MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt23S208

Periapical repair action and antimicrobial activity through calcium hydroxide-based dressings: a comprehensive review

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Email: linharesendodontia@hotmail.com
DOI: https://doi.org/10.54448/mdnt23S208
Received: 02-28-2023; Revised: 05-19-2023; Accepted: 05-20-2023; Published: 05-22-2023; MedNEXT-id: e23S208

Abstract

Introduction: Endodontic therapy aims at shaping, cleaning, and disinfecting the root canal, being performed by removing all pulp tissue or necrotic remains and microorganisms present in the root canal system. Among the substances proposed as a delay dressing in the endodontic treatment of teeth with chronic periapical reaction, calcium hydroxide stands out. **Objective:** It was to demonstrate, through a comprehensive review, the main properties of calcium hydroxide, as well as its antibacterial action mechanisms. **Methods:** After literary search criteria, the selected studies were explored for the construction of the present study, following the PRISMA review rules. The review protocol was based on literary search criteria in major databases such as PubMed, Medline, Bireme, EBSCO, Scielo, and Web of Science. **Results and Conclusion:** A total of 65 articles were found. Initially, duplication of articles was excluded, resulting in 35 articles. A total of 20 articles were evaluated and 12 were included and developed in this review study. Calcium hydroxide is the most commonly used medication to fight disease-causing bacteria, but when used alone, it may not be able to eliminate these microorganisms. The association of other medications incorporated into calcium hydroxide contributes to positive results with the elimination of more resistant bacteria. Intracanal medications based on calcium hydroxide allow a positive effect on microbial reduction, decreasing the levels of pro-inflammatory cytokines and metalloproteinases.

Keywords: Endodontic treatment. Peri-apical diseases. Calcium hydroxide. Oral microbiota.

Introduction

Endodontic therapy aims at shaping, cleaning, and disinfecting the root canal, being performed by removing all pulp tissue or necrotic remains and microorganisms present in the root canal system [1]. This procedure is followed by filling the root canal, to occupy all the space, preventing new invasion and bacterial colonization, in addition to making it impossible for remaining bacteria to reach the periapical tissues [1,2].

In this regard, a large number of studies have been focused on the development of basic and clinical concepts that guide the endodontic treatment of teeth without pulpal vitality [3]. Pulp necrosis represents the death of the pulp, meaning the cessation of its metabolic processes, with consequent loss of its structure as well as its natural defenses. The necrotic pulp tissue, in decomposition and disintegration, will allow the invasion of bacteria, which will find ideal conditions for multiplication, propagation, and proliferation. Concomitantly to the necrosis process, contamination of the root canal occurs, which is of fundamental importance for the establishment of periapical pathology [4-6].

In long-term infectious processes, mainly due to the existing nutritional relationships between microorganisms, combined with the gradual drop in oxygen tension inside the root canals, there is a natural selection process (microbial shift) leading to a predominance of gram-negative microorganisms, not only in the root canal lumen but also in the entire root canal system [6,7]. In addition to having different virulence factors, generators of products and by-products toxic to periapical tissues, gram-negative microorganisms contain, in their cell wall, an endotoxin of lipopolysaccharide (LPS) nature, which is released during bacterial multiplication or death, responsible for by a series of biological effects, promoting an inflammatory reaction and bone resorption in the periapical region [7,8].

Most endodontic infections are mixed and polymicrobial, with a predominance of strict anaerobes. However, the presence of Enterococcus faecalis, a facultative anaerobic bacterium, highly resistant to endodontic treatment, has been verified. This microorganism has been frequently found in root canals infected for a long time and with large periapical lesions, causing infections that are difficult to treat [9].

Still, the control of endodontic infection requires a correct chemical-mechanical preparation, responsible for the chemical and mechanical removal of microorganisms, through the auxiliary chemical substance and the action of the instruments and, if necessary, the use of an intracanal medication. In addition to these factors, respect for the periapex and a hermetic filling, with maximum waterproofing and minimum aggression to living tissues, are essential factors for the success of endodontic treatment [9,10].

Among the substances proposed as a delay dressing in the endodontic treatment of teeth with chronic periapical reaction, calcium hydroxide stands out, which has been widely disseminated, particularly due to its antimicrobial property. In addition to antimicrobial activity, calcium hydroxide has properties such as the dissolution of organic remnants, anti-inflammatory action, inhibition of inflammatory reabsorption, and physical barrier function [6-9].

