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Review Article

Intracanal Medication as Antibiotic Control in Case of Permanent Mature Teeth with Necrotic Pulp or Apical Periodontitis

Ana Moura Teles[1], Rebecca Lassarat[2], Cristina Pina[1] and Inês Lopes Cardoso[1]*

[1]*FP-I3ID - Institute of Investigation, Innovation and Development Fernando Pessoa, Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal*

[2]*Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal*

***Corresponding Author:** Inês Lopes Cardoso, FP-I3ID - Institute of Investigation, Innovation and Development Fernando Pessoa, Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal.

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Abstract

Non-Surgical Endodontic Treatment consists in the removal of dental pulp and the elimination of microorganisms that cause infection of the pulp space. This treatment can be performed in a single or in multiple sessions and, sometimes, the use of Intracanal Medication may be necessary.

The purpose of Intracanalar Medication is to reach bacteria present in places inaccessible to instrumentation or irrigants and, also, to inhibit the invasion of the root canal system by bacteria or its products by coronal, lateral or apical communications with the outside through dentinal tubules, apical foramen or accessories root canals.

The present work is a narrative review of the Literature that aims to analyse the different opinions among authors, in the case of permanent mature teeth with diagnosis of necrosis with or without apical periodontitis associated, and to understand in which situations it is necessary to apply Intracanal Medication, which should be chosen and how it should be applied. In this way, it is also intended that this work can be a useful guide for clinicians.

Keywords: Intracanal Medication; Endodontics; Root Canal Treatment; Antimicrobial Effect; Necrosis; Apical Periodontitis

Introduction

That Endodontics is practiced because of microorganisms (MO) is now an indisputable question [1]. Bacterial biofilms and their products in a necrotic root canal system (RCS) are the main etiologic factors of apical periodontitis (AP). Root canal infections have almost always a polymicrobial origin and can be classified as primary, secondary or persistent. In the primary infection, MO that colonize the necrotic pulp tissue are, predominantly, anaerobic Gram-negative. MO that are not present during the initial infection cause the secondary infection and, in this case, they are, predominantly, Gram-positive. These MO reach RCS, either during the Non-Surgical Root Canal Treatment (NSRCT), or between two sessions, or even after the end of the treatment. Finally, in a persistent infection, MO already present in the primary or in the secondary infections are able to survive in a very restrictive environment - the empty pulpal space. These MO are usually Gram-positive or yeasts [1]. According to Davido and Yasukawa [2], the bacterium mostly found in persistent infections is *E. faecalis*.

For these infections to occur, bacteria must cross a series of consecutive barriers, reaching the pulp space, find nutrients and, finally, but not less important, induce an inflammatory reaction in the apex that results in AP. The search for nutrients is complex because the protein sources within the RCS are restricted due to the degradation of the pulp tissue. Nevertheless, the induction of a periapical inflammation leads to an increase of the serum-like exudate in the proper canal space [3].

NSRCT plays a major role in the treatment of pulpal and periapical inflammation and/or infection. It can be performed in different ways: one-single session or multiple sessions. The experts conclusions from randomized clinical trials [4-6] lead to the following recommendations: when the main following conditions are met (optimal chemo-mechanical cleaning, dried RCS, no symptoms and sufficient time available), canal filling can be performed in the same session as the preparation regardless of the pulp status; if those conditions are not met, the filling must be postponed to a subsequent appointment, and, in some particular conditions, mainly when canal cleaning is not enough to complete the RCS disinfection, the use of antibacterial agents can be an option as Intracanal Medication (IM). In fact, when chemical products commonly used during cleaning and shaping, like Sodium Hypochlorite (NaOCl), Chlorhexidine (CHX) or Ethyl Diamine Tetra-acetic Acid Disodium (EDTA) cannot ensure the maximum desirable disinfection level, it seems logical to use other antibacterial agents to improve conditions for the elimination of the etiologic factor.

According to Kawashima., *et al*. [7], the general definition of IM is the temporary placement of medicines with good biocompatibility inside the RCS to inhibit its coronal, lateral or apical invasion by MO or their products as the RCS communicates with the outside through dentinal tubules, foramen and accessory canals.

