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IS THERE A BEST ENDODONTIC TREATMENT FOR IMMATURE NECROTIC PERMANENT TEETH? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Is there a best endodontic treatment for immature necrotic permanent teeth? A systematic review and meta-analysis

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Abstract

Background: Dental trauma is a frequent finding in children or adolescents that commonly leads to pulp necrosis. As a consequence, the root stops its development and managing these immature teeth are challenging due to a presence of an open apex.

Aim: To systematically review the literature available to elucidate if there is a best endodontic treatment for immature necrotic permanent teeth.

Methods: The literature was screened via PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials databases until August 2015 to select randomized clinical trials that compared at least two different treatments regarding immature necrotic permanent teeth comprising clinical and radiographic success as outcome. A total of 648 studies were retrieved from the databases, in which only 14 were selected to full-text analysis by appliance of inclusion criteria. After exclusion criteria, the remaining 7 studies had their data extracted and assessed for bias risk. Two reviewers independently performed the screening and evaluation of the articles. Pooled-effect estimates were obtained comparing clinical and radiographic success rates among MTA vs other treatments and Blood Clot vs other regenerative procedures.

Results: MTA showed statistically significant better results when compared to other endodontic treatments ($p < 0.05$) regarding clinical and radiographic outcomes. On

the other hand, it was not found a significant difference when Blood Clot was compared to any other regenerative procedure.

Conclusions: Necrotic immature teeth endodontic-treated with MTA plugs still present more reliable results when compared to any endodontic treatment, despite that there is in promising tendency to regenerative approaches.

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Introduction

Dental trauma in children and adolescents can be frequently associated with pulp necrosis over time. The traumatized immature teeth with pulp necrosis have the root development interrupted, leaving wide-open apexes and fragile dentin walls that are difficult to manage with convectional endodontic treatments (1, 2).

Apexification has been frequently employed as an option of treatment in these cases, which allows the formation of a calcified barrier across the open apex, thus creating a suitable environment for endodontic filling and periapical tissues repair (3). Apexification can be achieved through periodic changes of Calcium Hydroxide (CH) pastes and MTA plugs.

Several studies (4-6) have assessed the performance of CH pastes, and they have pointed out some disadvantages, as causing very brittle dentinal walls and higher risks of root fractures (7, 8), besides the long-time required. In these sense, the placement of apical MTA plugs were proposed to overcome these difficulties. As advantages, it can be stated the biocompatibility, sealing ability and shorter time required in this technique. Moreover, due to formation of an artificial barrier immediate obturation can be achieved, which in turn, reduces the risk of root fracture (2, 9-11).

Recently, regenerative endodontic procedures (REPs) have been assessed and they are suggested as an alternative treatment to apexification. Regenerative procedures can be defined as a biological approach designed to maintain, restore or improve the function of damaged organs and tissues, including the pulp-dentin complex (12). It also allows the reestablishment of pulp vitality, which can be considered one of the greatest advantages over aforementioned procedures. The most widely used strategy in REPs is the induction of Blood Clot (BC) within the root canals, which acts as a scaffold for the revascularization (13). Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) are alternatives suggested as being potentially ideal scaffolds in regenerative procedures (14). However, they are more laboring when compared to BC since some additional steps are required.

Despite the increasing number of studies in regard to these endodontic treatments, no consensus concerning the best alternative to manage immature necrotic permanent teeth have been established. Therefore, this systematic review aimed to assess all randomized clinical trials related to the management of immature necrotic permanent teeth to elucidate what is the best endodontic treatment available in these cases.

Materials and Methods

Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA) (15) was followed to report this review, which were registered at the International Prospective Register of Systematic Review (PROSPERO) database (CRD42015025844).

Focused PICO question

The following focused question was developed in accordance with the recognized Patient, Intervention, Comparison and Outcome (PICO) format (16): "What is the best endodontic treatment employed in the management of immature necrotic permanent teeth in relation to the clinical and radiographic success?", where the Population were patients with immature permanent teeth with pulp necrosis; the Intervention was any endodontic treatment; the Comparison was designated after data extraction, because the authors intended to consider the most cited endodontic treatment in the screened studies as a control group; and the Outcome was clinical and radiographic success, considered separately.

