Pulp Revascularization or Apexification for the Treatment of Immature Necrotic Permanent Teeth: Systematic Review and Meta-Analysis

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This systematic review and meta-analysis assessed clinical, radiographic and functional retention outcomes in immature necrotic permanent teeth treated either with pulp revascularization or apexification after a minimum of three months to determine which one provides the best results. The literature was screened via PubMed/MEDLINE and Embase databases up to June 2017 to select observational studies that compared pulp revascularization and apexification treatments assessing clinical, radiographic and functional retention outcomes. Two reviewers independently performed screening and evaluation of articles. A total of 231 articles were retrieved from databases, wherein only four articles were selected for full-text analyses. After exclusion criteria, three studies remained in quantitative and qualitative analyses. Pooled-effect estimates were obtained comparing clinical and radiographic outcomes ('overall outcome') and functional retention rates between apexification and pulp revascularization treatment. The meta-analysis comparing apexification vs. revascularization for 'overall outcome' (Z=0.113, p=0.910, RR=1.009, 95%CI:0.869-1.171) and functional retention rates (Z=1.438, p=0.150, RR=1.069, 95%CI:0.976-1.172) showed no statistically significant differences between the treatments. All studies were classified as high quality. The current literature regarding the clinical, radiographic and functional retention outcomes in immature necrotic permanent teeth treated either with pulp revascularization or apexification is limited. Based on our meta-analysis, the results do not favor one treatment modality over the other.

***Keywords**: Pulp revascularization, apexification, immature necro*tic *permanent teeth*

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INTRODUCTION

Pulp necrosis in children and adolescents, mainly due to trauma or caries, may arrest permanent tooth root development, resulting in thin dentinal walls, wide-open apexes and inadequate crown-root ratio[1,2]. These features may hamper the endodontic treatment, and its protocol for cleaning, shaping and filling root canals must be modified[3,4].

Traditionally, apexification has been employed as a treatment option for immature necrotic permanent teeth. Calcium hydroxide (CH) apexification requires long-term intracanal medication aiming to stimulate the formation of an apical calcified barrier, which may be time-consuming and enhance the incidence of root fracture. On the other hand, placement of mineral trioxide aggregate (MTA) apical plugs reduces the number of treatment sessions because there is a possibility to perform immediate obturation, and thus, may provide some advantages and more successful outcomes over CH apexification. However, neither CH nor MTA apexification promote additional root development, leaving fragile dentinal walls[3,5] that may eventually lead to tooth fracture over time. Is such conditions,

tooth extraction[5-7] is likely to be indicated affecting occlusal function, esthetic and self-esteem in young patients.

Other endodontic treatments, named as "regenerative endodontics", "pulp revascularization" or "revitalization" have been suggested. These techniques offer the possibility of additional root development, which is aimed to reduce the incidence of root fracture over time. The European Society of Endodontology (ESE) statement indicates that "pulp revitalization" is an alternative to apexification in properly selected cases, since a growing body of evidence shows clinical feasibility of this approach[8]. According to the American Association of Endodontics (AAE)[9], "pulp revascularization" is the first treatment option for immature necrotic permanent teeth that has incomplete root development (length) and wide-open apex. Pulp revascularization treatment consists basically of root canal chemical disinfection with irrigating solution and intracanal medication followed by blood clot (BC) induction, MTA coronal seal and placement of crown restoration[10]. BC induction is the most frequently technique employed, however, there are other pulp revascularization techniques, e.g., platelet rich-plasma (PRP) and platelet rich-fibrin (PRF), despite the results of these techniques showing similar outcomes to BC[11].

Regardless of the treatment performed, the endodontic success of these immature teeth should be assessed based on the remission of clinical signs and symptoms and resolution of periapical radiolucency[11]. Despite this formerly assessed outcomes, functional tooth retention is an outcome important to be considered, specifically in young patients, because before the age of eighteen, they may not choose to have dental implants if needed, as a proper maxillary and mandibular bone development is mandatory.

Recently, a systematic review of randomized clinical trials[11] reported that MTA apexification is likely to result in higher clinical and radiographic success rates than other endodontic treatments in immature necrotic permanent teeth. However, most of the included articles were considered of moderate and high bias risk, and did not evaluated the functional retention of treated teeth. In fact, randomized clinical trials may provide strong evidence on decision making regarding different treatments, but these controlled settings are likely to hamper extrapolation of the studies' results to daily clinical practice[12]. Hence, a systematic review of well-constructed observational studies is also important to be conduct because there is a tendency that the studies' results to be closer to practitioners' clinics reality.

