Revascularisation versus apexification for treatment of immature teeth based on periapical healing and root development: A systematic review and meta-analysis



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Abstract

Aim Immature necrotic teeth are frequent findings in adolescents that may lead to thin root walls and open apexes. The absence of an apical stop becomes a challenge for endodontic treatment because it is difficult or impossible to seal the immature root canal with conventional endodontic techniques. Revascularisation therapy (RET) may be more suitable for the treatment of immature necrotic teeth. However, clinicians are still more inclined to choose apexification (AP) when considering the predictability of treatment results.

Methods The literature was searched via PubMed/MEDLINE and the Cochrane Library, Web of Science data from June, 2001 to September, 2020 and randomised clinical trials were selected that compared RET with AP for the treatment of immature necrotic teeth assessing clinical and radiographic results.

Results A total of 556 articles were retrieved, though only five studies were included. There were no differences in the periapical healing rate, overall effective rate/invalid rate, or apical closure rate between RET and AP. The root length was significantly increased in the RET group compared with the AP group quantitatively (pooled difference in means=1.28, 95% CI: [1.08, 1.48], Z=12.69, P<0.00001) and qualitatively (pooled RR=4.12, 95% CI: [2.44, 6.97]), Z=5.28, P<0.00001). The effective rate of root thickness was significantly increased in the RET group compared with the AP group (pooled RR=22.63, 95% CI: [6.08, 84.26]), Z=4.65, P<0.00001).

Conclusions Both RET and AP were effective options regarding the healing of periapical periodontitis or the closure of open apices. Pulp revascularisation is more effective for root elongation and thickening without higher risk of overall invalid treatment.

KEYWORDS Apexification; Immature necrotic teeth; Revascularisation.

Introduction

Immature permanent teeth with incomplete root formation have presented a challenge for endodontic treatment for decades. The pulp cavity of the primary permanent teeth is wide, and the apical hole is open. Furthermore, these teeth are more prone to fracture because of thin, weak dentinal root canal walls. It takes 3–5 years for the root of immature teeth to mature. At this stage, if pulp necrosis or periapical inflammation occurs, conventional root canal treatment cannot meet the requirements of isolated infection, which will affect the retention and later restoration of the teeth.

The traditional treatment option in these cases was apexification, which allows the formation of a calcified barrier across the open apex by using calcium hydroxide, thus creating a suitable environment for periapical tissue repair and subsequent root canal therapy [Ghose et al., 1987; Sheehy et al., 1997]. For decades, many studies have evaluated the performance of calcium hydroxide (CH) pastes and pointed out some disadvantages of this material, such as wall brittleness and high risk of root fractures [Yassen et al., 2012; Andreasen et al., 2002]. Recently, it has been advocated that mineral trioxide aggregate (MTA) will replace CH for inducing root formation because of its advantages of having excellent biocompatibility and sealing ability [Bonte et al., 2015; Hachmeister et al., 2002]. However, although MTA apexification might be more effective and shorten the treatment period, it still cannot solve the problem of thin and weak dentinal root canal walls [Holden et al., 2008].

Recently, the American Association of Endodontics suggested that regenerative endodontic procedures could be an alternative treatment for infected immature permanent teeth [American Association of Endodontics, 2016]. Some studies have indicated that endodontic revascularisation has significant advantages in promoting an increase in root width and length. This technique provides an opportunity for additional root canal development, which might reduce the incidence of root fracture over time [Mittal and Parashar, 2019; Cymerman and Nosrat, 2020; Ulusoy et al., 2019]. This technique was more beneficial than traditional treatments, especially in growing subjects, as teeth preservation is critical for skeletal and dental development. However, another study reported that pulp revascularisation had no obvious effects on promoting root development or dentine formation in traumatised immature teeth [Nazzal et al., 2018]. Furthermore, adverse events such as a measurable

