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ORIGINAL ARTICLE/ARTICOLO ORIGINALE

Revascularization versus apical barrier technique with mineral trioxide aggregate plug: A systematic review

Rivascolarizzazione contro tecnica della barriera apicale con tappo di MTA: una revisione sistematica

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KEYWORDS
Apexification;
Mineral trioxide aggregate;
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Abstract
Aim: To compare the clinical and radiographic outcomes observed in Necrotic Immature Permanent Teeth (NIPT) after revascularization or apexification with MTA-apical plug.
Methodology: PubMed/MEDLINE, Web of science and Scopus were the databases used, up to July 30th, 2017, for article research. Independent reviewers read the titles and abstracts of all reports that met inclusion/exclusion criteria: prospective or retrospective clinical studies comparing the revascularization of root canal and apexification. Clinical success of therapies, deposition and thickening of lateral dentinal walls (root width) and the continuation of root development (root

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PAROLE CHIAVE
Apecificazione;
Mineral trioxide aggregate;
Rivascolarizzazione.

length) were investigated. Bias risk of included studies was assessed using the Cochrane risk of bias.
Results: From 1642 records, five papers fulfilled all inclusion criteria. Overall, 91 teeth were submitted to revascularization and 64 teeth to apexification with MTA. The mean follow-up was 23.2 months in revascularization and 21.8 in apexification. Clinical success rate was of 87.9% in the revascularization group and 90.6% in the apexification group. An increase on lateral dentinal walls thickening was observed in most revascularization cases (13%) while MTA as apical plug suggest a mild resorption of the root (−1.3%). High bias risk was observed on included studies.
Conclusions: Apexification with MTA-apical plug provides similar clinical success to revascularization. However, radiographic measurements showed an improvement in thickening of lateral dentinal walls in most of the revascularization cases in addition to a higher dental development. However, these results should be interpreted with caution.
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Riassunto
Obiettivi: Confrontare gli esiti clinici e radiografici osservati nei denti necrotici permanenti immaturi (NIPT) dopo rivascolarizzazione o apecificazione con un tappo apicale di MTA.
Materiali e metodi: PubMed/MEDLINE, Web of science e Scopus sono stati i database utilizzati fino al 30 luglio 2017 per la ricerca di articoli. Revisori indipendenti hanno letto i titoli e gli abstract di tutti i report che hanno soddisfatto i criteri di inclusione/esclusione: studi clinici prospettici o retrospettivi che hanno confrontato la rivascolarizzazione del canale radicolare e l'apecificazione. Sono stati studiati il successo clinico delle terapie, la deposizione e l'ispessimento delle pareti dentinali laterali (larghezza della radice) e la continuazione dello sviluppo della radice (lunghezza della radice). Il rischio di *bias* degli studi inclusi è stato valutato utilizzando il rischio di *bias* di *Cochrane*.
Risultati: Di 1.642 documenti, cinque articoli soddisfano tutti i criteri di inclusione. Complessivamente, 91 denti sono stati sottoposti a rivascolarizzazione e 64 denti all'apecificazione con MTA. Il follow-up medio è stato di 23,2 mesi per la rivascolarizzazione e 21,8 per la apecificazione. Il tasso di successo clinico è stato dell'87,9% nel gruppo di rivascolarizzazione e del 90,6% nel gruppo di apecificazione. Un aumento dell'ispessimento delle pareti dentinali laterali è stato osservato nella maggior parte dei casi di rivascolarizzazione (13%) mentre l'uso di MTA come tappo apicale riporta un lieve riassorbimento della radice (−1,3%). Un elevato rischio di *bias* è stato osservato per gli studi inclusi.
Conclusioni: L'apecificazione con il tappo apicale di MTA fornisce un successo clinico simile alla rivascolarizzazione. Tuttavia, le misurazioni radiografiche hanno mostrato un miglioramento dell'ispessimento delle pareti dentinali laterali nella maggior parte dei casi di rivascolarizzazione oltre a uno sviluppo dentale superiore. Tuttavia, questi risultati dovrebbero essere interpretati con cautela.
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Introduction

Traditionally, when pulp tissue undergoes necrosis a conventional endodontic therapy (CET) is performed, but despite good prognosis and favorable results observed [1], it comprises a challenging task to be carried out in necrotic immature permanent teeth (NIPT). NIPT possess thin root walls with a wide apical foramen, hampering to create an adequate apical stop [2].