Search strategy

A comprehensive literature search was conducted on MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials (http://www.clinicaltrials.gov) databases up to August 22nd, 2015. The following search strategy were used to explored the MEDLINE via PubMed database: ((((((((((((((((root canal therapy[MeSH Terms]) OR root canal therapy) OR Endodontics) OR Endodont*) OR Pulpectomy) OR Pulpect*) OR Revascularization) OR revitalization) OR Root maturation) OR Calcific barrier) OR Root strengthening) OR Regenerative endodontics) OR apexification[MeSH Terms]) OR Apexification*)) OR root canal treatment)) AND ((((((immature teeth) OR immature tooth) OR Immature dentition) OR Immature permanent teeth) OR Immature permanent tooth) OR Immature permanent dentition). Likewise, a sensitive search strategy was adapted for the other databases.

Eligibility criteria

The inclusion criteria of this review was: (1) study design: randomized clinical trials, (2) participants: patients with immature necrotic permanent teeth, (3) intervention: pulpectomy (pulpotomy cases were excluded), and (4) have assessed success by clinical and radiographic outcomes. On the other hand, an article was excluded based on the following criteria: evaluation of vital teeth presenting irreversible pulpitis (only teeth with diagnosed necrosis); teeth with previous treatment to necrosis; did not perform the outcome evaluation among, at least, two endodontic treatment; did not have a follow-up time of, at least, six months; studies with a dropout higher than 30% during the follow-up; or if it was a duplicate study (in this case, the most complete study was considered).

Study selection and data collection

Two reviewers (GFN and IGP) independently screened all of the titles and abstracts retrieved by the electronic search. Substantial agreement between reviewers in the study selection process was obtained, with a kappa score of 0.84. After, the same authors independently reviewed the full-text articles of the previous included studies, those that did not present any of the exclusion criteria were selected. Additionally, all references of the selected studies were manually screened for potentially relevant additional studies. Any possible discrepancies encountered during this process, i.e., inclusion or exclusion criteria, were resolved by discussion between the reviewers who selected the included studies. If a disagreement persisted, the judgment of a third reviewer (ROR) was considered decisive.

Data regarding the included studies were also independently extracted by the reviewers (GFN and IGP) based on a previously defined protocol including: year of publication, country, type of teeth (anterior or posterior teeth), presence of periapical

lesion, diagnosis of pulp necrosis, follow-up period after treatment, type of intervention performed as treatment, number of patients and teeth included in the randomized clinical trial and age of the patients.

Outcome measures

The primary outcomes measures were, separately, the clinical and radiographic success of the different endodontic treatment employed during the management of immature necrotic permanent teeth. Secondary outcome of interest was based on the formation of an apical barrier during the follow-up measurement. The success or failure were considered in a dichotomous way, based on the author's criteria previously defined in each study.

Quality and bias risk assessment

Two blinded reviewers (GFN and IGP) independently performed the quality assessment of the methodology of the included studies according to the revised recommendation of Cochrane Handbook for Systematic Reviews of Intervention (Version 5.1). The risk was estimated as follows: low risk of bias when all criteria were met; moderate risk when one or more criteria were partially met, and high risk of bias when one or more criteria were not met. There was no disagreement between the reviewers (kappa = 1.0).

Statistical methods for the meta-analysis

The meta-analysis was conducted using Review Manager Software version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) considering the random-effect model. Pooled-effect estimates were obtained by comparing the failure rate between groups. A *p-value* <0.05 was considered statistically significant (Z test). Statistical heterogeneity of the treatment effect (experimental endodontic treatment vs. control) among studies was assessed using Cochran's Q test, with a

threshold *p-value* of 0.1, and the inconsistency I^2 test, in which values greater than 50% were considered indicative of high heterogeneity.

Results

Study selection

Study selection flow diagram is shown in Figure 1. The literature search conducted yield 648 articles. After duplicates were removed, 640 studies remained to the inclusion criteria, which were applied upon titles and abstracts yielding a number of 11 studies. The references of these included studies were screened, and other three potential relevant articles were selected (17-19), which had their references again searched for additional studies, but none were identified. Thus, in the first phase, 14 potential studies were retrieved. Five studies were excluded because they did not perform the outcome evaluation between, at least, two endodontic treatments, e.g., compared two calcium hydroxide pastes in apexification (18, 20-23). One study was excluded because it was a duplicate (24). Another study was excluded because it was not an actual randomized clinical trial but rather a pilot study (25). After the exclusion criteria of all full-text articles, a total of 7 studies remained in the review (2, 17, 19, 26-29).