Resolution of a sinus tract, pain relief, the absence of percussion and/or palpation sensitivity are favorable clinical signs of effective root canal disinfection. Moreover, it is of crucial importance the understanding of the clinical factors that can potentially contribute to treatment failure, namely, among others [8]

- The medical condition of the host and presence of comorbidities such as diabetes, a well-studied chronic disease associated with lower success rates.
- The size of periapical lesion, being considered small till 5mm diameter and large when ≥10mm. The smaller ones have better prognosis [9].
- The anatomical complexity of the apical portion of the root canal.
- And the virulence and longevity of the bacterial infection.

The main reason for the use of IM for at least 7 days, is to allow medication to have time to diffuse and reach MO in places inaccessible to instruments and irrigant solutions [6].

The mechanism of protection of systemic antibiotics is based on several factors, including the distribution of the active ingredient to the infected area. Consequently, the infected zone - the RCS - requires a normal blood supply, which is no longer the case of teeth with necrotic pulp or without pulp tissue [10]. To overcome these inconveniences, the local administration of antibiotics may be a more effective method of delivery.

In addition, systemic antibiotics have some side effects, such as allergic reactions, toxicity, and the possible development of resistant bacterial strains, among others, that must be faced. At the level of the individual - the aesthetic problem of tooth staining (in the case of tetracycline), for instance, as well as that of populations: acquisition of bacterial resistance making them more difficult to eradicate. So, their possible use must be done within a well-defined framework, based on a precise diagnosis of the found clinical situation [11].

The goal of this review is, in case of permanent mature teeth with the diagnosis of necrotic pulp associated or not with AP, to understand what IM are available and suggest which one should be chosen and how it should be applied.

Intracanal medicines

Endodontic polymicrobial infections involve two major bacterial types: aerobic and anaerobic. Because of this duality, it is unlikely that a single antibiotic will be able to control and eradicate all MO. Hence, the association of several IM is still “magistral” [12], having the double advantage of addressing the diversity of the Endodontic flora and reducing the acquisition of resistance.

Calcium hydroxide (CH)

CH exists in a tube with the product ready to be applied or in the form of powder. This powder is mixed in a glass plate with saline solution, distilled water or other liquid vehicle by the clinician a few seconds before its application.

Nowadays, CH is recognized as one of the most used antimicrobial dressing during NSRCT. In fact, the European Society of Endodontics stipulates the general use of CH for many reasons like lack of time, presence of preoperative symptomatology or impossibility of obtaining a dry canal [13].

CH efficacy results from its alkaline pH (around 12.5) by its dissociation into hydroxyl and calcium ions. Most bacteria associated with root canals infection cannot survive at such a high pH, being eliminated after a short exposure to it. Nevertheless, the destruction of MO depends on the availability of the hydroxyl ions in the solution and CH effectiveness remains high only if high pH is maintained [14]. Moreover, CH activities (either antibacterial or anti-inflammatory) are muffled and inactivated by organic and inorganic components of dentine [15].

As reported by Siqueira [16], the efficiency of the CH is a subject of certain constraints. Undeniably, the optimal effect of CH is achieved through direct contact with bacteria. However, this direct contact is not always possible, mainly because of anatomical irregularities that difficult its proper application. Furthermore, some MO, such as *E. faecalis* and *Candida spp.*, can be resistant to the alkaline effect of CH, due to a proton pump that drives the protons into the cell and acidify the cytoplasm [17]. As these types of MO remain numerous in RC infections, CH cannot, therefore, be considered as the only possible IM in all cases.

Metapex® (MetaBiomed Co., Ltd., Chungbuk, Korea), CH with acidic-iodoform in an oil-based intracanal formulation presents as main advantage insolubility in water, resulting in lower solubility and minimal diffusion of the IM into the tissues [18]. This is desirable since, as intended, the IM remains inside the RCS when applied. The environmental pH starts as alkaline but, as observed in a study of Machado., *et al*. [19], a continuous decrease is observed reaching acidic pH [19].

Moreover, independent on the applied IM, this medicine must be totally removed before filling of the RCS. This may be a real challenge, especially in the apical third of the root canal [20]. Caspar., *et al*. suggested the use of ultrasonic activation of irrigants as more effective for removing CH than other manual agitation techniques [21].

