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Analysis of the most commonly used clinical protocols in regenerative endodontic treatment

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Abstract

Introduction: Regenerative endodontic treatment (RET) does not yet have a well-established clinical protocol. Objective: The aim of this study was to carry out a scoping review of the RET clinical protocols described in the literature. Methodology and resources: The question used was: "What are the differences among published RET protocols and which are the most widely used?" The search was carried out in the Lilacs, BVS, PubMed, and Scielo databases. Studies reporting on pulp revascularization protocols published in the last ten years were included. Results and discussion: Seventy-four studies met the inclusion criteria. Most of the studies used sodium hypochlorite (NaOCl) as an auxiliary substance, either alone or in combination with other substances; however, the concentration of NaOCl used in the protocols varied greatly (between 0.5% and 6%). In more than 90% of the studies, treatment was carried out in 2 or 3 sessions, with intervals between sessions that ranged from 24 hours to 4 weeks. The most used intracanal medication was triple antibiotic paste, followed by calcium hydroxide. Blood clots were the most used type of scaffold, mineral trioxide aggregate (MTA) was the most used material for cervical sealing, and composite resin was used for coronal shielding. Conclusions: Performing the technique over multiple sessions, using triple antibiotic paste as intracanal medication, blood clot as a scaffold, and MTA for cervical sealing are some of the most common characteristics and materials found in clinical protocols for RET.

Keywords: Clinical protocols; Regenerative Endodontics; Dental Trauma; Permanent Dentition.

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Introduction

The presence of pulp necrosis in teeth with incomplete root formation represents a clinical challenge for endodontic specialists. Following the occurrence of pulp necrosis, the development of the canal walls is interrupted, resulting in teeth with incomplete root maturation. These teeth are characterized by thin root dentin walls that are susceptible to fractures, even under normal physiological stress conditions, as well as a wide-open apex, which represents a complication for endodontic treatment.[1,2]

The conventional approach to these cases has been to apply the apexification technique. This technique can be carried out in two ways: the first and most widely used technique involves cleaning and filling the root canal with a temporary calcium hydroxide-based paste

to stimulate the formation of calcified tissue at the apex.[3,4,5] The second technique is carried out by placing an apical plug composed of mineral trioxide aggregate (MTA) to act as a barrier against the condensed gutta-percha.[6]

Regenerative endodontic treatment (RET), also called pulp revitalization or pulp revascularization, has emerged as an alternative technique for the treatment of pulp necrosis in teeth with incomplete root formation with the aim of improving their prognosis. The concept of "endodontic regeneration" is recognized by the American Association of Endodontists (AAE), regardless of whether the result of the application of the protocols is actually “regeneration” or “repair”.[7,8] This therapy can be conducted in two different ways: through the cultivation of stem cells and their subsequent transplantation into the root canal or through the stimulation of free cells with chemotactic capacity.[9] For a long time, it was believed that the RET technique was ideally and practically restricted to young patients; however, as its use has expanded, it has also been applied to permanent and fully developed teeth.[10]

Several successful RET clinical protocols have been reported in recent years. A consensus exists as to the general principles of treatment, such as elimination of the infection, followed by the application of an intracanal medication, creation of a scaffold, and prevention of reinfection by sealing above the clot, as well as coronal shielding.[11] However, no standard protocol exists for this technique, which may inhibit its use.[9]

Bearing in mind that — although all RET protocols have the common objectives of disinfecting the root canal system and creating an environment that promotes the growth and differentiation of mesenchymal cells, as well as restoring function —, the technique’s protocols are not yet fully established,[12] the aim of this study was to carry out a scoping review of the clinical RET protocols described in the literature.

Methodology

The question that guided this study was: “What are the differences among the published RET protocols and which are the most widely used?”. The studies included were selected using the PCC (Population, Concept and Context) mnemonic strategy, as recommended by the Joanna Briggs Institute (JBI) protocol. The population was defined as immature and mature human permanent teeth with pulp necrosis; the concept was defined as pulp revascularization protocols; and the context assigned was the differences between pulp revascularization protocols and which are the most used in immature and mature necrotic permanent teeth, published in the last 10 years.