Studies characteristics

Characteristics of each included studies are summarized in Table 1. Publication year of the studies ranged from 2006 to 2015. In general, none differentiation was given to sex (male or female) and stage of root development in the patients that treatment was performed. Thus, all patients who had an immature necrotic permanent teeth meeting the inclusion criteria previously determined could be enrolled in the clinical trial. All endodontic treatments among included studies

were performed with a previous isolation under rubber dam to the management of these teeth.

In five studies, the authors performed treatments only in anterior teeth (2, 17, 19, 26, 28). One study did not specify in which teeth they performed endodontic treatment (29) and another study included incisors and premolars (27). Five of them included teeth regardless the presence of periapical lesions (2, 17, 27-29) and the other two studies (19, 26) did not specify if they included teeth with periapical lesions or not.

Six of the included studies (2, 17, 19, 26, 27, 29) performed the diagnosis of pulp necrosis by, at least, clinical and radiographic exam and just one study did not clarify what strategy was used to assess dental necrosis (28). All of them follow the cases for at least 6 months after the treatment.

The patients included in the clinical trials have ages ranged from 6 to 20 years. At least 15 patients were included and a minimum of 20 teeth was evaluated in the randomized clinical trials. Thus, patients could have more than one immature tooth with pulp necrosis in which apexification or revascularization was performed.

The clinical and radiographic outcome was performed blindly in five studies (2, 26-29) whereas one study the examiners knew what treatment they performed in each group (17) and the other (19) the authors did not clarify if the blinding was performed. In all of the included studies, the authors did not mention whether the patients were aware of the treatment performed or not, with the exception of one study (17) that stated patients being aware of what treatment they received.

Quality and risk of bias assessment

Only one study were considered at high risk of bias (17), while the others were considered at moderate risk of bias, mainly because they did not specify if the patients

were blinded to the treatments or if the authors performed the reliability test (Kappa) on the outcome evaluations.

Meta-analysis

The comparisons were performed first considering MTA as a control treatment and any other treatments as experimental treatment (CH, PRP, PRF or bFGF). Likewise, it was compared BC (control) with the other REPs (experimental, PRP, PRF or bFGF) to evaluate what is the endodontic treatment with the best outcome within these groups. MTA was chosen to be our control as in six out of seven studies, it was the most cited endodontic treatment, even in the revascularization studies, it was preferred by the authors rather than CH pastes. Some of studies compared more than two endodontic treatments, and therefore, in these cases it is displayed in the meta-analysis each treatment as an independent study.

When the MTA as endodontic treatment was compared, the values of Cochran's Q and Z test were < 0.05 showing statistically significant differences between groups, favoring the control group (MTA plug) when the clinical and radiographic outcomes were compared, and the I^2 test was 0%. Contrary, when apical closure was evaluated there were no statistically significant differences between groups. Although, Narang et al. (2015) and Pradhan et al. (2006) were included in the meta-analysis they did not effective affected the odds ratio calculation, as a pre-requisite to be included in the statistical analysis is to have reported, at least, one failure among treated groups.

When the Blood Clot was compared, the values of Cochran's Q and Z test were > 0.05 showing no differences between groups, when clinical and radiographic outcomes and apical closure were evaluated, and the I^2 test was 0%.

Discussion

In dental practice, trauma or caries affecting immature teeth are common findings faced by practitioners. These conditions can lead to a loss of tooth vitality, and consequently, endodontic treatment is required. The management of these teeth can be considered a challenge situation, since is difficult to perform the mechanical preparation on the fragile dentin walls and reach hermetic sealing in open apexes. There are an increasing number of studies (6, 11, 30-32) evaluating either CH and MTA plugs or REPs on the management of immature necrotic permanent teeth. This systematic review aimed to compare all endodontic treatments available to manage these conditions. Based on the meta-analysis, the placement of MTA plugs is the best endodontic treatment available at the moment in such cases.

In the literature, Calcium Hydroxide is considered the gold standard to induce apexification in immature permanent teeth. Nevertheless, as changes of CH pastes until apical closure are usually time consuming and demand more number of sessions, which can lead to root fracture in the course of treatment, other alternatives have been proposed to overcome these difficulties. The biocompatibility of MTA and its high success rates reported in the studies (2, 9, 26) has encouraged its use in immature necrotic teeth. In the researches included in this review, six out of seven compared MTA with other endodontic treatments, either CH or regenerative endodontic procedures (REPs), whilst only four studies used CH as control. Based on these findings, we support the rationale of MTA choice over CH to be considered our control in the meta-analysis.