Apexification is an indicated technique to manage NIPT since it induces a calcified barrier at the immature apex performed in several clinical appointments [3,4]. This technique comprises removal of the necrotic tissue followed by debridement of the canal and use of disinfection solution (such as sodium hypochlorite) to control the infection. Thus, several placements of a medicament able to induce a calcified barrier in a root with an open Apex is needed, thus, a subsequent condensation of gutta-percha can be properly achieved [3,4]. Calcium hydroxide — $Ca(OH)_2$ — is the most used material in apexification to develop the apical barrier due to biological and healing performances. However, apexification with $Ca(OH)_2$ presents considerable drawbacks such as increased risk of root fracture and poor patient compliance due to the extended treatment time, since is need a range of approximately 5 to 20 months to apical barrier formation [5]. Therefore, in addition to risk of fracture, the vulnerability of the temporary coronal restoration to re-infection is a great challenge [5]. The apical barrier technique using an apical plug of MTA has been reported as an alternative to long-term $Ca(OH)_2$ application by presenting shorter treatment time and higher predictability for apical closure [6]. In this tech-

nique, the treatment can be performed in one-single visit, providing biocompatibility, bacteriostatic action and favourable sealing ability [6]. Similarly to apexification, the necrotic pulp is removed and debridement and disinfection of the canal is performed. In this stage, MTA is employed in the canal as an apical plug [6]. MTA apical plug offers an effective barrier at the end of the root canal allowing vertical condensation of warm guttapercha in the remainder of the canal [6]. Although clinical trials have shown the efficacy of apexification, literature has documented apical closure, but no root elongation or maturation of the apical region [2].

In such context, revascularization aims to induce the maturation of root apex on NIPT, relying on root canal decontamination and subsequent induction of bleeding from the periapical tissue. Briefly, decontamination is performed with irrigant (such as sodium hypochlorite - 0.5% to 6% - or chlorhexidine), mild mechanical debridement of the root canal (because mechanical instrumentation is contraindicated) and antibiotic slurries (traditionally the triple antibiotic paste -TAP - metronidazole, ciprofloxacin, and minocycline) [7—9]. Ethylenediaminetetraacetic acid (EDTA) has been also indicated because it showed to promote the release of growth factors embedded in dentine. After that, subsequent induction of bleeding from the periapical tissue is performed [7—9]. The blood is stimulated with the use of a file. Thus, blood fills the root canal and coagulates forming a natural scaffold (which will serve as an anchorage site for cells from the apical region), which is subsequently covered with MTA [9].

Thenceforth, revascularization has been an important alternative for NIPT treatment showing good clinical results in several clinical studies [9—15]. Studies have shown that tissues formed in the root canal comprised vital pulp-like tissues with blood vessels, bone and cementum deposition and few inflammatory cells without dentin deposition [16—19]. Thus, this new tissue deposited can provide an increase in root canal length and thickening of lateral dentinal walls generating apical closure, as well as a high deposition of mineralized tissue observed radiographically [20,21], which is not possible with apexification treatment. However, revascularization is still a not well-established therapy since very little is known about the exact outcomes in the long term [2].

Thus, the objective of this study was to conduct a systematic literature review comparing clinical and radiographic outcomes observed in NIPT after revascularization or apexification using apical barrier technique with an MTA apical plug.

Methodology

This systematic review is reported in accordance with PRISMA Statement guidelines [22].

Eligibility criteria

In this systematic review studies with randomized controlled clinical trials design as well as prospective or retrospective clinical trials were included. To be eligible, studies should compare the revascularization of root canal and apexification with MTA-apical plug. No restriction of language was performed, however, studies *in vitro*, letters to editor and reviews were not include in the present study.

Table 1 Structured search strategy carried in databases.