change in the colour of the crown associated with RET were also observed [Nazzal et al., 2018; Dabbagh et al., 2012]. Nagy et al. [2014] discovered that more failure cases occurred in the RET group than the AP group. A meta-analysis of observational studies revealed that RET was not superior to AP [Nicoloso et al., 2019]. Another meta-analysis also showed that MTA apexification produced better success rates in the endodontic treatment of immature necrotic permanent teeth [Nicoloso et al., 2017]. However, a review pointed out that the lack of meta-analysis base on randomised clinical trials comparing these two treatment modalities made the comparisons less conclusive [Torabinejad et al., 2017]. Such conditions make it difficult for dentists to choose the therapeutic plan for immature necrotic teeth. St Paul A [2017], in a survey of treatment decisions for immature permanent tooth disease, showed that the majority of dentists would prefer apexification when considering the evidence supporting treatment (60%) and the predictability of treatment results (77.8%). The evidence-based and risk prediction become the important factors affecting decision making, which is not conducive to the optimisation of treatment plans.

The histological basis for the treatment of immature necrotic teeth depends on the restoration of the residual pulp tissues and the vitality of the developing apical complex (DAC). The DAC consists of Hertwig's epithelial root sheath (HERS), dental papilla and dental follicle, which affords a suitable periodontal microenvironment and contains stem/progenitor cells capable of differentiation into multiple tooth root and periodontium-forming cells [Huang et al., 2008; Gronthos et al., 2000; Sonoyama et al., 2006; Sonoyama et al., 2008]. Inflammatory conditions may alter the characteristics and phenotype of stem/progenitor cells, affecting the therapeutic efficacy. Controlling periapical inflammation was the key point in the treatment of immature necrotic teeth. Thus, it is necessary to systematically analyse the efficacy of the treatments that promote periapical healing.

Currently, controversial findings on this topic have been reported, which made us wonder how these findings would influence the results of a new meta-analysis [Nagy et al., 2014; Huang et al., 2013]. Clinical decisions about the optimal treatment strategy for the patient should be made based on specific scientific evidence after assessing the validity of the treatment. To the best of our knowledge, this is the first systematic review and meta-analysis that synthesized data and results of randomized clinical trials that directly compared revascularisation with apexification in immature necrotic teeth. We are not simply comparing the success rate; we are also conducting a statistical analysis of the efficacy of periapical healing for the first time. Moreover, as no clear definitions of success and failure as a result in RET and AP, we attempt to classify and systematically analyze the overall outcomes via combining clinical and imaging results, which are considered to have stronger scientific evidence.

Materials and methods

Protocol and registration

This systematic review was based on the Cochrane review methodology and followed the criteria of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The protocol for this systematic review was registered on INPLASY (202090013) and is available in full at inplasy.com (https://doi.org/10.37766/inplasy2020.9.0013).

PICO question

The patient population, intervention, comparison, and outcome framework was used to formulate the following questions:

1. For the treatment of immature necrotic teeth, does revascularisation result in better periapical healing compared with the periapical healing associated with apexification?
2. For the treatment of immature necrotic teeth, does revascularisation result in a higher risk of unsuccessful treatment compared with that of apexification?
3. For the treatment of immature necrotic teeth, does revascularisation result in better root development compared with the outcomes of apexification?

Search strategy

A comprehensive literature search was conducted in MEDLINE via PubMed databases up to September 2020. The search strategy used to explore MEDLINE via the PubMed database was as follows: ((((((((((immature teeth) OR immature tooth) OR immature permanent teeth) OR immature permanent tooth) OR immature dentition) OR young permanent teeth) OR young permanent tooth) OR young permanent dentition)) AND ((((((((((((revascularisation) OR regeneration) OR revitalisation) OR pulp revascularisation) OR pulpal regeneration) OR pulp revitalisation) OR root canal revascularisation) OR root maturation) OR regenerative endodontic) OR regenerative endodontic therapy) OR regenerative endodontic procedure) OR endodontic angiogenesis)) AND ("Apexification" [MeSH] OR apexification OR apexogenesis OR root end formation OR root apex closure OR apical closure OR root induction))) AND ("2001/01/01"[PDAT] : "2020/09/07"[PDAT]).

