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Intracanal Medication in case of Permanent Mature Teeth with Necrotic Pulp or Apical Periodontitis

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Dissertação apresentada à Universidade Fernando Pessoa
como parte dos requisitos para obtenção do
grau de Mestre em Medicina Dentária.
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RESUMO

O Tratamento Endodôntico Não Cirúrgico consiste na remoção da polpa dentária e na eliminação de microrganismos causadores da infecção do espaço pulpar. Este tratamento pode ser realizado numa única ou em várias sessões e, por vezes, o uso de Medicação Intracanalar pode estar indicado.

O propósito da Medicação Intracanalar é atingir bactérias presentes em locais inacessíveis à instrumentação ou aos irrigantes e, também, inibir a invasão do sistema de canais radiculares, por bactérias ou seus produtos, já que este comunica, essencialmente, com o exterior, através de túbulos dentinários, do foramen apical e dos canais acessórios.

O presente trabalho é uma revisão narrativa da Literatura que tem como objetivo analisar as diferentes opiniões dos autores sobre as situações em que é necessário aplicar Medicação Intracanalar, qual deve ser escolhida e como deve ser aplicada, no caso de dentes permanents, com ápice formado e com diagnóstico de necrose com ou sem periodontite apical associada. Desta forma, também se pretende que este trabalho possa ser um guia útil para os Médicos Dentistas.

Palavras – chave: “medicacão intracanalar”; “Endodontia”; “tratamento do canal radicular”; “efeito antimicrobiano”; “necrose”; “periodontite apical”.

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 canals.

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

Key - words: "intracanal medication"; "Endodontics"; "root canal treatment"; "antimicrobial effect"; "necrosis"; "apical periodontitis".

DEDICATION

Gregoire, Mum, Dad, César, Victoire and Grandmother.

I dedicate my work to the six most important people of my life.

Thank you for your support, without you, none of this would have been possible.

Thank you for being there for me all these years, I love you.

THANKS TO:

To my teacher Dr. Ana Moura Teles, who was able to guide me with a lot of patience during this work.

To my lover Gregoire, who has always been an unfailing support.

To my very Big family that I love so much and especially to my cousin Capucine who spent this last year by my side.

To my friend Charlotte who has always been by my side during all those years and with whom I lived all the joys of being student.

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Index of abbreviations

MO : Microorgagnism

RCS : Root Canal System

AP : Apical Periodontitis

NSRCT : Non-Surgical Root Canal Treatment

IM : Intracanal Medication

EDTA : Ethyl Diamine Tetraacetic Acid Disodium

CH : Calcium Hydroxide

CHX : Chlorhexidine

TAP : Triple Antibiotic Paste

RC : Root Canal

WL : Working Length

PIPS : Photon Induced Photoacoustic Streaming

E faecalis: Enterococcus Faecalis

S.Mutans : Streptococcus Mutans

C.Albicans : Candida Albicans

I. INTRODUCTION:

That Endodontics is practiced because of microorganisms (MO) is now an indisputable question (Teles *et al.* 2013). Bacterial biofilms and their products in a necrotic root canal system (RCS) are the main etiologic factor of apical periodontitis (AP). Root canal infections have almost always a polymicrobial origin and can be classified in primary, secondary or persistent. In the primary infection, MO that colonize the necrotic pulp tissue are, predominantly, anaerobic Gram negative. MO that were not present during the initial infection cause the secondary infection and, in this case, they are, predominantly, Gram positive. These MO achieve RCS, either during the Non-Surgical Root Canal Treatment (NSRCT), between two sessions, or after the end of it. Finally, in a persistent infection, MO were already present either in primary or in secondary infections, and were able to survive in a very restrictive environment – the empty pulpal space. They are usually Gram positive or yeasts (Teles *et al.* 2013). According to Davido & Yasukawa (2017), with regard to persistent infection, the most studied bacterium is *E. Faecalis*.