Search syntaxes	
PubMed	
#1	((“clinical” [Title/Abstract] AND “trial” [Title/Abstract]) OR “clinical trials” [MeSH Terms] OR “clinical trial” [Publication Type] OR random[a] [Title/Abstract] OR “random allocation” [MeSH Terms] OR “Longitudinal Studies” [MeSH Terms] OR “Longitudinal Studies” [All Fields] OR “Longitudinal Study” [All Fields] OR “Studies, Longitudinal” [All Fields] OR “Study, Longitudinal” [All Fields] OR “Retrospective Studies” [MeSH Terms] OR “Studies, Retrospective” [All Fields] OR “Study, Retrospective” [All Fields] OR “Retrospective Study” [All Fields] OR “Clinical Evaluation” [All Fields] OR “Follow-up” [All Fields])
#2	“Immature Permanent Teeth” [All Fields]
#3	“Root Canal Revascularization” [All Fields] OR Revascularization [All Fields] OR Maturogenesis [All Fields]
#4	“apexification” [MeSH Terms] OR “apexification” [All Fields] OR “Apexifications” [All Fields] OR “Apexogenesis” [All Fields] OR (“apexification” [MeSH Terms] OR “apexification” [All Fields])
#5	“Mineral trioxide aggregate” [Supplementary Concept] OR “mineral trioxide aggregate” [All Fields]

[a] Searches were combined in each database.

Outcomes

The outcomes of this review were: clinical success of therapies (revascularization vs. apexification with MTA apical plug), deposition and thickening of lateral dentinal walls (root width) and the continuation of root development (root length).

Strategy of search

An electronic search was conducted in PubMed/MEDLINE, Web of Science and Scopus databases up to July 30th, 2017 following the inclusion criteria. The search structures followed Table 1, to answer the questions “Which technique (revascularization or apexification with MTA) provides higher clinical success?” and “Is revascularization able to promote higher deposition of mineral tissue and continuation of root development compared to apexification with MTA?”, based in the PICO model:

- Population: only human subjects
- Intervention: performing revascularization relying on blood clot formation after induced periapical bleeding
- Comparison: apexification of root canal using the barrier technique with MTA as apical plug
- Outcomes: clinical success, radiographic deposition of mineral tissue on root walls and continuation of root development.

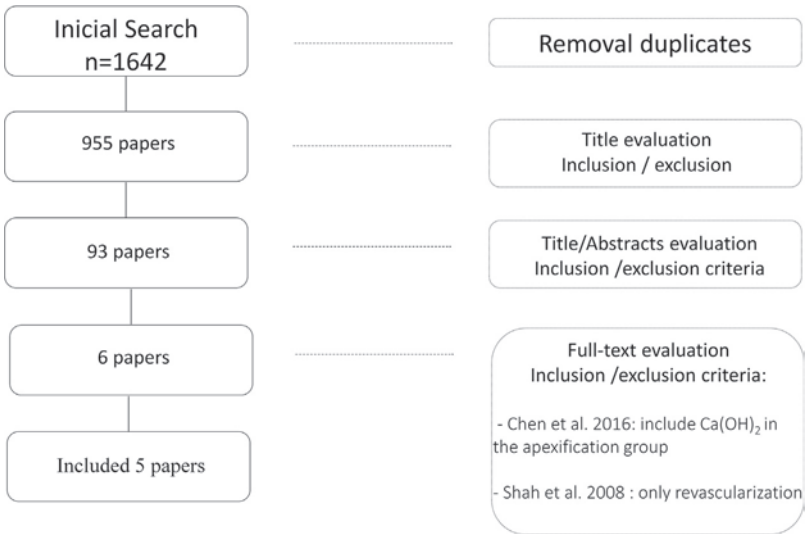

Figure 1 Prisma diagram flow.

Study selection

The records retrieved were uploaded into ENDNOTE® basic software (www.myendnoteweb.com), aiming to delete duplicates and to build up a virtual library (VL). Two independent reviewers (LAC and GG) read the titles and abstracts of all reports identified throughout the electronic searches, following the inclusion/exclusion criteria. Discrepancies between the reviewers were discussed to reach a consensus. In disagreement, a third reviewer decided (MCMC). Studies that filled the eligibility criteria were included in the review and processed for data extraction.

Table 2 Characteristics of included studies.

