occurrence of root canal exudation, all play a role in determining the effectiveness of $Ca(OH)_2$ in disinfecting the root canal.[19]

The resorption process can be stopped using a formulation of $Ca(OH)_2$ in a suitable vehicle that can maintain a high alkaline pH in the periapical region to prevent the activity of these inflammatory and clastic cells. It has been demonstrated that the most effective technique to release hydroxyl ions is through the breakdown of $Ca(OH)_2$ in various carriers.[20] According to the results of the current investigation, vehicles can also considerably increase the bioavailability of the medicine and extend the duration of the drug's action.

Most investigations use sterile water, sterile saline, and anesthetic solutions to simulate the aqueous vehicles. In addition, included in this group are Ringer's solution, methyl- and carboxymethylcellulose, and anionic detergent solutions such as sodium lauryl diethylene glycol or sodium lauryl sulfate.[21-29]

Aqueous vehicles in a glance

A brief overview of aqueous vehicles reveals that distilled water performed better than the other aqueous vehicles due to its better wettability and lower contact angle. When employed as vehicles, CHX and anesthetic solutions displayed nearly identical contact angles with pure water, with no statistically significant difference.[29] Distilled water, according to Ruth Hepsi[30] is the optimum medium for creating $Ca(OH)_2$ paste due to its superior wetting and therapeutic effects from hydroxyl ion diffusion.

Compared to other pastes made using viscous vehicles, water-based $Ca(OH)_2$ paste dissociates more hydroxyl ions and elevates the mouth pH, while there are still debates in the literature.[31-35]

Viscous vehicles at a glance

Glycerol, polyethylene glycol (PEG), and PG serve as vehicles of thick carriers that are soluble in water and gradually release Ca^{2+} and OH^- ions over an extended period. Due to the possibility that the paste would stay in the root canal for an extended period of time, these should be utilized for redressing. According to several researchers, the most optimal method for placing $Ca(OH)_2$ pastes into canals is by utilizing a Lentulo spiral. This approach ensures that the pastes are delivered with the ideal length and density. The advantage of using $Ca(OH)_2$ pastes is that they contain a higher concentration of $Ca(OH)_2$ compared to water vehicles.[36] In comparison to the watery carriers, the viscous glycerine produced wider zones of microbial growth inhibition. In place of a distilled water-$Ca(OH)_2$ combination, Alacam *et al*.,[37,38] suggested using a glycerin-water-$Ca(OH)_2$-combination in the intracanal space. Safavi and Nakayama,[39] concluded in their investigation that the utilization of non-aqueous blending agents could hinder the efficacy of $Ca(OH)_2$ as a root canal medication.

This could be due to the lesser contact angle of non-aqueous vehicles compared to aqueous vehicles, while Cwikla *et al*.[40] observed that iodoform-based $Ca(OH)_2$ was the most effective dentinal tubule disinfectant compared to many other vehicles.

Oily vehicles

Olive oil, CMPC, metacresylacetate, and eugenol are oily substances that have limited uses in clinical settings. These substances are used when a gradual separation of ions is needed, such as in the situation of a long-lasting root filling for perforation defects resulting from internal resorption.[14] Athanassiadis[41] discovered that the pastes with oily vehicles showed substantially higher mean zones of inhibition (8.42 mm) compared to those with watery (0.25 mm) or viscous vehicles. The previous study was confirmed by the weakest antimicrobial action exhibited by PEG, which is also a viscous vehicle.[42]

Based on the existing literature, most studies consistently demonstrate that aqueous vehicles exhibit a reduced contact angle with the substrate and outperform non-aqueous vehicles in the transportation of $Ca(OH)_2$ into the root canal. In addition, aqueous vehicles offer the advantage of improved wettability and a therapeutic effect resulting from the diffusion of hydroxyl ions.[30] On surfaces like radicular dentine, the liquid with the lower contact angle will spread more quickly.[43] The contact angle between a liquid and a solid surface can be influenced by various factors, such as the liquid's surface tension, the solid's surface free energy, the uniformity of the solid surface, the presence of surface contamination, and the roughness of the surface.[44] Nevertheless, the contact angle is just one of the physical characteristics that describe the clinical behavior of $Ca(OH)_2$.