Study selection criteria and data extraction

Study inclusion criteria were as follows.

1. Study: Randomized controlled trials.
2. Participants: Patients with immature necrotic permanent teeth.
3. Intervention: Regenerative endodontic therapy.
4. Comparison: Apexification therapy.
5. Outcomes: Reported clinical and radiographic outcomes.

Case reports, proceedings, letters, comments, editorials, and personal communications were excluded.

Data extraction was carried out by two researchers independently, and in cases of disagreement, discussion or judgment was made by a third party. The data extracted included the literature ID, author and year of publication, type of study, type of teeth, sample size, age of participants, etiology and diagnosis of pulp necrosis, use of irrigating solution and intracanal medication, presence of indicators signifying root development, periapical healing and overall effective rate.

Outcome measures

The main outcomes were clinical and radiographic results, including periapical periodontitis, changes in root length, root thickness and apex closure after intervention. The overall results were classified into the following 3 types.

1. Healed—the elimination of symptoms, and X-ray film showed complete resolution of periradicular radiolucency and an increase in the root length/thickness or apical closure of the affected teeth.
2. Improvement—asymptomatic with reduction of the periapex shadow and calcium in the root tips or a decrease in apical diameter.

Study	Lin J, et al.	Saravanan Poorni, et al.	Mohamed M. Nagy, et al.	Huang Y, et al.	Narang et al.
Country	China	India	Egypt	China	India
Year	2017	2016	2014	2013	2015
Type of study	Randomised controlled study	Randomised controlled study	Randomised controlled study	Randomised controlled study	Randomised controlled study
Age of patient (year)	6-18	7-16	9-13	7-13	<20
Type of teeth	Incisors/premolars	Anteriors/premolar	Anterior	NR	Anterior
Teeth (n) / Patients (n)	103/103	18/18	29/29	34/34	20/20
Aetiology	Dens evaginatus or trauma	NR	NR	Caries or trauma	NR
Diagnosis of pulp necrosis	Clinical and radiographic examinations	Clinical and radiographic examinations	Clinical and radiographic examinations	NR	Clinical and radiographic examinations
Type of intervention	CH, ACB	MTA, BC (TAP), BC (DAP)	MTA, BC, BC + FGF	CH, BC	MTA, BC, PRP, PRF
Root canal irrigants	NaOCl (1.5%)+NaCl (0.9%)+EDTA (18%)	Chlorhexidine (2%) + NaOCl (3%)	NaOCl (2.6%)	H2O2 (3%) + NaCl (0.9%)	NaOCl (2.5%)
Apical inducer	CH	MTA	MTA	CH	MTA
Type of intracanal medication	TAP	TAP, DAP	TAP	Metronidazole	TAP
Scaffold	ACB	BC	BC, BC + FGF	BC	BC, PRP, PRF
Type of the scaffold sealant	MTA	Glass ionomer cement	MTA	CH	Glass ionomer cement
Follow-up (month)	3, 6, 9, 12	6, 12	3, 6, 12, 18	6-18	6-18
Periapical healing (n%)	ACB: 100%; CH: 100%	NR	NR	NR	BC:60%;PRP:80%; PRF:100%; MTA: 100%
Changes in root length (mm)	ACB: 1. 64 ± 1.43; CH: 0.06 ± 1.06	BC (TAP): 0.92 ± 1.69; BC (DAP): -0.37 ± 2.05; MTA: 0.03 ± 1.17	BC: 1.20 ± 0.50; BC+FGF: 1.30 ± 0.50; MTA: 0.00 ± 0.00	NR	NR
Inclease in root length (n%)	ACB: 81.16%; CH: 26.47%	NR	NR	BC:58.8%; CH:0%	BC: 40%; PRP: 40%; PRF:100%; MTA:0%
Inclease in root thickness (n%)	ACB:82.60%,CH:0%	NR	NR	BC:82.35%,CH:0%	BC:50%,PRP:20%, PRF:100%,MTA:0%
Apical closure (n%)	ACB: 65.21%; CH: 82.35%	NR	NR	BC: 82.35%; CH: 70.59%	BC: 60%; PRP: 40%; PRF: 60%; MTA: 0%
Overall effective rate (n%)	ACB: 89.8%; CH: 97%	NR	BC: 90%; BC+FGF: 80%; MTA: 100%	BC: 82.35%; CH: 70.58%	NR