Author	Jeeruphan et al. [6]	Alobaid et al. [18]	Nagy et al. [23]	Narang et al. [24]	Silujjai et al. [17]
Study design	Retrospective	Retrospective	Prospective	Prospective and randomized	Restrospective
Number of teeth	Rev: 20; Ap: 19	Rev: 19; Ap: 5	Rev: 20; Ap: 9	Rev: 15; Ap: 5	Rev: 17; Ap: 26
Follow-up	Rev: 21 M; Ap: 14 M	17 M	18 M	18 M	Rev: 35 M; Ap: 49 M
Etiology of pulp necrosis	NR	Trauma, caries and *dens evaginatus*	NR	NR	Trauma, caries and *dens evaginatus*
Intracanal medication	TAP	$Ca(OH)_2$/TAP/DAP	Metronizadole, Ciprofloxacin, Doxycycline	TAP	TAP
Irrigation	2.25% NaOCl	NaOCl and chlorhexidine	Sodium hypochlorite 2.6%	2.5% NaOCl	1.5%—2.5% NaOCl and 17% EDTA
Clinical success	Rev: 20/20; Ap: 18/19	REV: 15/19; Ap: 5/5	Rev: 17/20; Ap: 9/9	Rev: 15/15; Ap: 5/5	Rev: 13/17; Ap: 21/26
Vitality pulp test	NR	NR	NR	NR	NR
Thickening of lateral dentinal walls (root width)	Rev 28.2%; Ap: 0%	Rev 10.2%; Ap: 1.4%	Rev 0.31%; Ap: 0.0%	NR	Rev 13.8%; Ap: −3.3%
Continuation of dental development (root length)	Rev: 14.9%; Ap: 6.1%	Rev: NE; Ap: NE Similar results	Rev: 1.25%; Ap: 0%	NR	Rev: 9.5%; Ap: 8.5%

Legend: Revascularization (Rev); mineral trioxide aggregate (MTA); apexification with mineral trioxide aggregate (Ap); triple antibiotic paste (TAP); double antibiotic paste (DAP); no reported (NR); no specified (NE); sodium hypochlorite (NaOCl); calcium hydroxide ($Ca(OH)_2$); months (M).

The reasons for exclusion were justified and reported in the flow chart (Fig. 1).

Data extraction

Data extraction was performed independently by two reviewers (LAC and GG). Disagreements were solved by discussion between reviewers. The mean follow-up, etiology of pulp necrosis, intracanal medication, irrigation solution, clinical and/or radiographic success, return of pulp vitality and deposition of dentinal walls thickening and root lengthening were collected (Table 2).

Bias risk

The bias risk of included studies was assessed using the Cochrane risk of bias tool. The bias tool considered were: judgment of the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias [23].

Data analysis

Papers included showed a high heterogeneity regarding study design and evaluation criteria. Thus, a qualitative analysis was carried on extracted data.

Results

The initial research found 1642 records corresponding to 955 studies. The titles of the studies were evaluated and 93 were selected for abstract evaluation. After full-text evaluation, five papers fulfilled all inclusion criteria and two [24,25] were excluded (Fig. 1). In relation to study design, three studies were retrospective [6,20,21] and two prospective [11,26], of which only one is a clinical trial [11]. Overall, 91 teeth were submitted to revascularization and 64 teeth to apexification with MTA (Table 2).

The follow-up ranged from 17 to 35 months (mean 23.2) in the revascularization groups and 14—49 months (mean 21.8) in the MTA apexification group. Intracanal irrigation was performed in all studies with sodium hypochlorite, whilst Alobaid et al. [21] also used chlorhexidine and Silujjai et al. [20] used EDTA 17%. In addition, a considerable variation of intracanal medication was observed, with the use of double [21] and triple antibiotic paste (DAP-TAP) [6,11,20,21], even as $Ca(OH)_2$ [21]. Etiology of pulp necrosis was reported only in two studies [20,21] they reported trauma, caries and *dens evaginatus* as reasons for the necrosis.

Thus, a clinical success rate of 87.9% ($n = 80$) in the revascularization group was observed and 90.6% ($n = 58$) in the apexification. Although no study evaluated the pulp vitality after revascularization procedure, a considerable increase on thickening of lateral dentinal walls was showed in most of revascularization cases (pondered mean = 13%) while apical barrier technique with MTA as apical plug showed an inferior outcome (pondered mean = −1.3%), also suggesting a mild resorption of the root. Similarly, continuation of dental development was higher in the revascularization group (pondered mean = 8.5%) compared to the MTA apexification group (pondered mean = 5.2%).

Regarding the bias risk, a high bias risk of the included studies was observed (Fig. 2). Allocation concealment, blinding of participants and personnel and selective reporting presented the highest risk of bias while blinding of outcome assessment and incomplete outcome data presented the lowest risk.