Chlorhexidine (CHX)

According to Cohen [22], CHX has a fairly wide range of activities against aerobic and anaerobic MO, as well as against *Candida spp.* Those abilities are more effective at alkaline pH than at an acidic one. CHX is a positively charged hydrophobic and lipophilic molecule that interacts with phospholipids and lipopolysaccharides present on the cell membrane of bacteria and enters cells through an active or passive transport mechanism. Its effectiveness is based on the interaction between the positive charge of the molecule and the negative charged phosphate groups on the bacterial cell wall. This increases the permeability of the cell wall, allowing the CHX molecule to enter the bacterium leading to intracellular toxic effects [23]. These effects depend on CHX concentration, but not on its application handling (liquid, gel or controlled release device).

CHX gel (2%, the most used concentration), has low toxicity to periapical tissues. Furthermore, the viscosity of the gel keeps the active agent in contact with the RCS walls and, consequently, within the dentinal tubules, where MO are present [14,24].

According to Lima., *et al.* [25] and confirmed by Pal., *et al*. [23], Chlorhexidine Digluconate can be used as a root canal irrigant and as an IM in the form of CHX gel, in 0.2 or 2% concentration, respectively.

Corticosteroids and their association with antibiotics

The use of Corticosteroids is mainly based on their anti-inflammatory effect and its capacity of pain relief in cases of Acute Apical Periodontitis [11,26].

Ledermix® (Lederle Laboratories, Wayne, NJ) contains tetracyclines (demethylchlortetracycline) and a corticosteroid agent (triamcinolone acetonide). These compounds are the origin of tooth discolouration. Exposure of tetracycline to the radiation of a lamp causes a drop in fluorescence and a change in colour from yellow to red-purple. The brown discoloration of the affected teeth is the result of a mixture of the unchanged tetracycline yellow colour and the red-purple tetracycline-modified colour, both of which are related to tooth dentin [27].

Tetracyclines are bacteriostatic *in vitro* and *in vivo* on Gram-negative and some Gram-positive bacteria but a significant percentage of resistant organisms have been observed. To overcome this resistance, Molander and Dahlén [28] have shown that CH in combination with tetracycline had a significant effect on *E. faecalis,* but the overall antimicrobial effect was relatively weak.

Athanassiadis., *et al.* [14] assessed two common antibiotics in combination with corticosteroids. The first one he quoted was the Ledermix® paste that permits the control of pain and associated inflammation. Sometimes, in periapical lesions, its components can diffuse through the dental tubules and cement reaching the periradicular tissues. The second tested combination was the Septomixine Forte® paste but, this last one, is no longer recommended because it has inadequate spectrum activity.

The discoloration caused by Ledermix® could be minimized if its application is limited to below the gingival margin. Therefore, clinicians should ensure that Ledermix® paste is not lost on the access cavities walls [29].

Attia., *et al*. [30] tested the antimicrobial effects of Pulpomixine® against *S. mutans*, *E. faecalis* and *C. albicans*. The poor obtained results were attributed to the fact that framycetin, as well as polymyxin B sulphate (Pulpomixine® compounds) have no antifungal action, and remain active, only, against Gram-negative bacteria.

Clindamycin

As reported by Mohammadi and Abbott [12], Clindamycin is effective against many of some usual endodontic pathogens, including *Actinomyces, Eubacterium, Fusobacterium, Propionobacterium, Microaerophilic Streptococci, Peptococci, Peptostreptococci, Veillonella spp.* and *Porphyromonas*. When used *in vitro*, this antibiotic is particularly effective against species of *Prevotella* and *Porphyromonas* - black-pigmented bacteria.

According to Segura-Egea., *et al*. [10], clindamycin belongs to the class of antibiotics of lincosamide, being effective against most Gram-positive aerobes, as well as against Gram-positive and Gram-negative bacteria and anaerobes.

Odontopaste® (Australian Dental Manufacturing, Kenmore Hills, Qld, Australia) is an IM of the Clindamycin family. This antibiotic provides bacteriostatic activity in addition to the benefits of a zinc oxide paste. It acts as a temporary dressing and prevents bacterial repopulation both in the RCS and in the dough itself. On the other hand, the steroid part, triamcinolone acetonide, reduces temporarily the inflammation, being useful for the transient reduction of postoperative pain [31].