In this sense, discussing medications based on calcium hydroxide enables knowledge and a literature review of this medication widely used in cases where endodontic treatment could not be concluded in the same session [10].

Therefore, the present study aimed to demonstrate, through a comprehensive review, the main properties of calcium hydroxide, as well as its antibacterial action mechanisms.

Methods

Study Design

After literary search criteria, the selected studies were explored for the construction of the present study, following the PRISMA review rules (Transparent reporting of systematic reviews and meta-analysis. Available at: www.prismastatement.org/).

Information Sources and Search Strategy

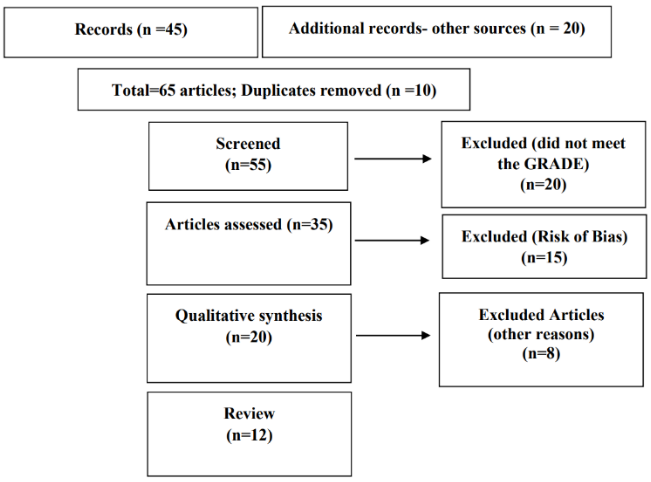
The review protocol was based on literary search criteria in major databases such as PubMed, Medline, Bireme, EBSCO, Scielo, and Web of Science. The search strategy followed the following MeSH Terms: *Endodontic treatment. Peri-apical diseases. Calcium hydroxide. Oral microbiota.* The booleans "and" were used between mesh terms and "or" between historical findings.

Results

Summary of Literary Findings

A total of 65 articles were found. Initially, duplication of articles was excluded, resulting in 35 articles. A total of 20 articles were evaluated and 12 were included and developed in this review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 15 studies with a high risk of bias and 20 studies that did not meet GRADE.

Figure 1. Selection of studies.



Source: Own authorship.

Highlights Findings

Based on the objective of this scientific work, it was evidenced that a study investigated in vivo the effects of intracanal medication based on calcium hydroxide (ICM) on the levels of bacteria, pro-inflammatory cytokines (PICs), and matrix metalloproteinases (MMPs) in root canals and periradicular tissues of teeth with endodontic treatment failure and apical periodontitis. A total of 20 infected root canals of single teeth were randomly divided into two groups according to the irrigant used for chemical-mechanical preparation (CMP) (n = 10 per group): G1 - 2% chlorhexidine gel (CHX) and G2 - 6% sodium hypochlorite (NaOCl). Root canal content was obtained using paper points before CMP (S1) and after 30 days of calcium hydroxide-based ICM (S2). Cultivable bacteria (101.2 ± 79.2), PICs (IL-1β 1.2 ± 0.4 and TNF-α 8.8 ± 4.7), MMP-2 (803.7 ± 96.4), MMP-3 (453.9 ± 229.3), MMP-8 (245.9 ± 122.4), MMP-9 (129.4 ± 29.6) and MMP-13 (70.8 ± 12.8) were present in all S1 samples. After 30 days of ICM (S2), a 99.5% microbial reduction was observed, along with a significant reduction of PICs in all groups. In general, there was a decrease in the levels of MMPs (S2), except for MMP-13, which was found in increased levels after ICM, regardless of the groups. Therefore, intracanal medications based on calcium hydroxide had a positive effect on microbial reduction, decreasing the levels of PICs and MMPs. Both auxiliary chemicals (ie 2% CHX and 6% NaOCl) showed similar effects when calcium hydroxide was used as an intracanal medication [11].