Narang et al. (2015) compared MTA with REPs (BC, PRP and PRF) in 20 patients either with or without periapical lesions over a period of 18 months. The authors divided these patients in four groups (n = 5), which could be a possible

limitation of the study, as an adequate sample size is desirable to detect some differences, if they exist, between treated groups (adequate power in the study). Nevertheless, they found that in terms of clinical success, all treatments had results considered, according to author's criteria, as excellent, but when peripical healing was evaluated radiographically, MTA and PRF groups showed excellent or good results. On the other hand, BC and PRP groups showed fair results in 40 and 20% of the cases, respectively. The authors also evaluated root lengthening, and reported that 99% of PRF cases showed excellent results with statistically significant differences (P = 0.002) in relation to BC and PRP groups (60% of cases with fair results). It is important to consider that there are no unsuccessful cases in any group regarding clinical outcomes and then, this study was not included on odds ratio estimation despite being included on meta-analysis. Nagy et al. (2014) also compared MTA with REPs (BC and BC + bFGF) being evaluated in 29 patients with or without periapical lesions in 18 months. The authors found a clinical and radiographic success of 100%, 90% and 80% to MTA, BC and BC+bFGF, respectively. They also observed an increase in root lengthening and root thickness in BC and BC + bFGF with no statistically significant differences among groups; however, no changes were observed for the MTA group. The last study included evaluating REPs was conducted by Bezgin et al. (2015) who compared BC and PRP in 18 patients. It was the only study that included premolars among the randomized clinical trials. Thus, carious teeth were also evaluated with or without periapical lesions over the follow up period. They found that clinically both groups had similar results (100% of success rates), but radiographically BC groups had one tooth exhibiting enlargement of a preexisting periapical pathology, and consequently, was judged as failure, whereas no failure was observed in PRP groups. Interestingly, the authors observed that 7 teeth had a

positively response regarding vitality (PRP, 5; BC, 2) with $P > 0.05$, which can be an advantage over conventional endodontic treatments, MTA or CH pastes. The authors also compared radiographic root areas in both groups and observed an increase in 12.6% and 9.86% for BC and PRP groups, respectively ($P > 0.05$). It is important to state that all REPs studies included in this review performed intracanal medication with triple antibiotic pastes, which can provide discoloration among treated teeth. As additional investigation, we performed a separate meta-analysis to elucidate if there is a best endodontic procedure among REPs groups. Regarding clinical and radiographic success (with or without considering apical closure) there was no statistically significant differences among BC (control) or experimental groups (PRP, PRF or BC+bFGF). Despite one study (27) stated that PRP had higher rates of teeth with vitality reestablishment, BC is an easier procedure to be conducted. Therefore, while there is little evidence regarding well-conducted randomized clinical trials evaluating REPs, the induction of blood clot can be chosen as a treatment of choice in the management of necrotic immature teeth instead of PRP or PRF.

Four of the included studies compared MTA and CH paste. Bonte et al. (2015) evaluated 30 patients over a period of 12 months finding that MTA and CH clinically have a success rate of 100% and 73.3%, respectively. Radiographic success was obtained in 93,3% of MTA groups and 80% of CH groups. Noteworthy, four out of 15 teeth in CH groups had cervical root fractures, which can be considered the main disadvantage of periodic changes of CH pastes. Damle et al. (2012) evaluated 20 patients in 12 months finding 100% of success for MTA and 93.3% for CH both in clinical and radiographic outcomes. This was the only study among the seven included ones that performed irrigation with normal saline solution instead of Sodium Hypochlorite. Pradhan et al. (2006) evaluated monthly 16 patients over a period of 11

months and observed 100% of clinical and radiographic success rates for both groups, but they reported that the time taken for the management from the beginning of the treatment until the gutta-percha placement was significantly less for MTA when compared to CH (MTA, 0.75 ± 0.49 months; CH, 7± 2.5 months). El Miligy and Avery (2006) evaluated 15 patients in 12 months, either in traumatized or carious teeth, observing a 100% of clinical and radiographic success rates for MTA groups, whilst a percentage of 86.6% for CH, in which two out of 15 teeth presented tenderness to percussion and an increasing in periapical radiolucency (same two teeth).