Triple antibiotic paste (TAP)

According to Parhizkar., *et al.* [32], the most effective combination against polymicrobial endodontic infections should be a mixture of Metronidazole, Ciprofloxacin and Minocycline, in an equal proportion of 1/1/1, with a final concentration of 0.1-1.0 mg/mL concentration of each drug, named TAP (Althumairy., *et al*. 2014) [33]. The most recommended clinical protocol to achieve a final TAP concentration of 1000 mg/mL is mixing equal proportions of each antibiotic powder totalizing 1000 mg in 1 mL of sterile water [34].

Due to the presence of minocycline, TAP can cause tooth discoloration. Consequently, it is recommended its application below the cement-enamel junction level to minimize crown staining [35]. To overcome this drawback, recently, few studies have substituted minocycline with cefaclor, amoxicillin or doxycycline [36].

Metronidazole

Metronidazole belongs to the antibiotic family of 5-nitroimidazoles and is particularly toxic to anaerobes and considered as an antimicrobial agent against protozoa and anaerobic bacteria. However, it is ineffective against facultative bacteria [22].

Minocycline

Minocycline is a broad-spectrum bacteriostatic antimicrobial antibiotic, effective against Gram-positive and Gram-negative MO, including most spirochetes and many anaerobic and facultative bacteria [10].

Ciprofloxacin

Synthetic fluoroquinolone (ciprofloxacin) has a very potent activity against Gram-negative pathogens, but limited activity against Gram-positive bacteria, and, therefore, most of anaerobic bacteria related to infection of endodontic origin are resistant to it [10].

N-acetylcysteine (NAC)

NAC is a potent thiol having antioxidant action [37] and high antimicrobial activity attributed to the disruption of disulfide bonds present in bacterial proteins. In this way, NAC induces irreversible damage to proteins affecting bacterial growth and metabolism. Consequently, it leads to biofilm disturbance [38,39]. Given its capabilities, NAC should be further investigated concerning its potential association with the gold standard CH or CHX as IM. A study [40] found promising results even against CH-resistant species.

Discussion

Comparison of the Success Rate (Table 1)

Antibiotic Compound	Antibiotic present	Effectivness againts bacteria	Success rate	References
CH		All bacteria (except *E. faecalis*)	CH > CHX gel on *E. faecalis* CH > CHX 2% gel, at 14 days, in AP CH > Clindamycin, in root canal infection and AP, at 14 days Mixture (50:50) CH + Ledermix®: destruction of the steroid coumpound Mixture (50:50) CH + Ledermix® and CH+ Odontopaste® on *E. faecalis*: no significant efficacy	[25] [32] [30] [31] [37]
CHX		Aerobic and anaerobic bacteria	CHX > Odontopaste® on *E. faecalis* CHX 2% > CH on *E. faecalis* CHX 2% > CH in root canal treatment failure CHX 2% > CHX 0.2% on *E. faecalis* at 50 days CH + CHX 2% > CH+ sterile water in Endodontics pathogens elimination CHX 2% and CH+CHX 2%: no statistical difference in colony forming units	[38] [39] [40] [41] [42] [31]
LEDER-MIX®	Triamicinolone acetonide Demethylchlortetracycline	+/-	Ledermix® > CH in AAP on post operative pain	[23]
ODONT-OPASTE®	Clindamycine hipochlorite Triamcinolone acetonide	+/some-	Odontopaste® > Ledermix® on *E. faecalis* Odontopaste® > placebo on post operative pain under 24h	[28] [31]
TAP	Metronidazol Ciprofloxacin minocycline	Anaerobic+/- +/- +/-	TAP > CH on *E. faecalis* Good results on healing a periapical lesion Good results on a large cyst-like lesion TAP at least = CH +CHX 2% in AP	[43] [44] [46] [45] [47] [48]
SEPTOM-IXINE FORTE®	Neomycin Polymyxin B sulfate Dexamethasone	- /some + - (Except proteus group)	Not in use nowadays	[63]
PULPO-MIXINE®	Framycetin Polymyxin B sulfate Dexamethasone	Aerobic -/some aerobic + - (Except proteus group)	Not in use nowadays	[63]

Table 1: Comparison of effectiveness in terms of success rate of Ledermix®, Calcium Hydroxide, Chlorhexidine, Odontopaste®, Triple Antibiotic Paste, Septomoxine® and Pulpomixine®.