The search was carried out in June 2023 on the Lilacs, Virtual Health Library (VHL), Pubmed and Scielo databases, using the following terms for the search strategy: “regenerative endodontics”, “pulp revascularization”, “tooth root” and “dental pulp necrosis” (Table 1). Platform filters were used so that only studies published in the last ten years were included. Duplicate studies were removed using EndNote Web.

The studies selected included randomized clinical trials; cross-sectional studies; longitudinal studies; and case reports on pulp revascularization protocols. Theses, literature reviews, dissertations, monographs and publications that could not be accessed were excluded. The title, abstract and type of study were screened by two independent examiners using the Rayyan web application. The selected abstracts were then screened again by two independent examiners who read the files in full. In cases of disagreement, a third examiner was consulted.

Regarding the general characteristics of the articles, the following data were extracted: year of publication, population and sample size (when applicable), type of study, objective and results. With regard to the specific characteristics of the clinical revascularization protocol described, the following data were extracted: auxiliary chemicals, number of sessions, interval between sessions, intracanal medication/disinfection, framework, cervical sealing and coronal shielding. These data were grouped to identify the general and specific information related to each study, as recommended by the Joanna Briggs protocol (2015). The data collected were analyzed and interpreted based on previously established criteria.

Table 1. Number of studies found in each database.

Database	Search strategy	Studies
BVS	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) AND (dental pulp necrosis)	36
BVS	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	131
BVS	(regenerative endodontics) OR (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	345
SCIELO	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) AND (dental pulp necrosis)	0
SCIELO	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	4
SCIELO	(regenerative endodontics) OR (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	12
PUBMED	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) AND (dental pulp necrosis)	11
PUBMED	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	475
PUBMED	(regenerative endodontics) OR (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	585
LILACS	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) AND (dental pulp necrosis)	6
LILACS	(regenerative endodontics) AND (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	9
LILACS	(regenerative endodontics) OR (pulp revascularization) AND (tooth root) OR (dental pulp necrosis)	30
	TOTAL	976

Source: The authors (2024).

Results

The chosen search strategy resulted in 976 articles (Table 1). Of these, 394 duplicates were removed. The remaining 582 files were screened by reading the title, abstract and type of study, as a result of which 91 articles were selected. Out of these, 17 articles were excluded because they did not describe a clinical protocol for pulp revascularization. Finally, 74 articles were included in the review (Figure 1)