In addition, a study presented the healing results of periapical lesions after root canal treatment (RCT) in one session with an application of Advanced Platelet Rich Fibrin plus (A-PRF+) in comparison with a two-session RCT with filling of calcium hydroxide between appointments. A comparison was based on changes in lesion volume CBCTPeriapical Index (PAI) and occurrence of post-endodontic pain. Results of 3D radiographic assessments of healing based on volume reduction criteria were different from CBCT-PAI. Based on volume changes, the healing assessment criteria - 9 cases from the Study Group and 6 cases from the Control Group were defined as healed. Based on the healing assessment criteria of the CBCT-PAI, 8 cases in the study group and 9 cases in the control group were categorized as healed. Apical radiolucency volumes were, on average, reduced by 85.93% in the study group and by 72.31% in the control group. Post-endodontic pain occurred more frequently in the Control Group than in the Study Group. The highest pain score in the Study Group was five (moderate pain, n = 1), while in the Control Group, the highest score was eight (severe pain, n = 2). At the 6-month follow-up, CBCT scans showed a better healing trend for patients in the study group [12].

In this sense, the ideal endodontic treatment aims at cleaning and modeling the entire root canal system, seeking to eliminate the infection, aided by indicated irrigating solutions and by appropriate intracanal medications, so that, in the end, a satisfactory obturation of the canal is obtained. root canal system [1,2]. The periapical lesion represents the localized immune-inflammatory response due to the increase in the number and progression of microorganisms from the contaminated root canals toward the apical and periapical tissues resulting in bone and tooth resorption [3,4]. The periapical inflammatory reaction is composed of a mixed inflammatory infiltrate, characterized by the presence of neutrophils, T and B lymphocytes, plasmocytes, and macrophages, with a higher cellular prevalence depending on the stage of the disease [5,6].

Furthermore, the presence of microorganisms, particularly gram-negative anaerobes, in the root canal system and the cementum resorption gaps, after root canal treatment, is considered one of the main causes of the persistence of periapical lesions and, therefore, of failure. of endodontic treatment [2,6]. Still, in experimental models of periodontal disease and periapical lesions, the presence of bacteria stimulates the local inflammatory response and the intense production of proteases that degrade the extracellular environment and facilitate the process of bone resorption [3,4]. Currently, calcium hydroxide has been considered the intracanal medication of choice because it has properties such as a) microbial control, b) dissolution of organic debris, c) antiinflammatory power, and d) inhibition of inflammatory resorptions [1-3].

Also, calcium hydroxide is characterized by being a strong base, with an approximate pH of 12.5. It comes in the form of a white, odorless powder, and therefore needs to be added to a vehicle to be used clinically [10]. The calcium hydroxide paste dissociates into calcium and hydroxyl ions, which are responsible for providing excellent properties to the drug [9,10]. Calcium hydroxide has two significant enzymatic properties, inhibiting bacterial enzymes, generating an antimicrobial effect, and activating tissue enzymes, such as alkaline phosphatase, influencing tissue mineralization. Alkaline phosphatase is a hydrolytic enzyme that acts by releasing inorganic phosphate from phosphate esters. Calcium hydroxide activates alkaline phosphatase from its high pH, which can initiate or favor mineralization [8-10].

Antimicrobial Activity

The effects of calcium hydroxide on bacterial lipopolysaccharides (LPS) were analyzed in vitro, based on the amount of fatty acids released after the interaction of calcium hydroxide with LPS. The analysis was performed by gas chromatography and mass spectrophotometer. The results show a large release of fatty acids after the reaction, characterizing hydrolysis of lipid A (a toxic portion of PLS) provided by calcium hydroxide. It is suggested that calcium hydroxide degrades LPS, but a favorable reason for its clinical use in endodontics [1,2].

Still, most microorganisms related to endodontic infection do not survive at alkaline pH, and the main antimicrobial action of calcium hydroxide is related to the alkalinization of the dentin mass. Hydroxyl ions are highly oxidizing free radicals that are extremely reactive, reacting with many biomolecules. This reactivity is high and indiscriminate, so these free radicals rarely diffuse away from the sites of generation. Its lethal effect on bacterial cells probably occurs through the following mechanisms [1-3]:

1- Damage to the cytoplasmic membrane of the bacterium

Hydroxyl ions induce lipid peroxidation destroying membrane phospholipids, removing hydrogen atoms from unsaturated fatty acids, generating lipid free radicals that react with oxygen, forming a lipid peroxide radical, which removes another hydrogen atom from the second fatty acid, generating another lipid peroxide, these, in turn, act as free radicals, initiating an autocatalytic reaction, which causes extreme destruction of the bacterial membrane;

2- Protein Denaturation

With the increase in pH promoted by calcium hydroxide, there is an induction of ionic adhesion breakdown that maintains the tertiary structure of the protein, as a consequence the enzyme remains with its covalent structure. With the loss of enzyme biological activity and disruption of cellular metabolism, structural proteins can also be damaged by hydroxyl ions;

3- Damage to bacterial DNA

Hydroxyl ions react with bacterial DNA and induce double-strand breakage, genes are lost, and as a consequence replication and cell activity are inhibited and cell activity is disorganized. Free radicals can also induce lethal mutations in cells.