Calcium hydroxide

Molander and Dahlén [28] studied the impact of two types of IM in cases of AP for a period of 14 days - CH and Clindamycin mixed with sterile saline solution - and found that Clindamycin offered no advantage when compared with CH.

Moreover, Teles., *et al*. [41] tested CH and 2% CHX gel, applied as IM for 14 days. No significant reduction on the bacteria load was observed since the first appointment of NSRCT. Nevertheless, after 14 days, CH led to better results than CHX, particularly in cases of necrosis associated with AP.

Plutzer., *et al*. [42] obtained similar results when CH and 0.2% CHX gel were compared on their effectiveness in eliminating *E. faecalis*. At 24 and 48 hours of exposure, they obtained, respectively, 99.9% and 97% reduction of bacterial load, and concluded that CH was more effective than 0.2% CHX gel.

Athanassiadis., *et al*. [14] believed that, in cases of RC infection, necrotic pulp, perforations, resorptions or treatment of large periapical lesions, a mixture of Ledermix® with CH (50:50) permits a slower diffusion of the active components and, thus, a longer action period. However, in 2011, Athanassiadis., *et al.* [43] tested a mixture of CH with 98.2% purity and Ledermix® and observed total destruction of triamcinolone acetonide at zero time-point (approximately 3 min). They concluded that the mixture of these two compounds would not allow the drug to last longer in the RC. In fact, as reported by Jarrett., *et al*. [44], this mixture results in the immediate destruction of the steroid component (triamcinolone acetonide).

In addition, Plutzer., *et al*. [42] confirmed that CH combined with Ledermix® or Odontopaste® led to a 99.9% reduction of *E. faecalis* viability, while 0.2% CHX gel resulted in a 97% reduction. However, this 99.9%result was also obtained by using the CH alone. So, these authors concluded that there was no significant efficacy of the 50:50 mixtures of Ledermix® or Odontopaste® and CH.

Chlorhexidine

Gomes., *et al*. [45] studied the combination of CH mixed with 2% CHX gel against endodontic pathogens and observed a greater antimicrobial activity when compared with CH and sterile water. On the other hand, Cook., *et al*. [46] showed that the treatment with 2% CHX was more effective in the removal of *E. faecalis* in comparison with CH. Ballal., *et al.* [47] obtained the same results in the context of NSRCT failure.

Endo., *et al.* [48] found that there was no significant statistical difference in the decrease of colony-forming units between CH mixed with 2% CHX gel (99.86%) and 2% CHX alone (99.57%) against endodontic bacteria.

Work of Ferrer-Luque., *et al.* [49] focused on the study of if a decrease in CHX concentration would engender a different impact on bacteria elimination, particularly *E. faecalis*. They observed that 2% CHX had a greater inhibitory capacity after 50 days, with only 34.61% growth of *E. faecalis* in comparison with 0.2% CHX which obtains 69.23% bacterial growth.

In the Plutzer., *et al*. [42] study, no significant statistical difference was found between Odontopaste® and 0.2% CHX. However, 0.2% CHX appeared to be more effective in eliminating *E. faecalis*.

Ledermix®

Ehrmann., *et al*. [26] evaluated the relationship of IM with post-operative pain in Endodontics, comparing the use of Ledermix® or CH with application of an IM in teeth with necrotic pulp or acute apical periodontitis (AAP). This study revealed that, in teeth with AAP, patients treated with Ledermix® experienced less pain than patients treated with CH or with no IM application.

Since one of our exclusion criteria were studies in animals, no additional paper could be added regarding the positive effects of Ledermix®.

Odontopaste®

By evaluating the analgesic effect of the Odontopaste®, Eftekhar.,. [31], demonstrated that it had significant reduction of post-operative pain compared with a., *et al.* placebo group, during 24 hours. Nevertheless, after 7 days, this reduction was no longer significant.

Plutzer., *et al*. [42] showed that Odontopaste® alone had little quantitative reduction of *E. coli* and *E. faecalis* viability. However, a significant difference was observed between Ledermix® and Odontopaste®, suggesting that Odontopaste® was better.