For these infections to occur, the bacteria must pass a series of consequent 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 small volume of pulp tissue. Nevertheless, the induction of a periapical inflamation leads to an increase of the serum-like exudate in the proper canal space. (Sundvist & Figdor 2003) (Figure1)

NSRCT plays a major role in response to pulpal and periapical inflammation and /or infection. It can be realised in different ways: one-single session or multiple sessions. The experts conclusions from randomized clinical trials (Sathorn *et al.* 2005, Paredes *et al.* 2012, Vera *et al.* 2012) lead to the following recommendations: when the main following conditions are met (optimal chemo-mechanical cleaning, RCS dried, 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 instrumentation is not enough to complete the RCS

disinfection, 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 Tetraacetic Acid Disodium (EDTA) can´t ensure the maximum desirable disinfection level, it seems logical to use other antibacterial agents to improve conditions of the etiologic factor' elimination.

According to Kawashima *et al.* (2009), the general definition of IM is the temporary placement of medicaments 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, besides its entrance (Figure 1).

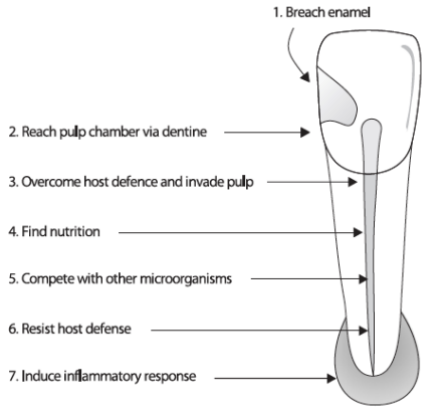

Figure 1 : Challenges for Microbes to Establish in the Untreated Root Canal. (Sundqvist et al. 2003)

The main indication 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. (Vera *et al.* 2012)

Systemic antibiotics have some side effects, such as allergic reactions, toxicity, and the possible development of resistant bacterial strains, among others. In addition, the systemic administration of antibiotics is based on several factors, including the distribution of the active ingredient to the infected area. Consequently, the infected zone in this case, the RCS, requires a normal blood supply, which is no longer the instance for teeth with necrotic pulp or without pulp tissue. (Segura *et al.* 2017) In order to overcome these inconveniences, the local administration of antibiotics may be a more effective method of delivery. However, these side effects mentioned before are encountered and must be faced. At the level of the individual - the aesthetic problem of

tooth staining (in the case of tetracycline), 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 clinical situation encountered. (Duboisdendien 2015)

The objective of this dissertation, in case of permanent mature teeth with the diagnosis of necrotic pulp associated or not with AP, is to understand in which situations it is necessary to apply IM, witch should be chosen and how does it should be apply.

II. DEVELOPMENT:

1. Materials and Methods:

For the elaboration of this review, articles were searched in different electronic databases (PUBMED, B-ON, Science direct, Cochane library, Google Shcolar, Web Of Sciences). It was also used several reference books in the area of Endodontics.

The following keywords were used in different combinations: “intracanal medication”; “Endodontics”; “root canal treatment”; “antimicrobial effect”; “necrosis” and “apical periodontitis”.

Most of the relevant articles were found in the PUBMED electronic database.

Inclusion criteria were used to narrow the search: publication date: 2000-2019; languages: English, French, Portuguese.

The following exclusion criteria were used: paid articles; articles with only abstract available; unavailable articles.

The final selection includes 42 articles included in the period 2000 until 2019 and 4 books.

2. Intracanal Medicaments

As mentioned before, Endodontic infection is of polymicrobial origin, concerning the two major metabolic bacterial types: aerobic and anaerobic. Because of this duality, it is

unlikely that a single antibiotic will be able to contain and eradicate all these MO. Hence, the association of several IM is still "magistral". (Mohammadi & Abbott, 2009) They have the double advantage of addressing the diversity of Endodontic flora encountered, and reducing the acquisition of resistance.