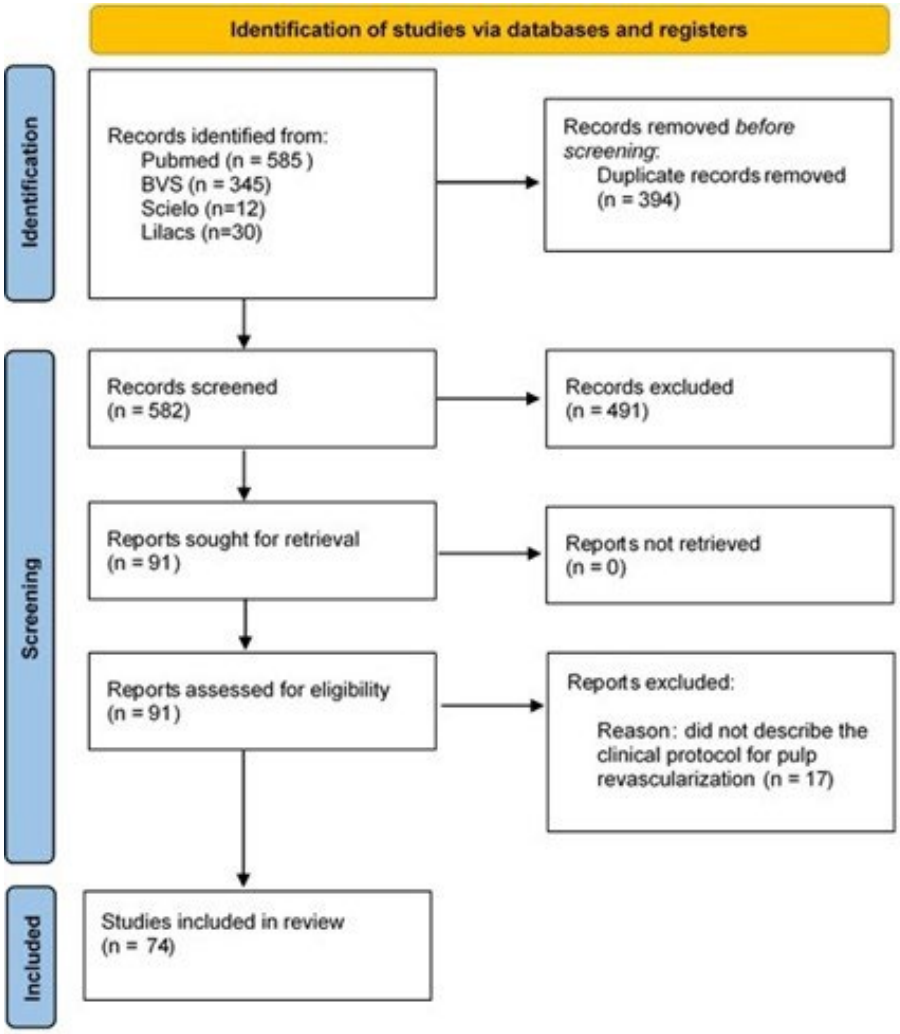

Figure 1. Flow diagram of the search.
Source: The authors (2024).

Analysis of the general characteristics of the selected studies in terms of year of publication found that around 62% of the studies were published in the last five years. With regard to the type of study, case reports and case series accounted for 74.3% of the publications. Prospective or retrospective clinical studies accounted for around 12.2% of all publications and their samples ranged from 10 to 116 treated teeth. Randomized clinical trials accounted for 13.5% of the studies and their samples ranged from 15 to 66 patients (Table 2).

With regard to the specific characteristics described in the RET protocols in terms of the auxiliary chemical substances used, the authors chose to use only hypochlorite as an irrigating solution in 13.5% of the articles. Other auxiliary chemical substances were mentioned during the chemical decontamination procedure, either in combination with hypochlorite or as a substitute. Among the substances most used in combination with hypochlorite was saline solution, found in 27% of the studies. In addition to this combination of saline solution and hypochlorite, the use of ethylenediaminetetraacetic acid (EDTA) was found in 27% of the articles. Some authors used only sodium hypochlorite and EDTA (18.9%) and a combination of sodium hypochlorite, saline solution, and chlorhexidine was cited in two articles, to which EDTA was also added in two studies (Table 3).

Table 2. General characteristics of the articles

Variable	Results
Year of publication 2013 to 2017 2018 to 2023	 28 (37.8%) 46 (62.2%)
Type of study Case reports or case series Prospective or retrospective studies	 55 (74.3%) 9 (12.2%)
Randomized clinical trials	10 (13.5%)

Source: The authors (2024).

Table 3. Specific characteristics of the RET protocols described

Features	Number of studies (%)
Auxiliary chemicals	
NaOCl only	10 (13.5%)
NaOCl + saline solution	20 (27.0%)
NaOCl + saline + EDTA	20 (27.0%)
NaOCl + EDTA	14 (18.9%)
NaOCl + saline + chlorhexidine	2 (2.7%)
NaOCl + saline + chlorhexidine +EDTA	2 (2.7%)
NaOCl + chlorhexidine	1 (1.4%)
NaOCl + other substances	3 (4.1%)
Saline only	2 (2.7%)
Sodium hypochlorite concentration	
NaOCl 1.0%	9 (12.2%)
NaOCl 1.5%	15 (20.2%)
NaOCl 2.5%	17 (23.0%)
NaOCl 5%	5 (6.7%)
NaOCl 5.25%	19 (25.7%)
Other concentrations (0.5%, 2%, 3%, 4%, 6%)	11 (14.9%)
Number of sessions	
Single session	2 (2.7%)
Two sessions	40 (54.0%)
Three sessions	32 (43.3%)
Interval between 1st and 2nd sessions	
Four weeks	18 (25.0%)
Three weeks	26 (36.1%)
Two weeks	12 (16.6%)
A week or less	9 (12.5%)
Not informed	7 (9.8%)
Interval between 2nd and 3rd sessions	
24 hours	10 (31.2%)
From 48 to 96 hours	8 (25.0%)
One week	9 (28.1%)
Two weeks or more	3 (9.4%)
Not informed	2 (6.3%)
Intracanal medication	
Metronidazole + minocycline + ciprofloxacin	34 (46.0%)
Metronidazole + ciprofloxacin	9 (12.2%)
Other combinations of antibiotics	10 (13.5%)
Calcium hydroxide only	13 (17.5%)
Combinations with calcium hydroxide	4 (5.4%)
Did not inform or did not use	4 (5.4%)

Source: The authors (2024).