Triple antibiotic paste (TAP) - a mixture of ciprofloxacin, metronidazole, and minocycline

As discussed previously, none of the IM responds fully to a polymicrobial infection. TAP was therefore included in this review since this mixture of three components allows a larger spectrum of action.

TAP led to good results in large cyst-like lesion healing when use as an antibacterial dressing [50]. Er., *et al.* [51] used this combination of antibiotics (Metronidazole, Ciprofloxacin and Minocycline), as an antibacterial dressing to cure large peri-radicular lesions. Similarly, Taneja and Kumari [52] reported a case of NSRCT where TAP healed a large peri-radicular lesion.

According to Kim and Kim [53], TAP has a larger zone of inhibition against *E. faecalis* than CH.

Dhillon., *et al*. [54] used TAP in the healing of periapical lesions and observed a remarkable reduction of symptoms. The swelling did not occur during the 14 days of the dressing and when the dressing was removed, no pus flow was observed. They conclude that TAP should be used as a first-choice treatment.

Arruda., *et al*. [55] compared the antibacterial efficacy in a protocol of inter-appointment medication in infected RC presenting a primary AP using TAP at a concentration of 1 mg/mL and CH paste mixed with 2% CHX. They concluded that TAP significantly improved RC disinfection and its effects were at least comparable to those of the CH/CHX. Therefore, these authors recommended TAP as an appropriate drug in a disinfection protocol for NSRCT.

Intracanal medication - clinical protocol guidelines

The manipulation of the chosen IM must be done according to the recommendations of the manufacturer.

Calcium hydroxide

After the access preparation, excision of the pulp and profuse irrigation with NaOCl, excess solution is aspirated from the canal and later properly dried with paper points.

In the case of the CH, it is not necessary to dry the entire RC because some moisture is necessary to increase its solubility [16]. The CH paste must be prepared just prior to the introduction into the canal by mixing the CH powder with a sterile physiological solution or distilled water until a creamy consistency is obtained [55] (Figure 1).

Figure 1: Tanipulation of Calcium Hydroxide paste.

It is worth to say that the working time is between 2 and 7 minutes. After that period of time, it becomes hard and impossible to manipulate [55].

In fact, already in 2006, Beer., *et al*. [56] stated that CH paste is difficult to apply in sharply curved canals and must be mixed with a liquid. Compared to CH diluted in water, CH diluted in synthetic glycerine in a paste commercial presentation, provides a better and more homogeneous filling of the RC. For curved canals prepared with files up to ISO size 25, these authors recommend the use of flexible McSpadden condensers and lentulos, which allow insertion of CH into the apical region in 87% of curved canals.

The selected lentulo should be the widest possible reaching 2 to 3mm from the working length (WL). Two or three insertions of the lentulo embedded in CH may be necessary for a good filling of the canal [56].

A cotton pellet or a plumber's tape (which is also known PTFE tape, thread seal tape or, erroneously, Teflon™ tape) is placed at the entrance of the canals and the cavity is cleaned from any residues of IM [16].

Finally, a temporary cement (at least with 4mm of thickness) is placed above the cotton pellet and an X-ray is taken to ensure the proper placement of the IM and checking the occlusion is mandatory.

The second appointment must take place, at least, one week after [16,55]. At this appointment, IM is usually withdrawn from the RCS by multiple irrigation cycles with 5mL of sterile saline or with 3% NaOCl solution using a proper needle (27 or 30G) in a circumferential motion. Then, the clinical protocol of NSRCT can be continued [57].

In the case of combination of CH with 2% CHX, the IM must be removed by irrigation with 5mL sterile saline solution or with a mixture of 5% Sodium Thiosulfate, 0.5% Tween 80, and 0.07% Soy Lectin to neutralize CHX in the circumferential filling motion, mentioned before [55].

The type of fluid movement that creates shear forces along the RC walls, the flow of the irrigant, and the relationship between the internal diameter of the RC and the diameter of the irrigation needle can also influence the success of irrigation [58].

Chou., *et al*. [59] reported that, when a 5 mm diameter syringe with a small tip is used, the technique that stands out as the most effective on a steroid pasta (Ledermix®, Odontopaste®) is the EndoActivator. However, these researchers concluded that no technique guarantees 100% efficiency. The most difficult material to remove is the CH when compared to Ledermix®, Odontopaste® and Doxypaste®. This is due to characteristics such as the thickness of the pulp, viscosity and its cellulose charge and the possibility of a partial conversion of some CH into calcium carbonate over time due to the reaction with carbon dioxide ions.