2.1. Calcium Hydroxide (CH)\

Nowadays, CH is recognized as one of the most used antimicrobial dressing during NSRCT. Indeed, the congress of the French Dental Association, stipulates the general use of CH for many reasons like lack of time, presence of preoperative symptomatology or impossibility of obtaining a dry canal.

In fact, CH efficacy is due to its alkaline pH (about 12.5): in the presence of water, CH dissociates 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: CH' effectiveness remains high only if high pH is maintained. (Athanassiadis *et al.* 2007)

Indeed, as reported by Siqueira (2011), the efficiency of the CH is a subject of certain constraints. Indeed, 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, like *E. Faecalis* and *Candida spp.*, can be resistant to the alkaline effect of CH. This seems to be due to a proton pump that drives the protons into the cell and acidify the cytoplasm. (Mohammadi *et al.* 2012) As these types of MO remain numerous in RC infections, CH cannot, therefore, be considered as the only possible IM in all cases.

CH exists in the form of powder to be mixed, in a glass plate, with saline solution, distilled water or other liquid vehicle by the clinician a few seconds before its application or in a tube with the product ready to be applied. Examples for this last version are: Calcicur® (Voco), Dycal® (Dentsply) or Life® (Kerr). (Miecaze *et al.* 2016)

2.2 Chlorhexidine (CHX)

According to Cohen (2011), CHX has a fairly wide range of activities against aerobic and anaerobic MO, as well as against *Candida spp.*, which are more effective at alkaline pH than at an acidic pH. 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 with intracellular toxic effects. (Himadri *et al.* 2019)

The effects of CHX depend on its concentration, but not on its application mode (liquid, gel or controlled release device).

CHX gel 2%, the most used concentration one, 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, local where there's been proven to exist MO. (Athanassiadis *et al.* 2007, Paquette *et al.* 2007)

According to Lima *et al.* (2001) and confirmed by Himadri *et al.* (2019), Chlorhexidine Digluconate can be used as a root canal irrigant and as an IM in the form of 0.2 or 2% CHX gel.

2.3 Corticosteroid Medications and its Association with Antibiotic(s)

The use of Corticosteroids is mainly based on their anti-inflammatory effect and also its capacity of pain relief in cases of Acute Apical Periodontitis. (Ehrmam *et al.* 2003, Duboisdendien2015).

Ledermix® (Lederle Laboratories, Wayne, NJ) contains tetracyclines (demethylchlortetracycline) and a Corticosteroids 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. (Kim *et al.* 2000)

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 noted. To overcome this resistance, Molander *et al.* (2003) 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.* (2007) assessed two common antibiotics in combination with Corticosteroids. The first one he quoted was the Ledermix® paste that permit a control of the pain and the inflammation associated, sometimes, with periapical lesions, whose components can diffuse through the dental tubules and cement reaching, so, the periradicular tissues. The second one quoted was the Septomixine Forte® paste but, this last one, is no longer recommended because it has inadequate spectrum activity. (Karim *et al. 2007)*

Concerning the discoloration due to Ledermix®, it could, however, be minimized if the location of the Ledermix® is limited below the gingival margin. In fact, clinicians should, therefore, ensure that Ledermix® paste is not lost on the access cavities walls. (Chen *et al.* 2012)

Attia *et al.* (2015) tested the antimicrobial effects of Pulpomixine® against *S. mutans*, *E. Faecalis* and *C. Albicans*. The poor results verified 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.

2.4 Clindamycin

As reported by Mohammadi *et al.* (2009), Clindamycin is effective against many of some usual Endodontic pathogens, including *Actinomyces, Eubacterium, Fusobacterium, Propionobacterium, Microaerophilic Streptococci, Peptococci, Peptostreptococci, Veillonella spp. and Porphyromonas*. *In vitro,* it is particularly effective against species of *Prevotella* and *Porphyromonas* – black-pigmented bacteria.

