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## Intracanal medicaments: A review

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### Abstract

**Introduction:** It is important to develop new therapeutic materials that have the required clinical actions, are safe and economical.

**Objective:** To analyze the literature on intracanal medicaments such as triple antibiotic paste, calcium hydroxide, chlorhexidine and antimicrobial nanoparticles.

**Methodology:** The search was performed in PubMed, Scopus and Google Scholar databases. The terms "calcium hydroxide", "triple antibiotic paste", "chlorhexidine", "nanoparticles", "intracanal medication" and "endodontic" were used.

**Results:** Triple antibiotic paste contains medication that helps to disinfect the root canal, it is the most used treatment in pulp regeneration and revascularization. Calcium hydroxide is the most commonly used intra-canal medication in endodontics, since it induces the formation of a mineralized layer and has an acceptable microbial effect, it is not as effective on *E. faecalis* and *C. albicans*. Chlorhexidine is a drug widely used in endodontics as an irrigant; it is broad spectrum and is a retentive agent in dentin, it has an antimicrobial effect against biofilm with better results after 7 days of placement. Antimicrobial nanoparticles are new products used as an intra-oral medication, so studies are still needed to verify their effect on dentin and their long-term efficacy.

**Conclusion:** Intracanal medicaments are used between appointments, for the elimination of bacteria or to avoid canal contamination. We could say that nanoparticles with calcium hydroxide have a promising future in terms of antimicrobial efficacy and looking for a better effect on dentin.

**Keywords:** Calcium hydroxide, triple antibiotic paste, chlorhexidine, nanoparticles, peptide, intracanal medication

### 1. Introduction

Due to increased resistance to intracanal drugs, new alternative procedures are needed <sup>[1]</sup>. The successful clinical use of dental materials depends on their physicochemical properties as well as their biological and toxicological reliability. Different local and systemic toxicities of dental materials have been reported <sup>[2]</sup>. The success of endodontic treatment derives from the complete elimination of microorganisms capable of causing intraradicular or extraradicular infection <sup>[3]</sup>; they depend on intraoperative factors such as irrigation, access size, the use of medications or the number of appointments <sup>[4]</sup>. In order to achieve a more effective eradication of these microorganisms, the use of intracanal medications between appointments began to be used when the pulp diagnosis was necrosis or periapical abscess. It is also used for when there are perforations or in revascularization, to avoid intracanal infection <sup>[5]</sup>. Calcium hydroxide is the commonly used intracanal medication for the treatment of apical periodontitis because of its antibacterial effect; it is used alone or together with 2% chlorhexidine to increase its efficacy against bacteria resistant to *E. faecalis*, it is the most frequently reported microorganism in cases of apical periodontitis <sup>[6]</sup>. This research is conducted to update information on advances in intracanal drugs, bacterial resistance and sensitivity to treatments because it is a persistent problem. Intracanal medicaments such as triple antibiotic paste, calcium hydroxide, chlorhexidine and antimicrobial nanoparticles were reviewed with their uses, their antimicrobial efficacy, effect on dentin, limitations and their cytotoxicity.

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## 2. Materials and Methods

Information from articles published in PubMed, Scopus and Google Scholar was analyzed, with emphasis on the last 5 years. The quality of articles was evaluated based on the standard guidelines, i.e., identification, review, choice and inclusion. The quality of the review was assessed using the measurement instrument for evaluating systemic reviews. The search was performed using the Boolean logical operators AND, OR and NOT. It was performed with the words "calcium hydroxide", "triple antibiotic paste", "chlorhexidine", "nanoparticles", "intracanal medication" and "endodontic" were used "diseases", "comorbidities", and "oral diseases". The keywords were used individually, as well as each of them related to each other.

## 3. Results and Discussion

### 3.1 Triple antibiotic paste

#### 3.1.1 Use

Triple antibiotic paste (TAP), which is a mixture of metronidazole, ciprofloxacin and minocycline, has been used as an intracanal drug to disinfect the root canal during regenerative procedures [7] are highly effective in eliminating endodontic pathological microbiota both in situ and *in vitro* [8]. TAP appears to be a successful combination of drugs in root canal disinfection or sterilization and pulp regeneration and revascularization protocol [9].

#### 3.1.2 Effect on dentin

Treatment of dentin with TAP for 4 weeks provided an improved microenvironment for viability and attachment of DPSCs [10]. TAP significantly increased the bond strength of methacrylate resin-based sealants [11].

#### 3.1.3 Antimicrobial Efficacy

It has been shown to be the most effective, providing action against different microorganisms and producing outstanding results due to the combination of antibiotics [12] 10 mg/mL of TAP resulted in complete elimination of *E. faecalis* [13] intracanal drug delivery solution of TAP resulted in >99% reduction in colony forming unit [14].