To date, there is no systematic review and meta-analysis that screened observational studies regarding pulp revascularization and apexification treatment. Therefore, the aim of this systematic review and meta-analysis was to assess the clinical, radiographic and functional retention outcomes in immature necrotic permanent teeth treated either with pulp revascularization or apexification after a minimum of three months to determine which one provides the best results.

METHODS

This systematic review was reported according to the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) study guideline[13]. It was registered at the International Prospective Register of Systematic Review (PROSPERO) database (CRD42017070058).

PICO/PECO research question

The following research question was developed according to the recognized Patient, Intervention/Exposition, Comparison and Outcome (PICO/PECO) format: "Are pulp revascularization treatments more effective than apexification ones regarding clinical, radiographic and functional retention outcomes to manage immature necrotic permanent teeth?". Population were patients with immature necrotic permanent teeth; Intervention/Exposition was pulp revascularization treatment; Comparison was apexification treatment; and Outcomes were clinical, radiographic and functional retention.

Search strategy

A comprehensive literature search was conducted on MEDLINE via PubMed database up to June 16th, 2017. The following search strategy were used to explore MEDLINE via PubMed database: ((((((((((immature teeth) OR immature tooth) OR immature dentition) OR immature permanent teeth) OR immature permanent tooth) OR immature permanent dentition) OR young permanent teeth) OR young permanent tooth) OR young permanent dentition)) AND ((((((((((pulp revascularization) OR pulpal regeneration) OR pulp revitalization) OR root canal revascularization) OR root maturation) OR regenerative endodontic*) OR regenerative endodontic therapy) OR regenerative endodontic treatment*) OR regenerative endodontic procedure*) OR blood clot) OR platelet-rich fibrin) OR platelet-rich plasma)) AND ((((((((((calcified barrier) OR apical closure) OR root end formation) OR root apex closure) OR apical plug) OR MTA plug) OR apexification[MeSH Terms]) OR apexification*) OR mineral trioxide aggregate) OR calcium hydroxide). Also, a search was conducted on Embase up to June 16th, 2017. On this database the following search strategy were used: 'immature teeth' OR 'immature tooth' OR 'immature dentition' OR 'immature permanent teeth' OR 'immature permanent tooth' OR 'immature permanent dentition' OR 'young permanent teeth' OR 'young permanent tooth' OR 'young permanent dentition' AND ('pulp revascularization' OR 'pulpal regeneration' OR 'pulp revitalization' OR 'root canal revascularization' OR 'root maturation' OR 'regenerative endodontic*' OR 'regenerative endodontic therapy' OR 'regenerative endodontic treatment*' OR 'regenerative endodontic procedure*' OR 'blood clot'/exp OR 'blood clot' OR 'platelet-rich fibrin' OR 'platelet-rich plasma') AND ('calcified barrier' OR 'apical closure' OR 'root end formation' OR 'root apex closure' OR 'apical plug' OR 'mta plug' OR 'apexification'/de OR apexification* OR 'mineral trioxide aggregate'/exp OR 'calcium hydroxide'/exp OR 'calasept' OR 'calcium hydroxide' OR 'calxyl' OR 'hypocal' OR 'limewater' OR 'pulpdent'. The results of these two databases searches were cross-checked to locate and eliminate duplicates.

Eligibility criteria

The inclusion criteria of this systematic review were: (1) Study design: observational studies (case-control and cohort design); (2) Participants: patients with immature necrotic permanent teeth; (3) Intervention: revascularization procedures; (4) Comparison: apexification procedures; (5) Outcomes: have assessed success by clinical, radiographic and functional retention outcomes; and (6) articles published in English.

The exclusion criteria were: (1) teeth presenting pulpitis and vital pulp therapy; (2) teeth with previous treatment to necrosis; (3) follow-up less than three months; (4) did not compare pulp revascularization with apexification; (5) clinical protocol for each proposed treatment incomplete, e.g., in CH apexification, should have performed root canal obturation with gutta-percha after the calcified barrier induction; or, in pulp revascularization cases, should have performed blood clot induction followed by MTA coronal seal and placement of crown restoration.

Study selection and data collection

Two reviewers (G.F.N. and G.M.G.) independently screened all titles and abstracts retrieved by the electronic search. Afterwards, full-text articles of previous included studies were independently assessed by the same authors in order to apply previous established exclusion criteria. Those articles that fulfilled all criteria were included in qualitative and quantitative syntheses.