NR: not reported; CH: calcium hydroxide; ACB: absorbable collagen barrier; MTA: mineral trioxide aggregate; BC: blood clot; FGF: fibroblast growth factor; TAP: triple antibiotic paste; DAP: double antibiotic paste; PRP: platelet-rich plasma; PRF: platelet-rich fibrin

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

3. Invalid—persistent clinical signs and symptoms or X-ray film showed that the root tips were not closed and there was no calcium deposit or absorption shadow inside or outside the root.

The total overall effective rate = (healed + improvement) number of teeth/total number of teeth × 100% and invalid rate = invalid number of teeth/total number of teeth × 100%. If the overall effective rate or the invalid rate adopted in the included study were consistent with the efficiency standards established in this paper, the experimental results were extracted directly; otherwise, the experimental results were extracted according to the standards established in this paper. Data extraction was carried out by two researchers independently. If there were differences, they were discussed or determined by a third party. If the data were incomplete, the original author of the article was contacted for clarification.

Quality and risk of bias assessment

Two reviewers independently assessed the quality of the selected studies according to the Cochrane Collaboration's tool for randomised controlled trials, and items were evaluated in three categories: low risk of bias, unclear bias and high risk of bias. The following characteristics were evaluated: random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting risk. Other biases resulting from these questions were graphed and assessed using Review Manager 5.3.

Statistical methods for meta-analysis

Meta-analysis was conducted using Cochrane RevMan version 5.3. A random-effect model was presented as a forest plot with a 95% confidence interval (CI). Pooled-effect estimates were obtained comparing periapical healing, the overall effective rate and indicators of root development between groups; this information was reported as the risk ratio (RR). $P<0.05$ was considered statistically significant (Z test). The Cochran Q test was used to assess heterogeneity

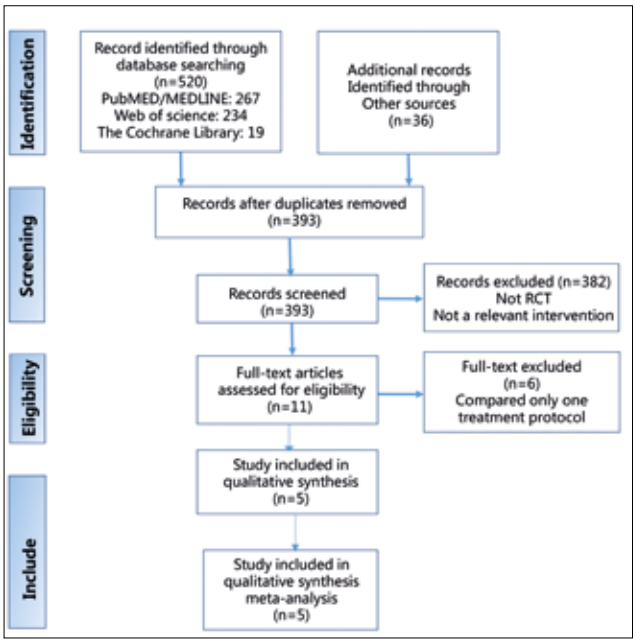


FIG. 1 Flow diagram of the study selection.

among studies, with a threshold p-value of 0.1, and the inconsistent I2 test, in which values between 25-50% were considered indicative of low heterogeneity, values between 50-75% indicated moderate heterogeneity and values greater than 75% indicated high heterogeneity.