#### 3.1.4 Limitations and cytotoxicity

Development of resistant bacterial strains and tooth discoloration are some of its drawbacks [9]. Similar toxicity effect of TAP at a concentration of 100 µg/ml at the studied time intervals on apical papilla stem cells; cell growth is observed in binary combinations of antibiotics at low concentrations (25 and 50 µg/ml). These findings may show similar behavior of antibiotics at lower concentrations, while having different effects at higher concentrations [15].

Triple antibiotic paste contains medication that helps to disinfect the root canal. It is most commonly used as a treatment in pulp regeneration and revascularization, as it provides a better microenvironment for dentin to regenerate. It provides greater efficacy against bacteria, especially it eliminates *E. faecalis* from the canal, but bacteria could develop resistance and also discolor the teeth.

## 3.2 Calcium hydroxide

### 3.2.1 Use

Calcium hydroxide is the most commonly used intracanal medication and is recommended in clinical guidelines for the treatment of avulsed teeth in multiple visits [16]. It is also the most commonly used interappointment dressing for root canal disinfection, and is effective against gram-negative species. It

can realize its antibacterial effect by inactivating membrane transport mechanisms [17]. Calcium hydroxide can be used in pregnant patients [18].

### 3.2.2 Effect on dentin

Dentin is considered the best pulp protector, and calcium hydroxide has demonstrated through numerous studies its ability to induce the formation of a mineralized layer that serves as a bridge over the pulp tissue [19]. For apexification of immature permanent teeth, the time period to form apical barrier was longer compared to the other drugs [20]. Calcium hydroxide as a pulp capping agent has properties such as the ability to form reparative dentin, maintain pulp vitality, kill bacteria, be sterile, radiopaque and provide a good bacterial seal [21].

### 3.2.3 Antimicrobial efficacy

In one study it was demonstrated that calcium hydroxide showed 99.41% antimicrobial effect against the control group [22]. Clinical studies in humans showed less efficient limited antimicrobial effects against specific species such as *E. faecalis* or *C. albicans*, whose microorganisms were reduced but not completely eliminated after treatments, and some species had resistance; their efficacy has been questioned or indicated that other agents should be mixed to improve their antimicrobial activity [23]. The lethal effect on microorganisms has been attributed to the following mechanisms: damage to the bacterial cytoplasmic membrane, protein denaturation, and DNA damage; however, it is difficult to establish the main mechanism involved in bacterial death [19]. The efficacy of calcium hydroxide against *Enterococcus faecalis* was best in the first 72 hours of duration [24].

### 3.2.4 Limitations and cytotoxicity

Calcium hydroxide is less effective against specific species such as *E. faecalis* or *C. albicans* [25]. There are some disadvantages that restrict its use, such as poor adhesive quality and inadequate seal; disintegration and presence of so-called "tunnel defects" in the restorative dentin formed beneath it [21]. If the drug is not removed from the root canal, drug residues may hinder the sealing ability of endodontic sealers, which will obstruct the diffusion of the sealers from the root canal into the dentinal tubules [26].

Calcium hydroxide is the most commonly used intracanal medication in endodontics, as it induces the formation of a mineralized layer and has an acceptable microbial effect, however, it is not as effective on *E. faecalis* or against *C. albicans*. When used between control appointments, it is known that it is not completely eliminated from the canal, which causes residues to obstruct the diffusion of cements at the time of obturation.

## 3.3 Chlorhexidine

### 3.3.1 Use

Chlorhexidine is a broad-spectrum antimicrobial agent and has been recommended as an effective intracanal medication in endodontics. The advantages of chlorhexidine are its retentive nature in root canal dentin and its relatively low toxicity. In addition, it is also effective against calcium hydroxide resistant strains. Some studies have suggested that chlorhexidine could be used in combination with calcium hydroxide to improve antimicrobial efficacy against calcium hydroxide-resistant microorganisms [27]. In pregnant patients experiencing endodontic pain, emergency opening, removal of inflamed pulp or drainage of pus and pain relief,

chlorhexidine/metronidazole can be used [18].

### 3.3.2 Effect on dentin

The most effective against *E. faecalis* within dentinal tubules at 200 and 400 µm depth compared to calcium hydroxide. It was reported that 2% chlorhexidine placement for 7 days increased its action against *E. faecalis*, especially at 400 µm depth [28].