Additionally, all references of included studies were manually screened for potentially relevant articles. Any possible discrepancies encountered during this process were discussed between the reviewers, and if disagreement still persisted, the judgment of a third reviewer (L.C.) was considered decisive.

Data regarding the included studies were independently extracted by the reviewers (G.F.N. and G.M.G.) based on a previously defined protocol in a specific form in the Microsoft Office Excel 2007 software (Microsoft Corporation, Redmond, WA, USA). The data extracted included: type of study, year of publication, country, type of teeth (anterior or posterior teeth), number of patients and treated teeth, age of patients, etiology and diagnosis of pulp necrosis, presence of periapical lesion at the beginning, type of intervention, type of irrigating solution and intracanal medication, number of successful cases (clinically, radiographically and functional retention), increase in root length and width, calcified barrier formation, crown discoloration, reasons for failures and follow-up of observed cases.

Outcome measures

The primary outcomes of interest were clinical, radiographic and functional retention outcomes of either pulp revascularization or apexification treatment performed in immature necrotic permanent teeth. In this case, only remission of periapical radiolucency (either healing or healed cases) were considered as successful radiographic outcome. Secondary outcome of interest was assessed based on root maturation (increase in root length and width during the follow-up) and formation of calcified barrier, observed in radiographic images.

Clinical and radiographic outcomes were pooled together as single outcome, and consequently, reported as 'overall outcome' (because the authors of the included studies combined them together). The success or failure of the 'overall outcome' was considered in a dichotomous manner (yes or no), based on the author's criteria previously defined in each study. Functional retention outcome was also assessed in a dichotomous manner, loss or remained.

Quality assessment of the included studies

Two blinded reviewers (G.F.N. and G.M.G.) independently assessed the methodological quality of included studies according to Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses[14], adapted for the design of included studies. It is based on a 'star system', ranging from zero to nine stars, in which a study is judged on three broad perspectives: selection of study groups (four stars); comparability of groups (two stars); and ascertainment of either exposure or outcome of interest (three stars) for case-control or cohort studies, respectively. We considered the threshold 'seven stars' for "high" and "low" quality studies, i.e., if a study received seven or more stars it was considered of "high" quality.

Statistical methods for the meta-analysis and assessment of heterogeneity

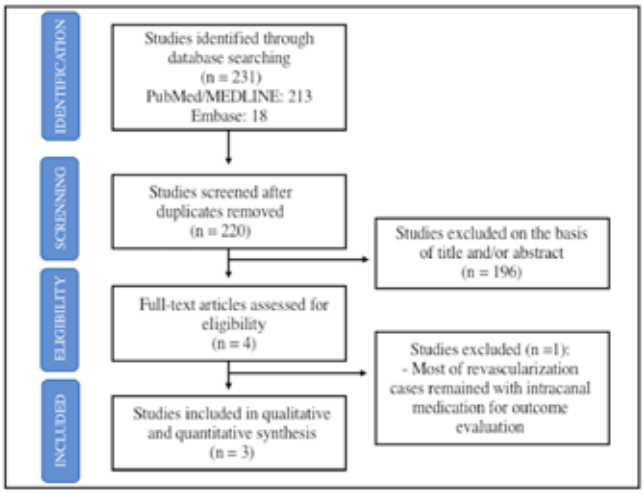
The meta-analysis was conducted using Comprehensive Meta-Analysis Software version 3.3 (Biostat, Englewood, NJ) using random-effect models presented as forest plot with 95% Confidence Interval (CI). Pooled-effect estimates were obtained comparing the failure rate between groups, and it was reported as risk ratio (RR). 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 between 25-50% were considered indicative of low heterogeneity, between 50-75% moderate and greater than 75% of high heterogeneity.

RESULTS

Study selection

Study selection flow diagram is shown in Figure 1. The literature search conducted yield 231 articles. After duplicates were removed (11 coincided from PubMed/MEDLINE and Embase), 220 studies remained. The inclusion criteria were applied upon titles and abstracts yielding a number of four articles. Afterwards, references of these articles were manually searched from potential relevant articles, but none were identified. Then, full text articles were assessed applying the exclusion criteria. One study[15] was excluded because clinical proposed treatment protocol was incomplete, i.e., most of revascularization cases remained with intracanal medication for outcome evaluation. Therefore, a total of three studies[1,2,6] were included in quantitative and qualitative analyses. Perfect agreement between reviewer's study selection was obtained (kappa = 1.0)

Figure 1. Flowchart of study selection.