Table 3. Specific characteristics of the RET protocols described (cont.)

Features	Number of studies (%)
Frame type	
Blood clot only	43 (58.1%)
PRF only	17 (23.0%)
PRP only	4 (5.4%)
Clot + PRF or PRP	6 (8.1%)
Other variations	4 (5.4%)
Cervical sealing	
Traditional MTA	40 (54.0%)
White MTA	16 (21.6%)
White MTA + collagen matrix	6 (8.1%)
Other materials	11 (15.0%)
No cervical sealing	1 (1.3%)
Coronary shielding	
Composite resin	32 (43.2%)
IVC + composite resin	21 (28.4%)
CIV only	15 (20.3%)
Other materials	5 (6.8%)
Not informed	1 (1.3%)

Source: The authors (2024).

In one article, chlorhexidine was used together with sodium hypochlorite, and in another article, together with EDTA. The following combinations were also used in only one publication each: sodium hypochlorite and hydrogen peroxide; sodium hypochlorite, saline solution, EDTA and distilled water; sodium hypochlorite, saline solution, EDTA, chlorhexidine, 5% sodium thiosulfate, 5% Tween 80 and 0.07% soy lecithin. In two publications, only saline solution was used as an auxiliary irrigating substance (Table 3).

The concentrations of sodium hypochlorite used in the protocols described showed a predominance of the 5.25% concentration, which was used in 25.7% of the publications. A 2.5% concentration was used in 23% of the studies, a 1.5% concentration in around 20%, and a 1% solution was mentioned in around 12% of the publications. Sodium hypochlorite at 5% was mentioned in 6.7% of the articles. The 3% and 0.5% concentrations were used in 4 studies each, while the 2%, 4% and 6% concentrations were mentioned in only one study each. Five studies tested two of the hypochlorite concentrations mentioned above. Two studies did not use sodium hypochlorite, and one did not state the concentration used (Table 3).

With regard to the number of sessions carried out, most studies described the procedure as being conducted in two (54%) or three sessions (43.2%). In 25% of the studies, the interval between the first and second sessions lasted four weeks. Three-week intervals were mentioned in 36.4% of the articles, 16.6% preferred a two-week interval and 11% chose to wait just one week between sessions. In only one study did the authors opt for a 48-hour interval (Table 3). Among the articles where the protocol was carried out in three sessions (32 studies), the 24-hour interval was the most used, being mentioned in 31% of the studies. The one-week interval was the second most cited (28.0%). Intervals of 48 hours, 72 hours or 96 hours were mentioned in 25% of the studies. Another 9.3% chose to wait two weeks or more. Two studies did not report the length of the second interval (Table 3).

The most prevalent procedures described used triple antibiotic paste (metronidazole, minocycline and ciprofloxacin) as intracanal medication, being present in 46% of the articles. The use

of doxycycline as a substitute for minocycline was noted in 2.7% of the studies, while clindamycin, cefaclor, spiramycin and amoxicillin were used as substitutes for minocycline in one article each. Use of a double antibiotic paste (metronidazole and ciprofloxacin) was recommended in 12.1% of the articles. In one publication, double antibiotic paste and zinc oxide were used in combination, while a combination of tetracycline and cortisone was used as medication in another study (Table 3).

Calcium hydroxide was used as an intracanal medication in 17.5% of the publications, as well as in association with 2% chlorhexidine in 2.7% of the studies. The combination of calcium hydroxide, 0.12% chlorhexidine and zinc oxide was used in only one article. Odontopaste, which is a combination of calcium hydroxide, clindamycin hydrochloride 5% and triamcinolone 1%, was also used in one study. Other disinfection methods that do not qualify as intracanal medication were mentioned, including photoactivated light and a perovskite laser, which were mentioned in one article each (Table 3).