### 3.3.3 Antimicrobial Efficacy

It has a limited antimicrobial effect against polymicrobial biofilm found inside the root canal such as gram-negative and gram-positive bacteria. The 2% gel has a time-dependent antimicrobial effect [29]. Its potency is due to its ability to alter the osmotic balance of the cell. It has the ability to maintain its antibacterial action for a prolonged period due to its substantivity and optimal microbial activity at pH 5.5 to 7 [30]. There was a highly significant difference ( $p < 0.005$ ) in *E. faecalis* count in a study after day 7 of intracanal drug placement [31]. Chlorhexidine showed maximum antimicrobial activity, followed by chitosan, in both single and dual-species biofilms [32].

### 3.3.4 Limitations and cytotoxicity

Chlorhexidine exhibits the highest level of cytotoxicity and is associated with increased antimicrobial efficacy soon after application, also persists over time for up to 14 days and inhibits wound healing in a human skin xenograft mouse model *in vivo* [33].

Chlorhexidine 2% is a medication widely used in dentistry, in endodontics it is used more as an irrigant than as an intraoral medication between appointments. It is broad spectrum, effective against *E. faecalis*, as it is a retentive agent in dentin, having an antimicrobial effect against polymicrobial biofilm with better results after 7 days of placement. It is the most cytotoxic inhibiting wound healing after prolonged use.

## 3.4 Antimicrobial nanoparticles

### 3.4.1 Use

Silver nanoparticles (AgNPs) have high antibacterial activity due to their small particles and large surface area [34]. In one study, a synthesis of CaOHAgAN was made that produced an effective nanoparticle preparation that could be used against common oral pathogens as a potential therapeutic agent in the form of root canal irrigant or intracanal medication in the field of dentistry [35].

### 3.4.2 Effect on dentin

Due to their nanoscale, AgNPs penetrate deeper into the intricacies of root canal systems and dentinal tubules, in addition to enhancing the antibacterial properties of endodontic irrigants and sealants. AgNPs gradually increase dentin hardness in endodontically treated teeth and promote antibacterial properties when used as intracanal medication carriers [36].

### 3.4.3 Antimicrobial Efficacy

Silver nanoparticles (size 20 nm) can be mixed with calcium hydroxide, which showed enhanced antibacterial action when calcium hydroxide is used alone or in combination with chlorhexidine [37]. Biosynthesized AgNPs exhibit efficient antibacterial activity against *E. faecalis* and, therefore, can be used as root canal irrigants or intracanal drugs for root canal disinfection [38, 39]. Although there is a statistically significant decrease in the mean CFU value, the nanogroup performed

the best. The highest percentage of dead bacteria was detected in the BAG-np group, with a significant difference from the BAG group. The reduction of particle size and the use of a BAG nanoform improved the antimicrobial properties of the intracanal treatment of *E. faecalis* biofilms [40].

### 3.4.4 Limitations and cytotoxicity

In one study the cytotoxic effect of Nano TAPC was lower than that of calcium hydroxide and higher than that of TAPC. Although Nano TAPC has the highest apoptotic value compared to TAPC and calcium hydroxide, there is still no statistically significant difference between them [41]. The cytotoxicity and proliferation of DPSCs in response to AgNP gel were comparable to those of calcium hydroxide. This suggests that gel AgNPs may represent a promising future candidate for clinical use in regenerative endodontics. However, their effects may be concentration dependent, which warrants further investigation [42].

Antimicrobial nanoparticles are new products used as an intra-endodontic drug so studies are still needed to verify their effect on dentin and their long-term efficacy. As for the present studies, we can know that it has good antimicrobial efficacy when combined with calcium hydroxide and minimal toxicity, although limitations have not yet been found.

## 4. Conclusion

Use of intracanal medicaments plays a fundamental role in endodontics, especially when there is any infection, pulp regeneration and revascularization. Triple antibiotic paste, despite its efficacy against bacteria, presents concerns related to bacterial resistance and possible tooth discoloration. On the other hand, calcium hydroxide is widely used because of its ability to induce the formation of a mineralized layer, but its effectiveness against certain bacteria, such as *E. faecalis* and *C. albicans*, is limited, and its persistence in the canal can affect obturation. Chlorhexidine 2% is a broad-spectrum agent, especially effective against *E. faecalis*, but prolonged use may have cytotoxic effects. The introduction of antimicrobial nanoparticles represents an exciting prospect in the field of intraoral drugs, but more research is needed to fully understand their long-term efficacy and safety.

In general, the choice of intracanal medicament should be based on case-specific considerations and the need to address already known bacteria, taking into account potential side effects and biocompatibility. Endodontics continues to evolve with the goal of providing more effective and safer treatments to preserve patients' dental health.

## 5. Conflict of Interest

Not available.

## 6. Financial Support

Not available.

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