It is important to state that all randomized clinical trials included in this systematic review evaluated both clinical and radiographic outcomes over a short period of time and in considerably few numbers of patients, and therefore, different results could be observed over longer periods of follow-ups or greater sample sizes. Also, only one study (2) performed the allocation concealment by an external person, whereas the others did not state clearly whether it was performed or not, which could lead to bias regarding treatments performed. Moreover, two studies (26, 28) did not stated clearly how randomization was performed and two (17, 27) did inadequately the randomization process. Noteworthy, five studies were considered at moderate risk of bias, mainly because the patients were not blindly to which treatment they received and any interexaminer reliability evaluation was done. Two studies were classified at high risk of bias. Another possible limitation is concerned to the evaluation criteria used on the randomized clinical trials included, as there is no consensus regarding the criteria used (lack of a unique criterion in each outcome) to evaluate clinically and radiographically the success rates among the studies. It is noteworthy that the American Association of Endodontics recently suggested the follow-up parameters

for clinical and radiographic exam and also the goals to be achieved with the regenerative procedures. Within these recommendations, the follow up suggested was 24 months, which among the included studies was not evaluated and could lead to an overestimation of the results. No evidence of heterogeneity, except for the outcome apical closure using MTA as control treatment, was detected among the present studies. This homogeneity could be attributable to the use of strict eligibility criteria in the selection of the studies, few methodological differences and dichotomous outcomes.

To extent of our knowledge there is only one systematic review and meta-analysis (33) evaluating immature necrotic permanent teeth. Nevertheless, the authors included only two studies and compared only MTA and CH to evaluate the outcomes. Therefore, this is the first systematic review and meta-analysis that compared REPs as an alternative in the management of immature necrotic permanent teeth. Based on the meta-analysis, MTA plugs are the best endodontic treatment regarding the management of these teeth, which provide a satisfactory outcome in less operative time, and consequently, it may be considered the "new" gold standard. Regenerative endodontic procedures are promising techniques, mainly because of its possibility of reestablishment of pulpal vitality and reinforcement of dentin walls, based on the growth and development of cells and vascularization. There is still a need of long-term and well-conducted randomized clinical trials with larger sample size to consolidate these REPs and definitively indicate their use.

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Table 1. Detailed characteristics of the included studies in the systematic review

Study	Narang et al	Bezgin et al	Bonte et al	Nagy et al	Damle et al	El Meligy & Avery	Pradhan et al
Year	2015	2015	2015	2014	2012	2006	2006
Country	India	Turkey	France	Egypt	India	Egypt	India
Type of teeth	Anterior (?)*	Incisors and Premolars	Anterior	Anterior	Anterior	Anterior	Anterior
Periapical Lesion	With or without	With or without	With or without	With or without	Did not specify	Did not specify	With or without
Diagnosis of pulp necrosis	Dental history, clinical and radiographic exams	Dental history, clinical and radiographic exams	Clinical and radiographic exams	Dental history and radiographic exams	Clinical and radiographic exams	Clinical and radiographic exams	Clinical and radiographic exams
Outcome assessment	6 and 18 months	18 months	6 and 12 months	3, 6, 12 and 18 months	1, 3, 6, 9 and 12 months	3, 6 and 12 months	11 months**
Type of Intervention	MTA, BC, PRP and PRF	PRP and BC	MTA and CH	MTA, BC and BC+bFGF	MTA and CH	MTA and CH	MTA and CH
Patients* (number)**	20	18	30	29	20	15	16
Teeth* (number)**	20	20	30	29	30	30	20
Age	Lower than 20 years	7-13 years	6-18 years	9-13 years	8-12 years	6-12 years	8-15 years

*Authors did not specify whether only anterior teeth were treated or not
**Authors performed outcome assessment monthly
***The final number of patients and teeth were considered after dropout

Table 2. Quality and risk of bias assessment of in included studies

	Adequate random sequence generation?	Allocation concealment?	Blinding of participants and personnel?	Blinding of outcome assessment?	Free of incomplete outcome data?	Free from baseline imbalance?	Adequate reliability?
Narang et al., 2015	+	?	?	+	+	+	?
Bezgin et al., 2015	-	?	?	+	+	+	+
Bonte et al., 2015	+	+	?	+	+	+	+
Nagy et al., 2014	?	?	?	+	+	+	?
Damle et al., 2012	+	?	?	?	+	+	?
El Miligy & Avery, 2006	?	?	?	+	+	+	?
Pradhan et al., 2012	-	-	-	-	+	+	+