With regard to the framework used in the regenerative procedure, blood clot stimulated by over instrumentation was chosen in the vast majority of protocols. In 43 studies (58.1%) only blood clot was used; in four studies, the clot was supplemented with fibrin-rich plasma (PRF); in one study there was a combination of clot and platelet-rich plasma (PRP); and in another the authors used a combination of blood clot and Gengigel. PRF and PRP were also used by themselves, PRF in 23% of the studies and PRP in 5.4%. Other scaffold variations were mentioned in the studies, including the use of collagen as a scaffold in two studies (2.7%), while hydroxyapatite and amniotic membrane were used in one study each (Table 3).

Another aspect subject to analysis was the cervical sealant used. MTA was the most commonly used material for this purpose, with traditional MTA being used in 54% of the studies. White MTA was the sealant of choice in 21.6% of the studies and was used in conjunction with collagen in 8% of the studies. Gray MTA was used in one study. Biodentine and Iroot BP are examples of other materials used for sealing the cervical region, having been selected in 5.4% and 4% of the publications, respectively. Iroot BP was also used in combination with collagen in one of the cases described, as was BC Sealer. Cem cement was used in two studies and only one study did not use cervical sealing in its protocol (Table 3).

Finally, coronal shielding is the last stage of the revascularization protocol and in 43.2% of cases the restorative material chosen was composite resin, followed by the use of glass ionomer cement (GIC) in around 28.3% of cases. GIC alone was also frequently cited, with this material being used on its own in 20.2% of the studies. Composite resin and Cavit were the materials used in 4% of the studies. In only one case was composite resin used in conjunction with zinc oxide, and eugenol and amalgam were also used in one study. In one of the publications, the authors did not inform which material was used for the shielding (Table 3).

Discussion

The number of studies included in this review and the predominance of case reports are evidence of the increasing popularity of the RET procedure. In addition, the progressive increase in the number of studies has promoted experimentation with new tools and materials, reflecting advances in protocols.

When analyzing the specific characteristics of the protocols mentioned in the studies, it can be seen that sodium hypochlorite (NaOCl) was used as the irrigating solution in more than 97% of

the RET protocols included. It is the main and most widely used irrigating solution substance for intraradicular canals, due to its antimicrobial activity and ability to dissolve tissue, as well as its deodorizing, whitening and lubricating action.[13] However, only 13% of the studies used only NaOCl; other auxiliary chemicals were mentioned during the chemical decontamination procedure.

Among the substances most commonly used in combination with hypochlorite is saline solution, which was found in 27% of the studies. The use of saline solution as an irrigant reduces the likelihood of allergic reactions to NaOCl and its interactions with other substances used in the treatment; however, this agent does not have any chemical disinfection properties, it acts solely mechanically and is susceptible to contamination.[14]

EDTA was also used in some protocols, either in addition to the combination of saline solution and hypochlorite (25.6%) or with NaOCl alone (18.9%). The use of EDTA is common in dentistry and it is the most widely used chelator, used to dissolve inorganic material. In regenerative procedures, it is capable of increasing the adhesion and differentiation of dental pulp stem cells and neutralizing the cytotoxic effects of sodium hypochlorite.[15,16]

Chlorhexidine was also added to the disinfection protocol in combination with hypochlorite, serum and/or EDTA in five of the studies analyzed. Chlorhexidine is one of the substances that has been mentioned in regenerative endodontics protocols, and has also been widely used in conventional endodontics, since it has broad-spectrum antibacterial activity and high substantivity, as well as the ability to suspend debris, although it has the disadvantage of not acting in tissue dissolution.[17]

Another important piece of information about the disinfection stage of the canals refers to the concentration of sodium hypochlorite used; among the studies analyzed, this concentration varied between 0.5% and 6%. In the protocols described, around a quarter of the studies used a hypochlorite concentration of 5.25%, which can be justified because of its greater antibacterial efficacy in comparison to other concentrations.14 A 2.5% concentration was used in 23% of the studies, a 1.5% concentration in 20%, and a 1% concentration was mentioned in 12% of the publications. The choice of lower concentrations of sodium hypochlorite is aimed at reducing its cytotoxic effect.[14]

With regard to the number of sessions performed, a significant predominance of the cases described procedures that lasted two or three sessions, indicating a preference for an interval when using intracanal medication in the RET procedure. This pattern is in line with the findings of Botero *et al.*,[18] who demonstrated a 33% success rate for single-session RET, compared to a 71% success rate when there was a break in the procedure.