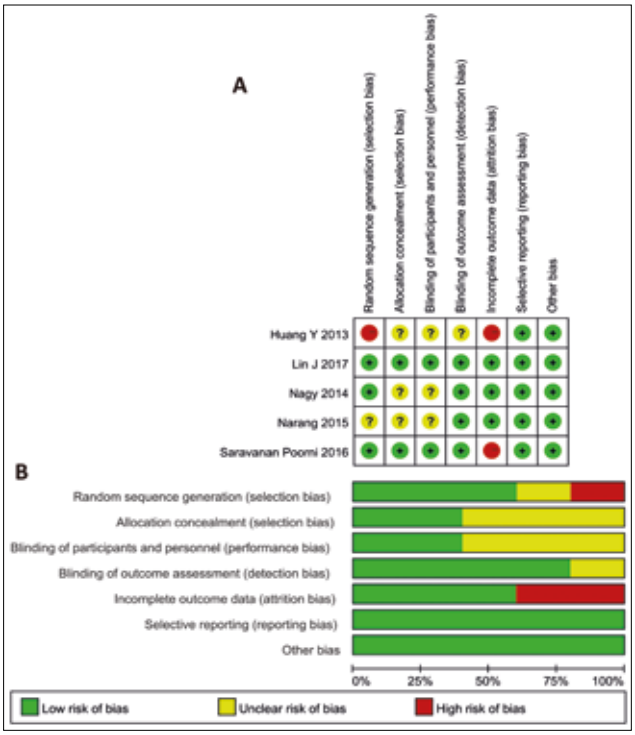


FIG. 2 Quality assessment results using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.3.0). A: The risk of bias summary. B: The overall assessment of risk of bias.

Results

Study selection

For the study selection (Fig. 1) a total of 556 articles were identified in the database search. After duplicates were removed, 393 articles remained and 382 studies were excluded because they were non-randomised controlled trials or nonrelevant studies. The full texts of 11 articles were examined for eligibility and 6 one-arm studies were excluded. Finally, 5 studies were included in the meta-analysis [Nagy et al., 2014; Huang et al., 2013; Lin et al., 2017; Poorni et al., 2017; Narang et al., 2015].

Study characteristics

The characteristics of each included article are summarised in Table 1. The included studies were prospective randomised controlled studies. A total of 204 teeth were included in the five studies. Pulp necrosis was diagnosed and evaluated based on the clinical examination combined with radiographic results. The publication years ranged from 2013 to 2017. Two of the five studies were carried out in China, one was conducted in Egypt and the other two were conducted in India. The age of the patients included in the clinical trials ranged from 7 to 20 years. In most of the studies [Lin et al., 2017; Poorni et al., 2017; Narang et al., 2015], sodium hypochlorite (1.5%-3%) was the main irrigant in the AP and RET groups, and the other [Huang et al., 2013] used hydrogen peroxide (3%) and normal saline (0.9%). All of the studies used antibiotics as the intracanal medicament in the RET group. Triple antibiotic paste (TAP), a combination of ciprofloxacin, metronidazole, and minocycline or clindamycin hydrochloride or doxycycline, was the most common type. In one study, only metronidazole was used to eliminate the bacteria [Huang et al., 2013]. Another study compared the clinical outcomes of triple antibiotic paste versus a double antibiotic paste intracanal medicament [Poorni et al., 2017]. In the RET group, the most common scaffolds were a blood clot (4 groups) and an injectable scaffold (4 groups). The most common types of scaffold sealant were MTA (2 studies) and glass ionomer cement (2 studies); the other study used CH. The shortest follow-up period was 12 months, and the longest was 18 months.

Quality assessment of included studies

Results of the quality assessment of the studies are shown in Figure 2. Three of the five included studies had low risk of bias in random sequence generation. All included studies had low risk of bias in incomplete selective reporting. However, three studies had an unclear risk in blinding of participants and personnel and allocation concealment, and two studies of high risk of bias in incomplete outcome assessment.