+ criteria totally met, ? criteria partially met, - criteria not met

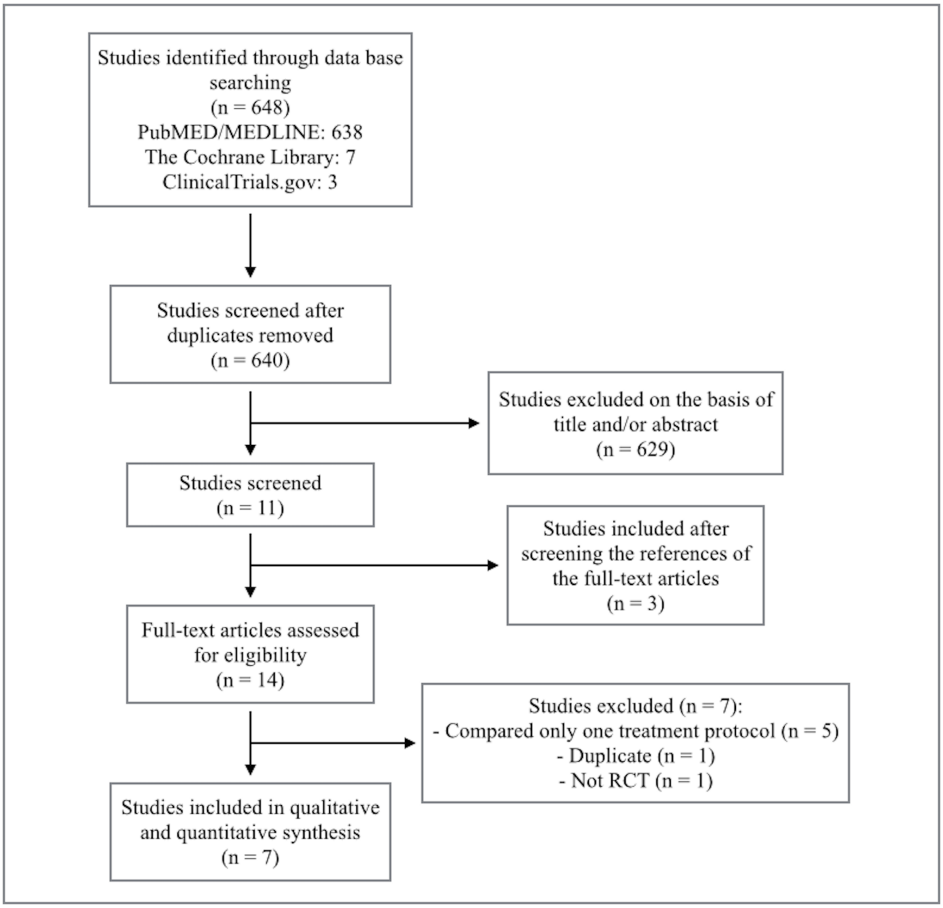

Figure 1. Flowchart of studies selection according to PRISMA statement

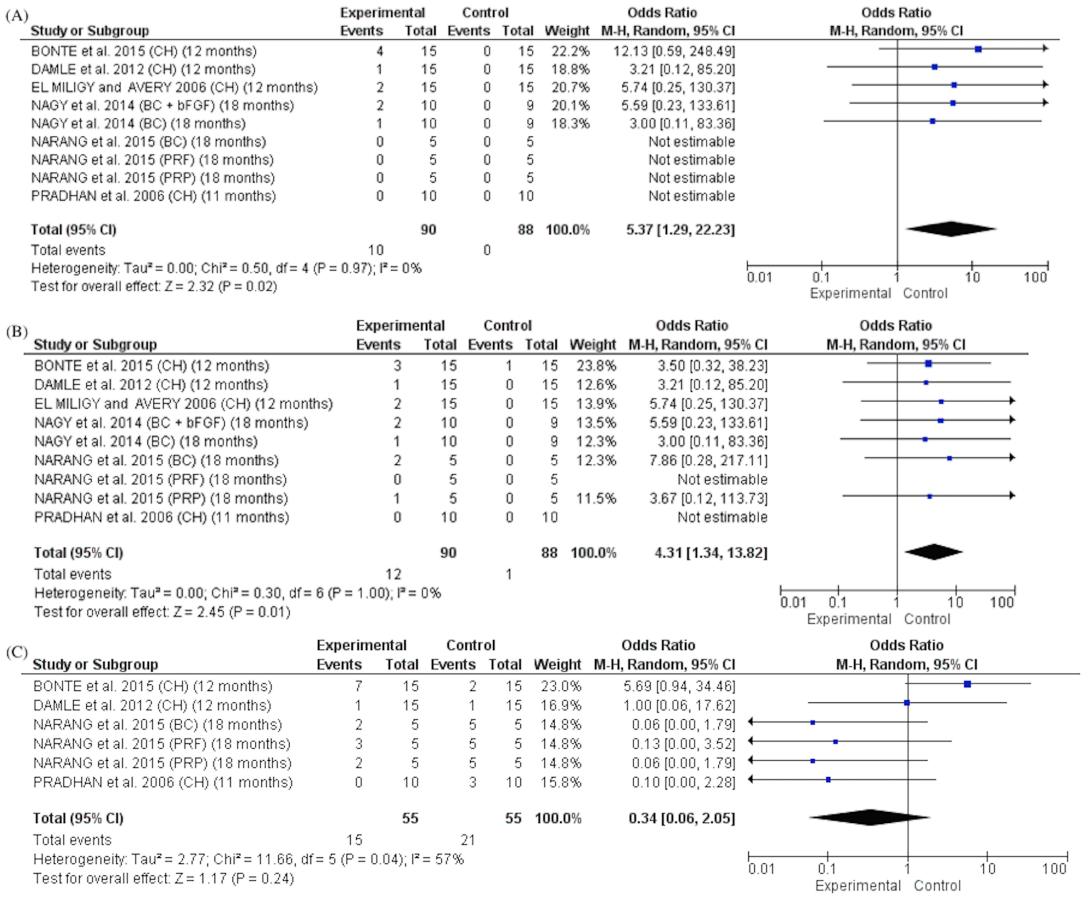

Figure 2. Forest plots of overall (a) clinical