Indeed, according to Segura *et al.* (2017), Clindamycin belongs to the class of antibiotics of lincosamide. It is 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, temporarily reduces inflammation. It is useful for the transient reduction of postoperative pain. (Eftekhar B *et al.* 2013)

2.5 Triple Antibiotic Paste (TAP)

Being an Endodontic infection of polymicrobial nature, according to Parhizkar *et al.* (2018), the most effective combination should be a mixture of Metronidazole, Ciprofloxacin and Minocycline, in an equal proportion of 1/1/1, named TAP.

2.5.1 Metronidazole

Metronidazole belongs to the antibiotic family of 5-nitroimidazoles. It is particularly toxic to anaerobes and considered as an antimicrobial agent against protozoa and anaerobic bacteria. However, it is ineffective against facultative bacteria. (Cohen *et al.* 2011)

2.5.2 Minocycline

Minocycline is a broad-spectrum bacteriostatic antimicrobial, being effective against Gram-positive and Gram-negative MO, including most spirochetes and many anaerobic and facultative bacteria. (Segura *et al.* 2017)

2.5.3 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. (Segura *et al.* 2017)

III. DISCUSSION

1. Comparison Of the Effectiveness in terms of the Success Rate (Table 1)

1.1 Calcium Hidroxyde

Molander *et al.* (2003) compared the CH with Clindamycin mixed with sterile saline solution as IM in cases of AP, over a period of 14 days. They concluded that Clindamycin offered no advantage in comparison with CH.

Teles *et al.* (2014) concluded that, although the IM tested (CH and 2% CHX gel) did not obtain significant reduction of the bacteria load, in comparison with the end of the first visit of NSRCT, CH had, nevertheless, obtained better results with respect to the CHX 2% gel on a delay of 14 days, particularly in those cases of necrosis associated with AP.

Plutzer *et al.* (2018) obtained the same 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%. They concluded that CH was more effective than 0.2% CHX gel.

Athanassiadis *et al.* (2007) believed that a mixture of Ledermix® with CH (50:50), in the event of RC infection, necrotic pulp, perforations, resorptions or treatment of large periapical lesions permits a slower diffusion of the active components and, thus, a longer duration of action. However, in 2011, Athanassiadis *et al.* tested a mixture of CH with 98.2% purity and Ledermix®, and obtained an entire destruction of triamcinolone acetonide at zero time-point (approximately 3 min). They conclued that the mixture of these two compounds would not allow the drug to last longer in the RC.

Indeed, as reported later by Jarrett *et al.* (2018), this mixture results in a destruction of the steroid component (triamcinolone acetonide) with an immediate effect.

In the same year, Plutzer *et al.* (2018) confirmed that CH combined with Ledermix® or Odontopaste® reduced the viability of *E. Faecalis* in 99.9% compared to 97% of a 0.2% CHX gel. But this result of 99.9% was also obtained by CH alone. So, they concluded that there wasn't a significant efficacy of the 50:50 mixtures of Ledermix® or Odontopaste® and CH.

1.2 Clorhexidine

Gomes *et al.* (2006) studied the combination of CH mixed with 2% CHX gel against Endodontic pathogens. They compared it to CH and sterile water: the first combination proved greater antimicrobial activity.

Contrary to the previous results (cf CH), Cook *et al.* (2007) showed that a treatment with 2% CHX was more effective in the removal of *E. Faecalis* in comparison with CH. Ballal et al., also in 2007, obtained the same results in the context of NSRCT failure.

Endo *et al.* (2013) 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 Endondontic bacteria.

Ferrer *et al.* (2014) have decided to study if a decrease in CHX concentration will engender a different impact on bacteria elimination, in particular on *E. Faecalis*. Indeed, 2% CHX has obtained a greater inhibitory capacity at 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.* (2018) study, a significant statistical difference was not found between Odontopaste® and 0.2% CHX; however, 0.2% CHX appeared to be more effective in eliminating *E. Faecalis*.