Study characteristics

Characteristics of each included study are summarized in Table 1. The included studies were retrospective cohorts. Publication year ranged from 2012 to 2017. Two studies[1,2] were carried out in Thailand and one[6] in the United States. Either anterior or posterior teeth were assessed for outcomes of interest, with or without periapical lesions at the beginning of the study. Trauma was main cause of endodontic treatment in immature necrotic permanent teeth, followed by dens invaginatus and caries. Diagnosis of pulp necrosis and outcome assessment were made by clinical and radiographic evaluation (combined together) in the included studies. A total of 135 teeth were evaluated with a follow-up (mean) ranging from one to four years.

All revascularization cases were performed with a rubber dam isolation. Authors did not state clearly whether CH or MTA apexification were performed under rubber dam isolation, with the exception of one study[2] that reported all endodontic treatments being performed under rubber dam isolation. The usual irrigating solution for revascularization cases was sodium hypochlorite (various concentrations), followed by EDTA in some cases[6], or in all cases[2]. Only one study[2] stated clearly that 2.5% sodium hypochlorite was used for MTA apexification. One study[1] used triple antibiotic paste in all revascularization cases; another one[6] used triple antibiotic paste, double antibiotic paste or calcium hydroxide as intracanal medicament; and Silujjai and Linsuwanont[2] used either triple antibiotic paste or calcium hydroxide.

Considering 'overall outcomes' (clinical and radiographic outcomes combined), there was no significant difference between pulp revascularization with BC induction and MTA apexification among the included studies. There was no difference between CH apexification and MTA or BC according to Alobaid *et al* [6], however, authors included only few cases, which may lead to some bias, and consequently, should be interpreted with caution. A statistically significant difference was observed according to Jeeruphan *et al* (1) favoring BC or MTA when compared to CH apexification. On the other hand, when functional retention was assessed, only one study (1) reported inferior rates for CH apexification in comparison to BC or MTA apexification.

None of the included studies assessed the formation of calcified barrier as an outcome of interest. Alobaid *et al*[6] was the only study that reported crown discoloration (crown staining) as an adverse event of revascularization procedures. They observed that two out of 19 teeth (10.5%) treated with BC induction presented crown discoloration. There were no cases of crown discoloration for apexification techniques[6]. There was a statistically significant increase in root length and width favoring BC cases according to Jeeruphan *et al*[1] Alobaid *et al* [6] did not found a statistically significant difference among the treatments, and Silujjai and Linsuwanont[2] observed only a statistically significant increase in root width favoring BC cases when compared to MTA apexification.

Regarding the reasons for failure, two studies[1,2] reported root or tooth fracture as the main cause in apexification cases. Two studies[2,6] stated that in BC cases, the most common reasons for failure was reinfection or persistent infection.

Quality assessment of included studies

The results of the quality assessment using the Newcastle-Ottawa Scale (NOS) for verifying the quality of nonrandomized studies are presented in Table 2. The scores were 'seven stars' in one study[6] and 'eight stars' in two studies[1,2], and therefore, were considered of high quality. In all studies the patients were reviewed retrospectively, which may account for some risk of bias in case selection. Alobaid *et al* [6] reported that the stage of root development was different between revascularization and apexification cases. This may have contributed for differences in quantitative analyses, such as increase in root width and length. Hence, this study[6] was judged of potentially biased in the 'comparability domain', and thus, received only 'one star'. Perfect agreement between reviewer's quality assessment was obtained (kappa = 1.0)

Meta-analysis

The comparisons were performed between apexification (CH and MTA) and revascularization treatments (BC induction). Two independent meta-analyses were performed to evaluate whether apexification or pulp revascularization present better 'overall outcomes' (clinical and radiographic) or functional retention outcomes. Although Alobaid *et al* [6] presented CH and MTA as a 'single' treatment, the authors stated that the success were 100% for apexification. Therefore, as the authors reported 12 cases of success, we preferred to separate the results and present 'overall outcomes' and functional retention outcomes as 7 cases of success for CH and 5 cases of success for MTA apexification.

There was no statistically significant difference concerning 'overall outcomes' (Z=0.113, p=0.910, RR=1.009, 95%CI:0.869-1.171, I^2 = 43%) (Figure 2) and functional retention outcomes (Z=1.438, p=0.150, RR=1.069, 95%CI:0.976-1.172, I = 0%) (Figure 3) when apexification (CH or MTA) was compared to revascularization (BC) treatments.