The protocols that were conducted in multiple sessions showed variations in the length of each interval. Regarding the interval between the first and second sessions, which represents the period of exposure of the root dentin to intracanal medication, around two thirds of the protocols suggested an interval of four (25%) or three weeks (36%). It is important to note that prolonged exposure of root dentin to intracanal medication can result in changes to its structure, increasing susceptibility to fractures due to excessive demineralization and degradation of the collagen present in the dentin.[16]

The articles that opted to carry out the protocol in three sessions had a second interval between the procedures, now with the framework in the root canal. In these cases, more than 80% of the studies suggested that this interval should be less than 7 days, with a 24-hour

interval being the most used (31%). This interval was commonly used by the authors as a safety interval, prior to definitive restoration of the element, during which X-rays were taken to check for signs of interference in the procedure.[19,20,21]

With regard to intracanal medication, most authors (46%) used the triple antibiotic paste containing metronidazole, minocycline and ciprofloxacin. The current literature cites the triple paste recommended by Hoshino *et al.*[22] as the main intracanal medication in RET.[23,24,25] This combination of antibiotics demonstrates high antimicrobial efficacy and, when used in revascularization protocols, produces remarkable results in terms of the thickening of dentin walls.[25,26] Some authors made changes to the formulation of the triple antibiotic paste, either by the removal of minocycline or its replacement by other antibiotic agents, such as doxycycline, clindamycin, cefaclor, spiramycin and amoxicillin. This adjustment was probably motivated by the darkening of the dental crown associated with the use of minocycline.[24,25]

Calcium hydroxide was used as an intracanal medication in 17.5% of the publications, as well as being used in association with other agents, such as chlorhexidine, zinc oxide and clindamycin hydrochloride. Calcium hydroxide is an alkaline substance with a high pH level, which, when it comes into contact with fluids, dissociates into calcium and hydroxyl ions, providing it with antimicrobial properties. Due to these characteristics, it has been used as an intracanal medication in endodontics. In addition, evidence exists that suggests that its use in regenerative endodontics results in better apical closure performance compared to the use of triple antibiotic paste.[26,27,28]

With regard to the framework used in the regenerative procedure, the majority of protocols used blood clot stimulated by over instrumentation (scaffold) (71.6%). This phenomenon can be understood by the fact that it is a simple technique that does not require complex resources, just irrigants, intracanal medication and the framework formed by the blood clot stimulated in the apical region of the tooth. Although blood clot has been most commonly used, some authors have employed new techniques and a variety of framework materials, including PRF, PRP, collagen, hydroxyapatite and amniotic membrane.

With regard to the cervical sealer, MTA was the most common material used, either in traditional or white form. Since it is a biocompatible, bioinductive material with good marginal adaptation, MTA is an excellent choice for cervical sealing, as well as having a high pH, which gives it antibacterial action. One disadvantage of its use is that it can cause tooth discoloration.[27]

With regard to coronal shielding, which is the last stage of the RET protocol, the most prevalent restorative material was composite resin, followed by its use in conjunction with IVC. The materials used for this purpose need to maintain the seal of the root canals, as well as withstand the loads exerted on the restoration. Composite resins perform this function well, since they have excellent mechanical properties, such as surface smoothness and mechanical resistance, as do IVCs, which have a certain resistance, adhesion and marginal sealing.[29,30]

Finally, when analyzing the specific characteristics of the published protocols, no well-established protocol exists among the studies. Although all the techniques agree on disinfection without or with minimal mechanical instrumentation, the need for a framework, cervical sealing and coronary shielding, there is no standardization in terms of the number of sessions required, the interval between sessions, the chemical substances used for irrigation and the concentration of sodium hypochlorite. Therefore, new studies must be carried out in order to

ascertain the effectiveness of variations in protocols so that a single protocol can be better established, to continually seek the best clinical results.

In conclusion, studies show that RET is a procedure that is becoming more popular and new techniques and materials are being added to its protocol. Performing the technique over multiple sessions, using triple antibiotic paste as intracanal medication, blood clot as a scaffold, and MTA for cervical sealing are some of the most common characteristics and materials in the clinical protocols for RET.

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