Outcomes of synthesis of data

Two studies qualitatively reported the healing of periapical periodontitis [Lin et al., 2017; Narang et al., 2015]. Because no significant heterogeneity was shown when pooling the data from the included studies (χ^2=0.10, df=4, P=0.10, I2=52%), a fixed-effects model of analysis was performed (Fig. 3). No significant difference in the periapical healing rate was observed between the RET and AP groups (pooled RR = 0.95, 95% CI: [0.88, 1.03]), Z= 0.19, P=0.23).

Three studies quantitatively reported changes in root length [Nagy et al., 2014; Lin et al., 2017; Poorni et al., 2017]. All of those included studies defined root length as a straight line

from the cementoenamel junction (CEJ) to the radiographic apex of the tooth in millimeters. A fixed-effects model of analysis was performed (Fig. 4A). The root length was significantly increased in millimeters in the RET group compared with the AP group (pooled difference in means=1.28, 95% CI:[1.08,1.48], Z=12.69, P<0.00001,I2=22%). Furthermore, a fixed-effects model of analysis on the effective rate of root lengthening was used (Fig. 4B), as no significant heterogeneity was shown in the pooled data from the included studies (χ^2=2.92, df=4, P=0.57, I2=0%) [Huang et al., 2013; Lin et al., 2017; Narang et al., 2015]. The effective rate of root lengthening was significantly increased in the RET group compared with the AP group (pooled RR = 3.58, 95% CI: [2.11, 6.07]), Z= 4.73, P <0.00001).

Apical closure was analysed qualitatively in three studies [Huang et al., 2013; Lin et al., 2017; Narang et al., 2015]. A random model of analysis was used (Fig. 5A) and no significant difference was observed in the apical closure rate between the RET group and the AP group (pooled RR =1.18, 95% CI: [0.68, 2.04]), Z= 0.59, P=0.56, I2=61%). A fixed-effects model of analysis on root thickness was used (Fig. 5B), as no significant heterogeneity was shown in the pooled data from the three included studies (χ^2=4.03, df=4, P=0.66, I2=1%). The effective rate of root thickness was significantly different in the RET group compared with the apexification group (pooled RR = 22.63, 95% CI: [6.08, 84.26]), Z= 4.65, P<0.00001).

The overall effective rate was calculated and extracted from three studies [Nagy et al., 2014; Huang et al., 2013; Lin et al., 2017]. A fixed-effects model of analysis was used (Fig. 5C). Analysis results showed no significant difference in the overall effective rate between revascularisation and apexification among the included studies (pooled RR = 0.94, 95% CI: [0.85, 1.04]), Z=1.17, P=0.24, I2=0).

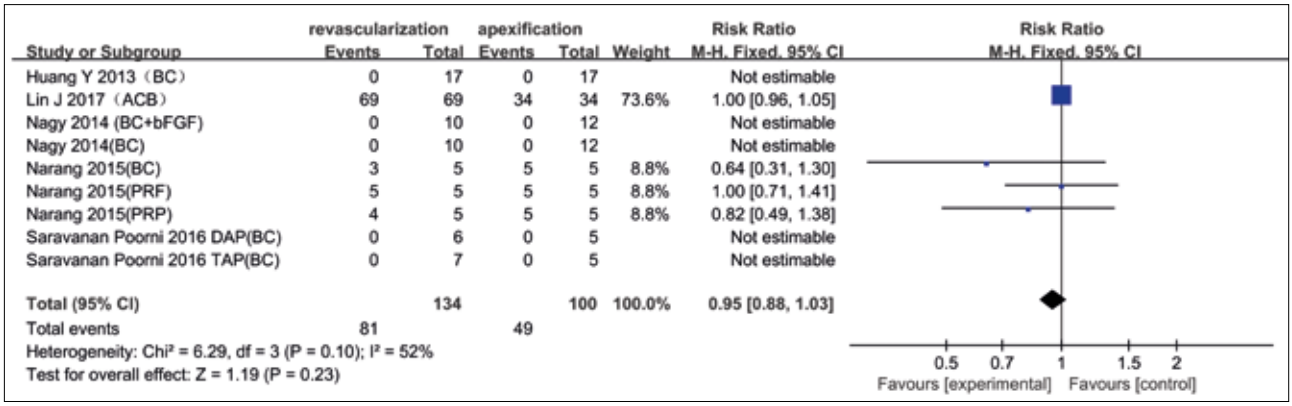


FIG. 3 Forest plot for the meta-analysis of periapical healing.