DISCUSSION

The treatment effectiveness of pulp revascularization and apexification in immature necrotic permanent teeth may be similar. According to our meta-analyses there is no statistically significant difference concerning 'overall outcomes' (clinical and radiographic) and functional retention outcomes between BC revascularization and MTA or CH apexification.

Comparison of results with previous studies

In our previous systematic review (2017) of randomized clinical trials, we observed that MTA is likely to result in higher clinical and radiographic success rates than other endodontic treatments[11]. However, despite randomized clinical trials may provide strong evidence on decision making regarding different treatments, these controlled settings are likely to hamper extrapolation of the studies' results to daily clinical practice[12]. Moreover, none of the randomized clinical trials assessed functional retention outcomes, which is deemed as an important outcome in young patients. Thus, well-constructed observational studies are also important to be assessed because there is a tendency that the studies' results to be closer to practitioners' clinics reality. To our knowledge, this is the first systematic review and meta-analysis that screened observational studies to assess clinical, radiographic and functional retention outcomes in immature necrotic permanent teeth.

Figure 2. Forest plots of 'overall outcomes' (clinical and radiographic) comparing BC revascularization to MTA and CH apexification.

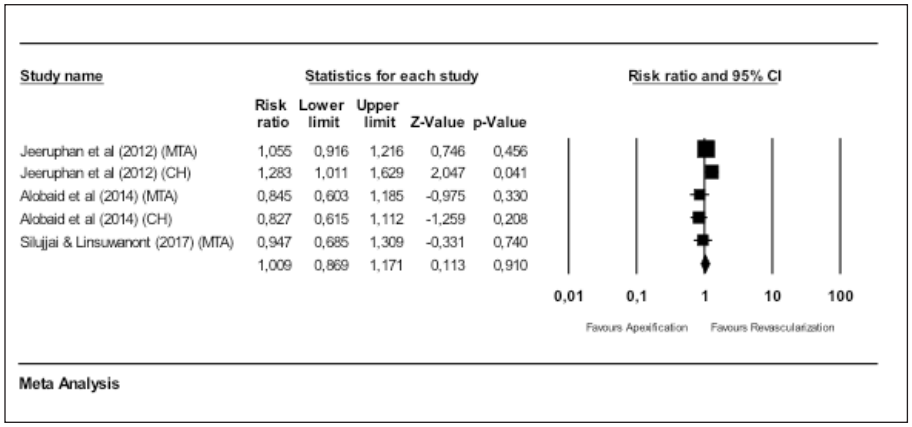
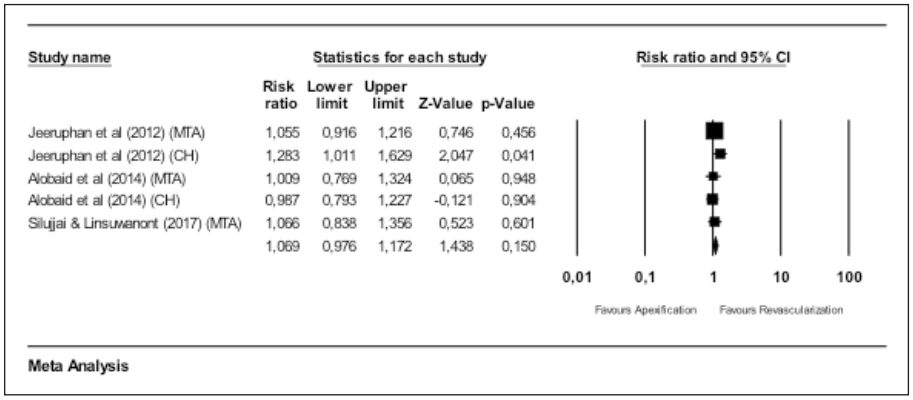


Figure 3. Forest plots of functional retention outcomes comparing BC revascularization to MTA and CH apexification.