1.3 Ledermix®

Ehrmann *et al.* (2003) 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 animals' studies, no additional article could not be added regarding the positive effects of Ledermix®.

1.4 Odontopaste®

By evaluating the analgesic effect of the Odontopaste®, Eftekhar *et al.* (2013), demonstrated that it had significant different results, compared with a placebo group, in reducing post-operative pain under 24 hours. Nevertheless, after 7 days, the result obtained was no longer significant.

Plutzer *et al.* (2018) showed that Odontopaste®, alone, has little quantitative effect on reducing the viability of *E. coli* and *E. Faecalis*. However, a significant difference was observed between Ledermix® and Odontopaste®, suggesting that Odontopaste® was superior.

1.5 Triple Antibiotic Paste (TAP) - a mixture of Ciprofloxacin, Metronidazole, and Minocycline

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

TAP obtained good results in large cyst-like lesion healing when use as an antibacterial dressing. (Ozan *et al.* 2005) Just as reported by Er *et al.* (2007), they used this

combination of antibiotics (Metronidazole, Ciprofloxacin and Minocycline), as an antibacterial dressing to cure large periradicular lesions. Later, S. Taneja & M. Kumari (2012) reported a case of NSRCT where TAP was used that has healed a large periradicular lesion.

According to Kim *et al.* (2014), TAP has a larger zone of inhibition against *E. Faecalis* than CH.

Indeed, Dhillon *et al.* (2014) used TAP in the healing of periapical lesions. A remarkable reduction in symptoms after the use of TAP was found. The swelling did not occur within 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.* (2018) 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, they recommended, supported by the effectiveness and easiness of administration, TAP as an appropriate drug in a disinfection protocol for NSRCT.

2. Intracanal Medication - Clinical Protocol Guidelines

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

2.1 Calcium Hidroxyde

After the access preparation, excision of the pulp and profuse irrigation with NaOCl, excess' solution is aspirated from the canal that must be proper 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. (Siqueira 2011)

In case of CH paste, it must be prepared just before introduction into the canal by mixing the CH powder with a sterile physiological solution or distilled water until a creamy consistency is obtained. (Arruda *et al.* 2018)

Figure 2: Manipulation of Calcium Hydroxide paste (Courtesy of Natália Vasconcelos)

It is worth to say that the working time is between 2 and 7 minutes before it become hard and impossible to manipulate. (Arruda *et al.* 2018)

In fact, already in 2006, Beer *et al.* 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 in a paste commercial presentation, diluted in synthetic glycerin provides a better and more homogeneous filling of the RC. For curved canals prepared with files up to ISO size 25, they 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 that arrives at 2 or 3mm from the working length (WL). Two or three insertions of the lentulo embebed in CH may be necessary for a good filling of the canal. (Beer *et al.* 2006)

A cotton pellet or a plumber's tape (which is also known PTFE tape, thread seal tape or, erroneously, Teflon^{TM} tape) is placed at the entrance of the canals and the cavity is cleaned from any residues of IM. (Siqueira, 2011)

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

The second appointment must take place, at least, a week after. (Siqueira 2011, Arruda *et al*, 2018)

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 from the phase reached in the last appointment. (Martinho *et al.* 2018)

In the case of CH had been combined with 2% CHX, the IM must be mandatory removen by irrigation with 5mL sterile saline solution or other 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. (Arruda *et al*. 2018)

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. (Sedgley *et al.* 2005)

Chou *et al.* (2013), reported that, when a 5 mm diameter syringe with a small tip is used, the technique that stands out as the most effective on streroid pasta (Ledermix®, Odontopaste®) is the EndoActivator. However, he concluded that no technique guarantees 100% efficiency. The material being the most difficult to remove is the CH compared to Ledermix®, Odontopaste® and Doxypaste®.

Indeed, 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 a portion of the CH to calcium carbonate over time due to the reaction with ambient 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 over 2mm with a file or, mechanical, using ultrasonic instruments or pulsed lasers.