Vehicles

Various vehicles that have been studied for their synergistic action on $Ca(OH)_2$ are – CHX, Silver nanoparticles (AgNPs), PG, PEG, Chitosan, and N-2-methyl pyrrolidone (NMP).

CHX

CHX is a disinfection agent with a large antibacterial spectrum and strong substantivity.[45-47] To enhance its antibacterial activities and create synergistic effects, it has been combined with $Ca(OH)_2$.[48] In contrast to $Ca(OH)_2$, Evans *et al*.[49] demonstrated that the combination of $Ca(OH)_2$ and a 2% CHX solution exhibits superior efficacy in eradicating *Enterococcus faecalis* from dentinal tubules. Turk *et al*.[50] conducted a s study that revealed that the effectiveness of $Ca(OH)_2$ as an antibacterial agent depends on the carrier used. The most optimal disinfection outcome was observed when $Ca(OH)_2$ was combined with CHX. Schäfer and Bössmann,[51] in contrast to these investigations, the addition of CHX did not result in any improvement in the effectiveness of $Ca(OH)_2$ in eliminating *E. faecalis* bacteria from dentinal tubules. Carbajal Mejía JB,[52] observed that the antibacterial effect of a combination of $Ca(OH)_2$ and CHX on *E. faecalis* after a week or a month was similar to what was seen in the Ca(OH) group. This finding is similar to that of Haenni *et al*.,[53] study. Consequently, the search for a more efficient vehicle with respect to $Ca(OH)_2$ continued.

AgNPs

AgNPs are currently incorporated into various medical materials and devices, including those used in dentistry, due to their ability to inhibit the growth of microbes.[54] According to a number of studies, AgNPs with a size between 10 nm and 100 nm are capable of having significant potential for antibacterial effect on both Gram negative and positive bacteria**.** Furthermore, it has been demonstrated that these particles work even against bacteria that are multidrug resistant.[55]

Afkhami *et al*.[22] utilized AgNPs as a carrier to examine the antibacterial effectiveness of Ca(OH)2 on the *E. faecalis* biofilm that had developed on the root dentine of a human tooth after one week and one month. This mixture had a greater impact on biofilm during the evaluation period than either $Ca(OH)_2$ or the combination of $Ca(OH)_2$ and CHX.

After using it for a week, the *E. faecalis* biofilm's structure was greatly damaged, and the number of bacterial cells fell sharply. These results concur with those of the in vitro study by Javidi *et al.*[56] that the research showed the impact of this combination on the bacterial biofilm present in the dentinal tubules.

AgNPs' bacterial inhibitory activity has a partially understood mechanism. The formation of pits in the walls of bacterial cells is one hypothesis for antibacterial action of nanoparticles, which results in their accumulation and increase membrane permeability, eventually leading to cell death.[54] The other potential process is the formation of pits with irregular shapes in the bacteria's outer membrane after metal precipitation. The result is the release of membrane proteins and lipopolysaccharides, leading ultimately to a change in bacterial permeability.[57] According to Kim *et al*.,[54], the production of free radicals is what causes AgNPs' antibacterial action. They argued that the cell membranes were damaged by free radicals on the nanoparticles surface.

PG, PEG, and Chitosan

According to Ballal *et al*.,[24] PEG, PG, and Chitosan, all showed maximum calcium ion release when used as vehicles. Chitosan, further, exhibited the prolonged discharge of calcium ions from $Ca(OH)_2$ throughout an extended duration. This might be connected to how viscous the various formulations are. The most viscous substances are Chitosan, PEG, and PG.