success, (b) radiographic success and (c) apical closure when MTA was considered control group.

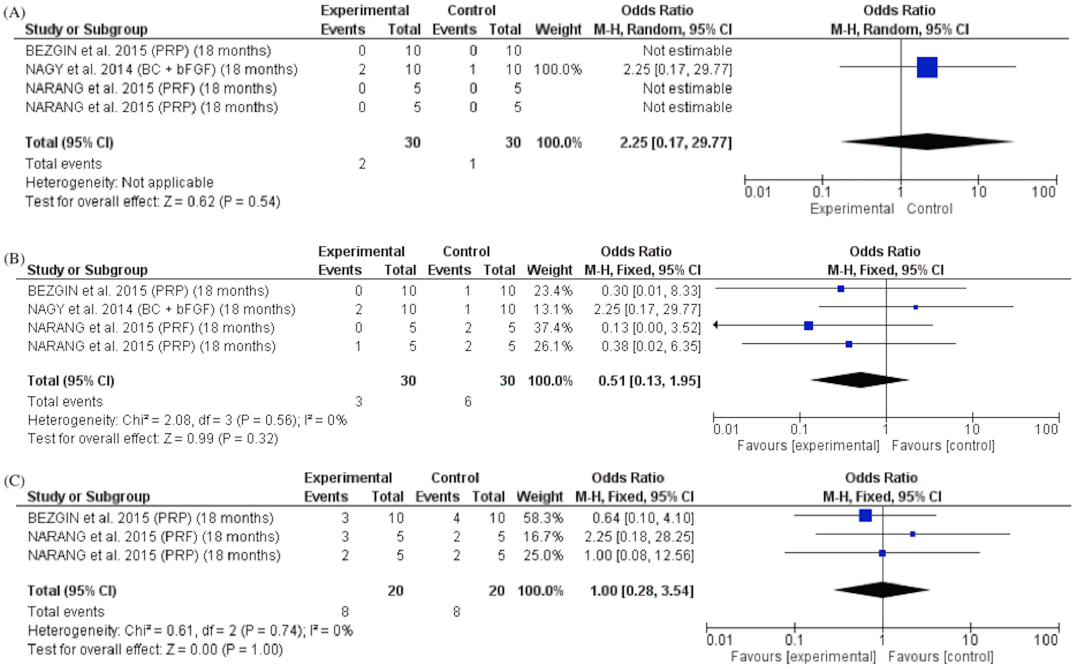

Figure 3. Forest plots of overall (a) clinical success, (b) radiographic success and (c) apical closure when Blood Clot was considered control group.