The included studies in this systematic review reported clinical successes for MTA apexification of 80.77%[2], 94.70%[1] and 100%[6]. In controlled scenarios (randomized clinical trials), clinical successes were 100% according to Bonte *et al*.[7] and several others[4,16-19]. On the other hand, clinical successes of BC revascularization were 76.47%[2], 79%[6] and 100%[1]. In randomized clinical trials, clinical successes were 90% according to Nagy *et al*.[4] and Benzin *et al*.[20] and 100% according to Narang *et al*.[19]. Unfortunately, there are several differences in the studies' design that cannot allow a meta-analysis to be performed between randomized clinical trials and observational studies. However, according to the individual data aforementioned, one must expect that MTA apexification is likely to result in higher success rates, which is in accordance with our previous systematic review[11]. Consequently, whenever there is adequate crown-root ratio in immature necrotic permanent teeth that are not prone to fracture over time, MTA apexification may be a suitable treatment option.

Despite its advantages, MTA apexification has some inherent limitations, such as the difficulty of placement and cost. Additionally, it is not likely that this technique provides further root maturation[4,19]. On the other hand, pulp revascularization provides the possibility of additional root maturation, especially dentinal wall thickening[21] that might strengthen these thin and fragile dentinal walls, diminishing the incidence of root fracture observed either with calcium hydroxide[7] or MTA apexification[2]. One point to be discussed is the proper disinfection of the root canal, as the most cases of failure in revascularization procedures are due to persistent infection or reinfection[2,6].

Recently, Diogenes *et al* [22] evaluated concentrations of disinfection solutions and intracanal medicaments. Authors reported that irrigation with 1.5% NaOCl followed by 17% EDTA and intracanal medicaments with either TAP in concentrations of 0.1-1mg/ml or $Ca(OH)_2$ with 1mg/ml provide a higher survival of SCAP (stems cells of apical papilla) that may play an important role in root maturation. Interestingly, the treatment protocols adopted in the included studies[1,2,6] did not use this proposed concentration. Therefore, it is likely that these higher concentrations of irrigating solutions used by the authors may be harming the SCAP precluding a potential benefit of root maturation. There is still a necessity of further investigation on this topic, because most of the failures observed in these studies were due to persistent infection or reinfection[1,2,6].

Jeeruphan *et al* [1] found a statistically significant difference in root width and length favoring BC revascularization in comparison to CH and MTA apexification. Silujjai and Linsuwanont[2] found a statistically difference increase in root width favoring BC revascularization when compared to MTA apexification. Alobaid *et al* [6] did not observed a statistically difference among BC revascularization and CH or MTA apexification. In controlled settings, Narang *et al*.[19] observed an increase of root length and width for

BC revascularization when compared to MTA apexification. Nagy *et al*.[4] observed a statistically significant increase from baseline of 1.2 ± 0.5 (11.8 ± 4.9) and 0.32 ± 0.12 (12.7 ± 4.7) of root length and width favoring BC in comparison to MTA. Thus, it seems that there is an additional increase, mainly in root width in revascularization treatments, however, whether this increase is truly from dentin deposition or cementum-like and bone-like tissue[23,24] needs further investigation.

There are some drawbacks regarding pulp revascularization treatments, such as root canal obliteration[20], crown staining[20,25,26], impossibility of post cementation and difficulty of blood clot induction. Canal obliteration may hamper the future endodontic treatment if the revascularization technique fail over time. However, it is not recommended to perform any re-intervention unless treated teeth become symptomatic[27].

Crown discoloration (crown staining) may be an undesirable event, especially in young patients (teenagers) where esthetic is considered of utmost importance. This adverse event may be related to the placement of minocycline or MTA (coronal seal). Alobaid *et al* [6] reported that two out of 19 teeth (10.5%) treated with BC revascularization presented crown staining; however, as the authors used various types of intracanal medication (including TAP with minocycline) the main cause of crown discoloration remains uncertain. Bezgin *et al* [20] reported that 12 of 20 teeth (60%) treated with pulp revascularization presented crown discoloration. The authors reported that this adverse event was caused by MTA placement, despite the use of white MTA instead of grey MTA as coronal plug[20]. The fact that the white MTA may induce crown discoloration is likely to be related to the interaction of its bismuth oxide with the dentin collagen[28].

Apexification treatments may present more favorable results regarding crown discoloration. On the other hand, patients treated with pulp revascularization may be benefited with further root strengthening. Hence, clinicians should balance the importance of outcomes in each procedure, once inadequate crown-root ratio may increase the risk of crown or root fractures diminishing functional retention over time. Moreover, there are some alternatives that attempt to diminish crown discoloration, such as, sealing the pulp chamber with dentin bonding agent before placement of TAP or MTA[20], replacement of the bismuth oxide present in the white MTA for other components[28] or use of biocompatible MTA-like cements[29].