Due to its high viscosity, Chitosan only releases 86% of the medication in 30 days.[24] Chitosan exhibits a biphasic release profile, characterized by an initial rapid burst release, succeeded by a gradual release over an extended duration. The initial release of calcium ions when Chitosan is used may be due to the presence of medication on the polymer's surface, which can quickly spread into the surrounding media.[58] Drug diffusion occurs once the polymer first swells, releasing the active ingredient from the matrix. The primary factors affecting swelling and drug release are the ionic interactions between Chitosan chains, which are determined by the density of cross-linking formed during the matrix network formation.[59] The amount of cross-linking has a notable impact on the drug's release from the Chitosan matrix system. Drug release is typically slowed more by higher cross-linking densities than by lower densities.[60] Chitosan showed a regulated medication release pattern when comparing the percentage of the drug release from 30 min to 1 month with the different formulations evaluated.[24]

Regarding PG, Olitzky[61] noted that its usage as a vehicle may offer a potential for preventing or treating microbial illnesses due to its notable germicidal efficacy in concentrated solutions. Despite being more viscous than pure water, PG has a low surface tension. As a result, it has an advantage over using distilled water as a vehicle in that it can pass through dentinal tubules.[62] In addition, when combined with triple antibiotic paste (TAP), it may also supply a low concentration of TAP, which is better for the survival of the apical papilla's stem cells.[63] However, when PG was utilized as a vehicle, TAP's antibacterial properties persisted. To provide a more precise comparison, additional research should be done on the antibacterial properties of TAP when PG was utilized as a vehicle.

Glycerine

Glycerine is capable of dissolving $Ca(OH)_2$ more readily. $Ca(OH)_2$ is more easily dissolved in glycerine than in water, but it cannot be hydrolyzed into its active components. Aneja[64] there are no huge crystals as there are in a water solution of $Ca(OH)_2$, because glycerine breaks down the large crystals of $Ca(OH)_2$ to individual molecules of $Ca(OH)_2$. Therefore, a glycerine fraction has a larger chance of penetrating dentinal tubules than a fraction made of pure water.[25] Gomes *et al*.,[25] found that the pH values of the $Ca(OH)_2$ -glycerine-water mixture at various dentin depths in our investigation were significantly higher than those of the $Ca(OH)_2$ -distilled water combination. Camoes *et al*.,[65] observed similar results regarding the pH of $Ca(OH)_2$.

NMP

Having a high boiling point, low viscosity, low toxicity, and good biocompatibility, NMP is a colorless organic solvent.[66] According to Phaechamud *et al*.,[67] NMP exhibits antibacterial efficacy against a number of microorganisms. It is well known that NMP solubilizes membrane lipids and encourages microbial cell membrane permeability. Hence, CleaniCal®'s effect on biofilms can be partially explained by the antibacterial characteristic of NMP.

The essential part of the protective shelter in oral biofilms is extracellular polysaccharide (EPS).[68] To make biofilms resistant to intracanal medicine, it gives them mechanical stability and drug tolerance. As a result, EPS is now the new target for antibacterial treatments, and quantifying the amount of EPS still present can indicate the effectiveness of biofilm eradication, just as in CleaniCal®.

Hosoya[69] found that when compared to water-based Calasept Plus™ ($Ca(OH)_2$ paste containing saline), the biofilms treated with CleaniCal®($Ca(OH)_2$ paste containing NMP) and Calcipex II® ($Ca(OH)_2$ paste containing PG), which contain viscous vehicles, had much lower amounts of bacteria and EPS, indicating that they were more effective at removing biofilms. According to research by Lim *et al*.,[70] CleaniCal® was also more efficient in removing PEG and

Calcipex II®-containing ApexCal® (Ivoclar Vivadent, Schaan, Liechtenstein) from human root canals.

In this regard, it was shown that CleaniCal®, a medication based on NMP, had the best dispelling effect on *E. faecalis* biofilms when compared to other medications containing water or PG. It was also suggested that this positive effect may have been caused by NMP's higher solubilizing efficiency when compared to PEG or PG.

CONCLUSION

The literature reviewed suggests that the type of vehicle utilized affects the dentinal penetration/diffusion ability and ionization, thus affecting the antimicrobial activity of $Ca(OH)_2$. However, it must be analyzed carefully with more studies before extrapolating to clinical conditions. Judicious use of these vehicles based on the clinical situation in hand promises improved clinical results. Although further research is needed to conclusively arrive at the best vehicle to be used, the literature available suggests enhanced action of $Ca(OH)_2$ with viscous vehicles due to the ability to dissolve it better (glycerine-water), biphasic release of ions (Chitosan), germicidal efficiency (PG), and being tensioactive agents, they all improve dentinal penetration of $Ca(OH)_2$.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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