2.2 Clorhexidine

As for CHX, according to Cohen (2011), 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 filling. 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.* (2007), before the IM application, the RC must be dried and irrigated with 2 mL of 2% liquid chlorhexidine (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.

2.3 Triple Antibiotic Paste

In the context of TAP, it 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, TAP can be prepared also manually in the clinic by mixing at the time of the 3 antibiotics as reported by Afkhami *et al.* (2018)

For TAP, the canal is filled and a cotton pellet soaked with this same solution is disposed at the level of the pulp chamber. (Arruda *et al.* 2018)

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

Reynolds *et al.* (2009) use a stop-and-go syringe system - up to 2 mm below the WL - in the context of pulpal revascularization. Others 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. (Parhizkar *et al.* 2018)

Arslan *et al.* (2014) have shown that "photon-induced photoacoustic flux" (PIPS), a contemporary technique used to remove materials from RC walls, was more effective than needle irrigation in removing TAP from the RCS.

Ultrasonic activation of 5.25% NaOCl appears to be the most effective method for pulp disposal. (Parhizkar *et al.* 2018)

IV. Conclusions:

Endodontics is an area that faces a lot of controversy, whether it's about performing treatment on one or multiple sessions, but also about the use of IM.

In pulpal necrosis and its periapical complications, the loss of vascularization of the endodont makes systemic antibiotics ineffective. Deprived of this distribution on the infected site, no resolution of the pathology is to be considered 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 necessary, the choice of it still seems controversial.

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

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

With regard to Ledermix® and Odontopaste®, these IM do not seem to respond positively to the elimination of bacteria in relation with Endodontic infections; moreover, the effects of dental discoloration described for Ledermix® confirm its inoperability.

Nowadays, CH and CHX remain the most used for their good results.

However, in view of the inefficiency of the CH and CHX on *E. Faecalis*, TAP has been envisaged. Indeed, this formula takes into account the polymicrobial nature of the Endodontic infection and obtains good results, at least equal to CH. Although its effectiveness in the context of pulpal revascularization has been extensively studied, its use in cases of pulp necrosis and AP should be further, clinical investigated in the future, in order to confirm its potential indication in these specific Endodontic diagnosis.

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VI. ANNEX:

Table 1 : Comparison of Effectivness in terms of Success Rate of Ledermix®, Calcium Hydroxide, Chlorhexidine, Odontopaste®,Triple Antibiotic Paste, Septomoxine® and Pulpomixine®

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 efficacity	**Molander 2003, Athaniassiadis 2011 Teles 2014, Plutzer 2018, Jarrett 2018**
CHX		bacteria aerobes and anaerobes	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	**Gomes 2006, Cook 2007, Ballal 2007 Endo 2013 , Ferrer 2014, Plutzer 2018**
LEDER-MIX®	Triamicinolone acetonide Demethylchlortetracycline	+/-	Ledermix® > CH in AAP on post operative pain	**Erhmann 2003**
ODONT-OPASTE®	Clindamycine hipochlorite Triamcinolone acetonide	+/some-	Odontopaste® > Ledermix® on *E. Faecalis* Odontopaste® > placebo on post operative pain under 24h	**Eftekhar 2013, Plutzer 2018**
TAP	Metronidazol Ciprofloxacin minocycline	anaerobic+/- +/- +/-	TAP > CH on *E. Faecalis* Good result on healing a periapical lesion Good result on a large cyst-like lesion TAP at least = CH +CHX 2% in AP	**Ozan 2005, Er 2007, Kim 2014 Taneja 2011, Dhillon 2014, Arruda 2018**
SEPTOM-IXINE FORTE®	Neomycin Polymyxin B sulfate Dexamethasone	- / some + - (except proteus group)	Not use nowadays	**Karim 2007**

PULPO-MIXINE®	Framycetin Polymyxin B sulfate Dexamethasone	aerobic – / some aerobic + - (except proteus group)	Not use nowadays	**Karim 2007**