Another point of discussion is related to the choice of CH or MTA for apexification treatments. Jeeruphan *et al* [1] observed a success of 77.3% for CH and 94.7% for MTA being the failures related to catastrophic fractures. It is well known that longer periods of calcium hydroxide exposure may increase dentin brittleness over time[30,31]. This increase in dentin brittleness might be related to the increased risk of root fracture[7]. Therefore, as more teeth have been extracted when treated with CH apexification, it seems that MTA apexification should be preferred[1,7].

In young patients, functional retention in immature necrotic permanent teeth may be of utmost importance. Thus, asymptomatic teeth retained to the age of eighteen might not be considered as failure, even with presence of periapical lesions, because at this age patients could choose to have dental implants if necessary. Functional retention was assessed in all studies[1,2,6] included in this systematic review. Comparing the 'overall outcomes' (86%, 116/135 teeth) to the retention outcomes (90%, 124/138 teeth), the success of treated teeth raised 4% regarding the treatments performed. More studies are desirable to evaluate what additional root maturation represents in terms of root strengthen, and consequently, functional retention over time. However, one must expect that over longer periods of follow-up, young patients with immature necrotic permanent teeth presenting inadequate crown-root ratio may be benefited. Moreover, pulp revascularization treatments offer the possibility of a second non-invasive treatment (MTA apexification) if it presents failure over time.

Strengths of study

This current systematic review included only studies of "high" quality. The included studies assessed their outcomes over longer periods of follow-up. We observed low heterogeneity among included studies.

Limitations of study

Some limitations have to be considered. We included only three studies in this systematic review with a total of 135 immature necrotic permanent teeth. The three studies were heterogenic in some important characteristics, such as the patients age-ranges and follow-up periods. There is still a need of greater sample size. Moreover, as we observed few apexification cases in the included studies, either CH or MTA, we decided to pool them together on our meta-analysis, however, this should be interpreted with caution, because the literature clearly point out some advantages of MTA over CH apexification. There are inherent limitations of observational studies, such as risk of bias due to case selection and or study executors' prejudice. Another limitation may be related to inclusion of articles published only in English language. However, according to Moher *et al* [32] the exclusion of non-English language articles might not be a limitation on the results of meta-analyses. Therefore, it is crucial to understand that, at this point, the current evidence based in observational studies is limited, and that the results may be consequently biased.

Implications for future researches

Although pulp revascularization procedures may increase root length and width, some attempts should be made to use standards methods to quantify the 'real gain' in root development, because some X-ray distortions may overestimate its increase. There is still a need of establishment of proper concentrations for root canal disinfectants that might enhance the survival of SCAP, but also reduce the microbial load and risk of reinfection.

CONCLUSIONS

Data concerning the current literature in regard to the clinical, radiographic and functional retention outcomes in immature necrotic permanent teeth treated either with pulp revascularization or apexification is limited. Based on our meta-analysis, the results do not favor one treatment modality over the other. More clinical studies are necessary to further investigate some topics of revascularization and apexification treatments.