Discussion

The main objective of revascularization is to generate a new pulp-like tissue inside the root canal to restore the tooth physiology and to reduce significantly the risk of tooth loss [10,27—30]. Therefore, it was observed that revascularization was slightly more effective than apexification through MTA apical barrier technique, providing an increase of the thickness of lateral dentinal walls and promoting the continuation of dental development. The global success rate showed equivalent results between revascularization and apexification through MTA apical barrier technique.

The unfavorable results regarding the survival rate in MTA were mostly related to non-restorable dental fracture [6,20], while revascularization failure was mostly related to a persistent infection [6,20]. Nagy et al. [26] reported that 3 teeth exhibited clinical and radiographic fail signs during examination while being treated with apexification. Alobaid et al. [21] described 4 failures in the revascularization group, of which one tooth failed due to trauma, needing to be extracted because of a complicated facture. The other failures were due to persistent infection of root canal systems, requiring a new endodontic reintervention. Extensive mechanical instrumentation is contraindicated in NIPT as it can make teeth more susceptible to fracture [2,9]. In this context, disinfection of radicular system canals is a crucial step in regenerative endodontics, which is mainly obtained by disinfectant solutions and intracanal medications [8,10]. Moreover, periapical tissues around immature teeth present a rich blood supply and a specific population of stem cells named stem cells from apical papilla (SCAP) that possess potential to regenerate tissue in response to injury [30]. If a sterile tissue matrix is present, providing an optimal environment for cells adhesion, proliferation and differentiation, pulp vitality can be restored [31,32].

While several irrigation solutions and intracanal medication can be employed in revascularization [8,10], the studies included in the present review employed the sodium hypochlorite as main irrigation solution [6,11,20,21,26] along with TAP [6,11,20] and their modifications [21,26] to obtain canal decontamination. The modifications of TAP are used to avoid tooth discoloration caused by the conventional paste [10]. Hoshinoet al et al. [33] showed that a TAP composed by ciprofloxacin, metronidazole and minocycline presented bactericidal effect against the colonizing-dentin microorganisms *in vitro*. Iwaya et al. [34] described a technique applying such TAP and observed an increase of thickening of the root dentinal walls. Some years later, a new procedure to disinfect NIPT root canals was published, which consisted on root disinfection with 5.25% sodium hypochlorite (NaOCl) irrigation without root instrumentation [35] and this protocol has been the most employed ever since [10].