In conclusion, because CH is a drug that is difficult to eliminate, efforts must be made to properly place the irrigation devices and use agitation to improve its elimination. This agitation can be manually delivered by making movements up and down (with an amplitude of 2mm) with a file or, can be mechanical, using ultrasonic instruments or pulsed lasers.

Chlorhexidine

As for CHX, according to Cohen [22], the combination of NaOCl and CHX causes colour changes and the formation of a neutral and potential toxic insoluble precipitate that can hinder the filling of the RC. Alternatively, the RC can be washed with alcohol or a saline solution and dried using paper points before the final CHX rinse.

According to the protocol used by Paquette., *et al.* [24], before the IM application, the RC must be dried and irrigated with 2 mL of 2% liquid CHX. At the end of the irrigation, the canal must be left with 2% CHX digluconate liquid. An ISO size 20K-type file must be inserted into the WL to facilitate the distribution of CHX in the apical part of the RC. A sterile cotton pellet soaked with CHX should be placed at the canal opening. Finally, the tooth is temporarily sealed.

Triple antibiotic paste

TAP can be prepared from capsules containing the same proportions of metronidazole, minocycline and ciprofloxacin, diluted in sterile distilled water, until a final concentration of 1 mg/mL, or instead manually in the clinic by mixing the 3 antibiotics at the moment of use, as reported by Afkhami., *et al.* [60]. TAP is used to fill the canal and a cotton pellet soaked with this same solution is disposed at the level of the pulp chamber [55].

Very few details are provided on how TAP is inserted in case of necrotic pulp or AP.

Reynolds., *et al.* [61] use a stop-and-go syringe system - up to 2 mm below the WL - in the context of pulpal revascularization. Other authors use the dough wad at low speed, with the insertion of a sterile paper tip to sufficiently condense the product.

The difficult removal of the paste is another “trap” to take into account when applying TAP in the pulpal space. Existing irrigation techniques do not completely remove TAP because it penetrates and binds to the dentin structure [32].

Arslan., *et al.* [62] have shown that “photon-induced photoacoustic flux” (PIPS), a contemporary technique used to remove materials from RC walls, was more effective in removing TAP from the RCS than needle irrigation.

Ultrasonic activation of 5.25% NaOCl appears to be the most effective method for pulp disposal [32].

Conclusions

Endodontics is an area with a lot of controversy concerning if the treatment should be applied in one or multiple sessions, but also concerning the use of IM.

In pulpal necrosis and its periapical complications, the loss of vascularization of the pulp space makes systemic antibiotics ineffective. Deprived of this distribution on the infected site, no efficient treatment of the pathology is expected with their use. If antibiotics were to be recommended, only an *in situ* application could be effective, in addition to a chemo-mechanical preparation of the RC.

When the use of IM is required - they are useful in cases with questionable or unfavorable prognosis - its choice seems still controversial.

In this study, seven IM were studied: CH, CHX, Ledermix®, Odontopaste®, TAP, Septomixine® and Pulpomixine®.

Since Septomixine® and Pulpomixine® are no longer used today due to their inefficacy against bacteria, only the five other IM have been further developed.

Ledermix® and Odontopaste® do not seem to respond positively to the elimination of bacteria in endodontic infections. Moreover, the effects on dental discoloration described for Ledermix® confirm its inoperability.

Nowadays, CH and CHX remain the most used for their good results. Nevertheless, well-designed prospective studies to assess the long-term outcomes of root canal treatment modalities should be implemented to achieve evidenced based clinical protocols.

In view of the inefficiency of the CH and CHX on *E. faecalis*, TAP and NAC have been envisaged. In fact, those formulas consider the polymicrobial nature of the endodontic infection and good results were observed, at least similar to CH. Although IM effectiveness in pulpal revascularization has been extensively studied, its use in cases of pulp necrosis and AP should be further investigated, to confirm its potential indication in these specific endodontic diagnoses. The use of nanoparticles and antimicrobial peptides as intracanal medicines is promissory, and more research in this area should be performed.

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