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

Study	Jeeruphan *et al.*	Alobaid *et al.*	Silujjai & Linsuwanont
Type of study	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort
Year	2012	2014	2017
Country	Thailand	United States (US)	Thailand
Type of teeth*	Anterior and Posterior	Anterior and Posterior	Anterior and Posterior
Patients (number)	BC: 20 CH: 19 MTA: 22	*	BC: 17 MTA: 26 (28****)
Teeth (number)	BC: 20 CH: 19 MTA: 22	BC: 19 CH: 7 MTA: 5	BC: 17 MTA: 26 (29***)
Age of patients	BC: 12.9 ± 5.07 years CH: 10.5 ± 3.85 years MTA: 14.6 ± 6.17 years	BC: 8.8 ± 1.6 years CH: 9.8 ± 2.0 years MTA: 9.8 ± 2.0 years	8-46 years
Etiology of pulp necrosis	Trauma (59%), Dens evaginatus (32,8) and Caries (8.2%)	Trauma (77.4%), Caries (12.9%), Anatomic anomalies (9.7%)	Trauma (46.51%), Dens evaginatus (41.86) and Caries (11.63%)
Diagnosis of pulp necrosis	Clinically and Radiographically	Clinically and Radiographically	Clinically and Radiographically
Periapical lesion at the beginning	Either present and absent	Either present and absent	*
Type of Intervention	BC, CH and MTA	BC, CH and MTA	BC and MTA
Type of Irrigating Solution	BC: 2.5% NaOCl CH and MTA*	BC: various concentrations of NaOCl, Chlorhexidine, and/or EDTA CH and MTA*	BC: 1.5-2.5% NaOCl and 17% EDTA MTA: 2.5% NaOCl
Type of Intracanal Medication	BC: TAP (ciprofloxacin, metronidazole and minocycline) CH and MTA*	BC: TAP (ciprofloxacin, metronidazole and minocycline), double antibiotic (ciprofloxacin, metronidazole), and/or calcium hydroxide CH and MTA: calcium hydroxide	BC: either ciprofloxacin, metronidazole and minocycline or calcium hydroxide MTA: calcium hydroxide
Number of clinical successful cases	BC: 100% (20/20) CH: 77.3% (17/22) MTA: 94.7% (18/19) (BC = MTA > CH (p<0.05))**	BC: 79% (15/19) CH: 100% (7/7) MTA: 100% (5/5) (BC = MTA = CH (p=0.09))**	BC: 76.47% (13/17) MTA: 80.77% (21/26) BC = MTA (p>0.05)
Number of radiographic successful cases	BC: 100% (20/20) CH: 77.3% (17/22) MTA: 94.7% (18/19) (BC = MTA > CH (p<0.05))**	*	BC: 76.47% (13/17) MTA: 80.77% (21/26) BC = MTA (p>0.05)
Retention rate	BC: 100% (20/20) CH: 77.3% (17/22) MTA: 94.7% (18/19) (BC = MTA > CH (p<0.05))**	BC: 95% (18/19) CH: 100% (7/7) MTA: 100% (5/5) (BC = MTA = CH (p=0.4))**	BC: 88.24% (15/17) MTA: 82.76% (24/29***) BC = MTA (p>0.05)
Increase in root length (percentage)	BC: 14.9% CH: 0.4% MTA: 6.1% (p<0.001)**	*	BC: 9.51% ± 18.14% MTA: 8.55% ±8.97% BC = MTA (p>0.05)
Increase in root width (percentage)	BC: 28.2% CH: 1.52% MTA: 0% (p<0.0001)**	BC: 10.2% ± 4.0% CH and MTA*	BC: 13.75% ± 19.91% MTA: -3.30% ± 14.14% BC > MTA (p<0.05)
Calcified barrier formation	*	*	*
Crown discoloration	*	BC: 2/19 (10.5%) CH and MTA: 0/12 (0%)	*
Reasons for failures	CH and MTA: catastrophic fracture deemed nonrestorable	BC: 3 teeth became reinfected and 1 tooth was retraumatized and extracted	BC: 3 teeth showed persistent infection and 1 tooth was reinfectioned MTA: 2 teeth had vertical root fracture, 1 teeth had horizontal root fracture and 2 teeth had unrestorable tooth fracture

Study	Jeeruphan *et al.*	Alobaid *et al.*	Silujjai & Linsuwanont
Follow-up (mean and SD)	BC: 21.15 ± 11.70 months CH: 27.32 ± 30.47 months MTA: 14.21 ± 7.84 months	BC: 14 ± 8.5 months CH: 21.8 ± 12.0 months MTA: 21.8 ± 12.0 months	BC: 35 ± 21.76 months MTA: 49 ± 31.09 months

[*]Authors did not state clearly

[**] According to authors (p value)

[***] Authors stated that 3 patients were unable to attend the recall visits but provided information that teeth were functional with no symptoms

[****] Two patients (which did not attend the recall visits) had 3 MTA apexified teeth

Abbreviations: CH: Calcium Hydroxide apexification; MTA: Mineral Trioxide Aggregate apexification; BC: Blood Clot revascularization; TAP: Triple Antibiotic Paste

Table 2. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies

Study	Jeeruphan *et al.*	Alobaid *et al.*	Silujjai & Linsuwanont
1. Selection			
1.1. Representativeness of cohorts	*	*	*
1.2. Selection of cohorts			
1.3. Ascertainment of treatment regimen	*	*	*
1.4. Demonstration that the outcome of interest was not present at start of study	*	*	*
2. Comparability			
1. Comparability of cohorts on the basis of the design or analysis (Age *; other controlled factors *)	**	*	**
3. Outcome			
3.1. Assessment of outcome	*	*	*
3.2. Was follow-up long enough	*	*	*
3.3. Adequacy of follow-up	*	*	*