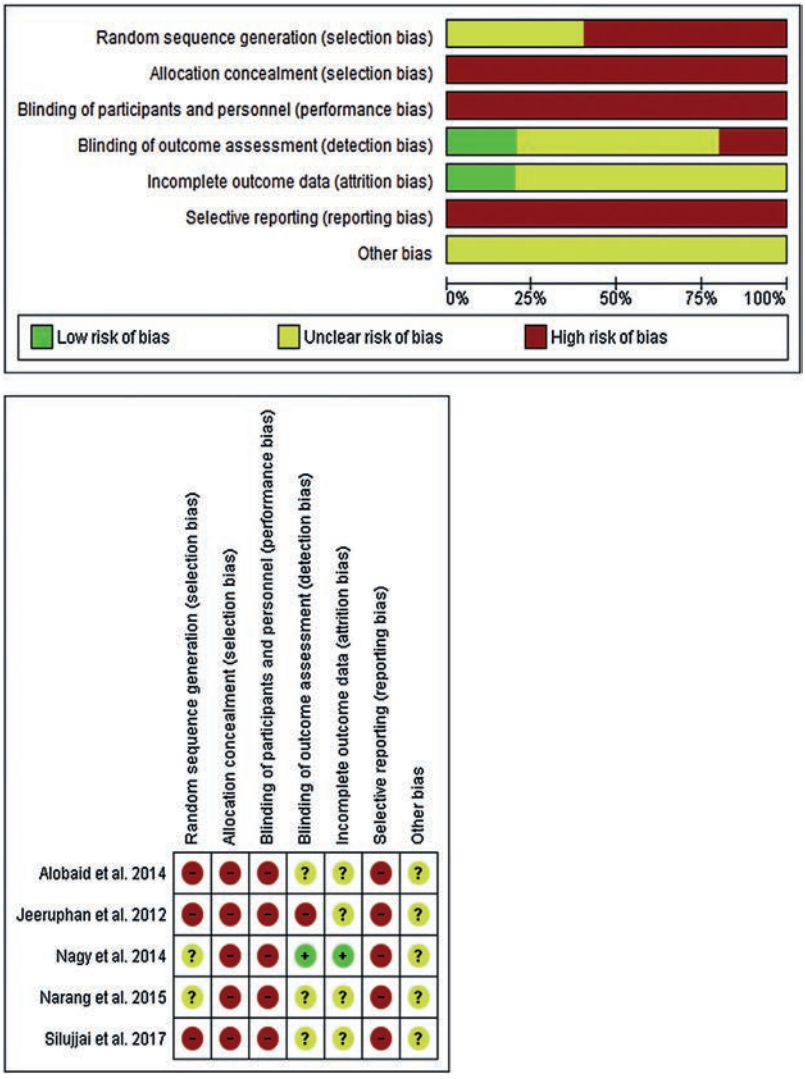

Figure 2 Bias risk of included studies.

Although the studies showed that TAP and their modifications can be effective to provide a sterile environment, some failures were observed due to reinfection of the canal, maybe due to residual bacteria in the root canal, effectively observed in histological analyses [16,21]. These variations in the ability to promote an effective disinfection could be explained by the different concentrations of the intracanal paste used. While the included studies did not report the final concentrations of the antibiotic paste, the American Association of Endodontists recommended the use of antibiotic pastes at a concentration ranging from 0.1 to 1 mg/mL [7]. This concentration seems to maintain the viability of stem cells from apical papilla, which will subsequently migrate and cling to the blood clot [7,10].

Blood clot acts as a natural scaffold, bringing a simple support for stem cell proliferation and differentiation [10,30]. It should act mimicking the original tissue and the extracellular matrix, which provides support for the cells presenting ligands and bioactive molecules to guide the stem cells behavior [36,37]. Fibrin present in the clot is a biopolymer, critical to hemostasis and wound healing, it serves as a natural scaffold to capture the blood cells and it contains in its structure ligand molecules [38]. When the induced bleeding starts inside the root canal, the evoked-bleeding enrolls the manipulation of the periapical tissues and this manipulation step seems to release stem cells from the surrounding tissues and results in their delivery to the canal system [39]. In such cases, fibrin is the main responsible for the blood clot formation and stabilization acting as a ''trap'' to retain SCAPs from apical site [39]. Recent studies have combined blood clot with a natural scaffold from platelet rich plasma (PRP) [13,40] and platelet rich fibrin (PRF) [11,41]. These blood concentrates showing a high range of biomolecules [42] can facilitate the migration of stem cells from apical papilla. Of the included studies, Narang et al. [11] also realized the revascularization both with PRP and PRF, describing that PRF showed better results of dentin wall thickness and continuation of root development than PRP, conventional revascularization and MTA apexification. Therefore, it was observed that the use of PRF could accelerate the potential of regeneration in NIPT [11].

In such context, revascularization seems to possess a range of advantages when compared to apexification with the apical barrier technique using MTA, including increased

thickening of the canal walls and continued root development, which was superior in the present systematic review. Histological and immuno-histochemical analyses in animals [43,44] and in humans [16—18] did not detect the presence of polarized cells resembling odontoblasts after revascularization [18,45]. Apical closure was generated by cellular/acellular cementum and bone-like tissue, expressing bone sialoprotein, instead of dentin sialoprotein [16,46,47]. However, it is important to highlight that the dental pulp is one of the most important biological structures of a tooth. Revascularization has revitalized teeth with irreversible pulpits and necrosis associated with apical periodontitis. Although this tissue seems not able to deposit dentin [16], observed mineralized tissue provides an increase in width and length of teeth and resolution of apical periodontitis.

The results of the present systematic review should be interpreted with caution, since it is based on studies with different methodological designs, limited sample and with high risk of bias. Thus, well-designed clinical trials comparing the two procedures should be conducted to provide more concise and safe information.

Conclusions

Apexification with the barrier technique using MTA-apical plug provides similar clinical success rate than revascularization. Moreover, radiographic measurements showed an improvement on thickening of lateral dentinal walls in most of the cases of revascularization. The continuation of dental development was also higher in the revascularization group. These results should be interpreted with caution.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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