Discussion

Since the introduction of calcium hydroxide in dentistry by Herman in 1920, the biological action of this drug established by creating a favorable environment for tissue repair, has been investigated and proven by numerous studies [1,2]. Calcium hydroxide has been widely used in endodontics, specifically in pulp protection and pulpotomies, as a dressing for delays between sessions and in the composition of obturator types of cement [2,3].

The effects of calcium hydroxide are attributed to its dissociation into hydroxyl ions (OH^-) and calcium ions (Ca^{2+}). In the extracellular environment, calcium hydroxide has mineralizing properties, since hydroxyl ions are involved in maintaining an alkaline environment and calcium ions affect the mineralization of the extracellular matrix [4].

Previous studies have shown that the application of calcium hydroxide inside the root canals allows the deposition of a mineralized tissue similar to cementum, by cells of the periodontal ligament, obliterating the foraminal opening. It was evidenced that the use of calcium hydroxide as a delay dressing in teeth with periapical lesions allowed the biological sealing of the apical foramen, unlike teeth with periapical lesions submitted to endodontic treatment in a single session, in which tissue deposition was not observed cemented [4,5].

Furthermore, the deposition of mineralized tissue in the specimens of this group was more advanced than in those teeth with pulp vitality submitted to endodontic treatment, suggesting a role for calcium hydroxide in apical cementogenesis [10]. As a result of this observation, the present study was proposed to evaluate the effects of increased extracellular calcium concentration on the differentiation of periodontal ligament cells into cementoplasts and subsequent cementogenesis. More specifically, cementum neoformation was evaluated in vivo in an animal model and from the results obtained was involved in the proliferation, migration, differentiation, and mineralization mediated by cells of the periodontal ligament of humans [11].

Another important property of calcium hydroxide is its antimicrobial effect, due to its dissociation into hydroxyl ions, which allows the medium to become alkaline, altering the action of enzymes present in the bacterial cell wall, which is essential for cell metabolism [9].

In addition, another property of calcium hydroxide with an antimicrobial effect was found, which showed another action of the medication against bacteria, through a laboratory study that demonstrated the ability of calcium hydroxide to reabsorb the carbon dioxide present in the medium, which is essential for bacterial survival [8].

As it is in the form of powder, calcium hydroxide must be associated with other substances to be inserted into the root canal. Usually, the calcium hydroxide used in endodontic practice is manipulated with saline solution, which is water-soluble, and, as these are an association, together they have chemical characteristics of dissociation, diffusibility, and filling capacity that are determinants for the biological behavior. However, specific microorganisms, mainly *Enterococcus faecalis*, are resistant to $Ca(OH)_2$ and, in addition, the long-term antimicrobial efficiency of pastes has been questioned [2-4].

In this way, research has been developed adding vehicles with antimicrobial properties associated with calcium hydroxide to increase this activity, without losing its other characteristics. The stages of endodontic treatment are dependent on each other and it is necessary to be very careful in carrying out each one of them to ensure the success of the treatment. In this way, the removal of calcium hydroxide-based pastes from the interior is also of great importance. Before filling the root canal system, all $Ca(OH)_2$ must be removed. The remnants of this medication present inside the root canals can form a type of barrier, thus hindering the extravasation of the cement throughout the dentin surface, preventing the formation of an efficient sealing for the success of the endodontic treatment [4,5].

Besides, the composition of root canal filling materials may affect complete periapical healing after root canal therapy. Thus, one study evaluated periapical healing in response to calcium silicate (iRoot SP) and calcium hydroxide (Apexit) based sealants. As a result, iRoot SP and Apexit promoted the healing of periapical tissues [10].

Conclusion

It was concluded that calcium hydroxide is the most used medication to fight disease-causing bacteria, but when used alone, it may not be able to eliminate these microorganisms. The association of other medications incorporated into calcium hydroxide contributes to positive results with the elimination of more resistant bacteria. Intracanal medications based on calcium hydroxide allow a positive effect on microbial reduction, decreasing the levels of pro-inflammatory cytokines and metalloproteinases.

Acknowledgement
Not applicable.

Funding
Not applicable.

Ethical Approval
Not applicable.

Informed consent
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

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