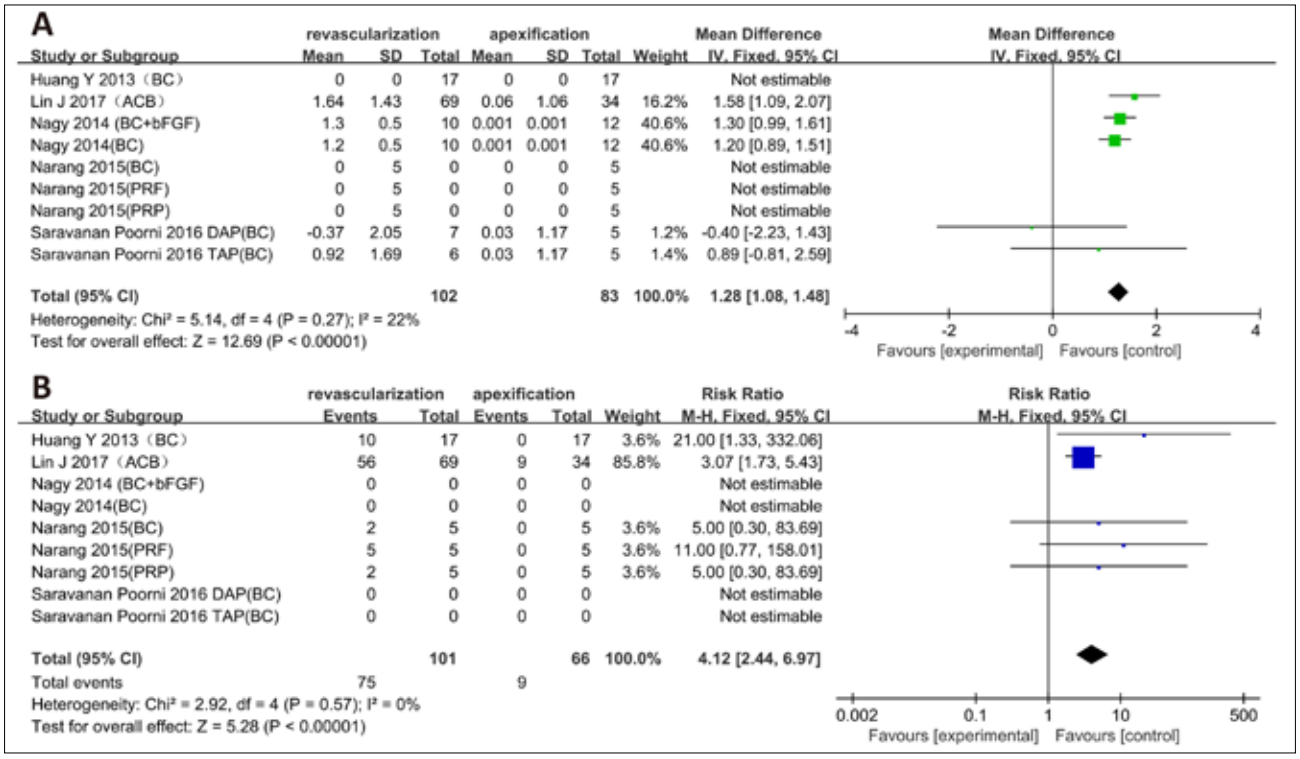


FIG. 4 Forest plot for the meta-analysis of the change of root length. (A: The change of root lengthening in the millimeters. B: The change of root lengthening in the effective rate.

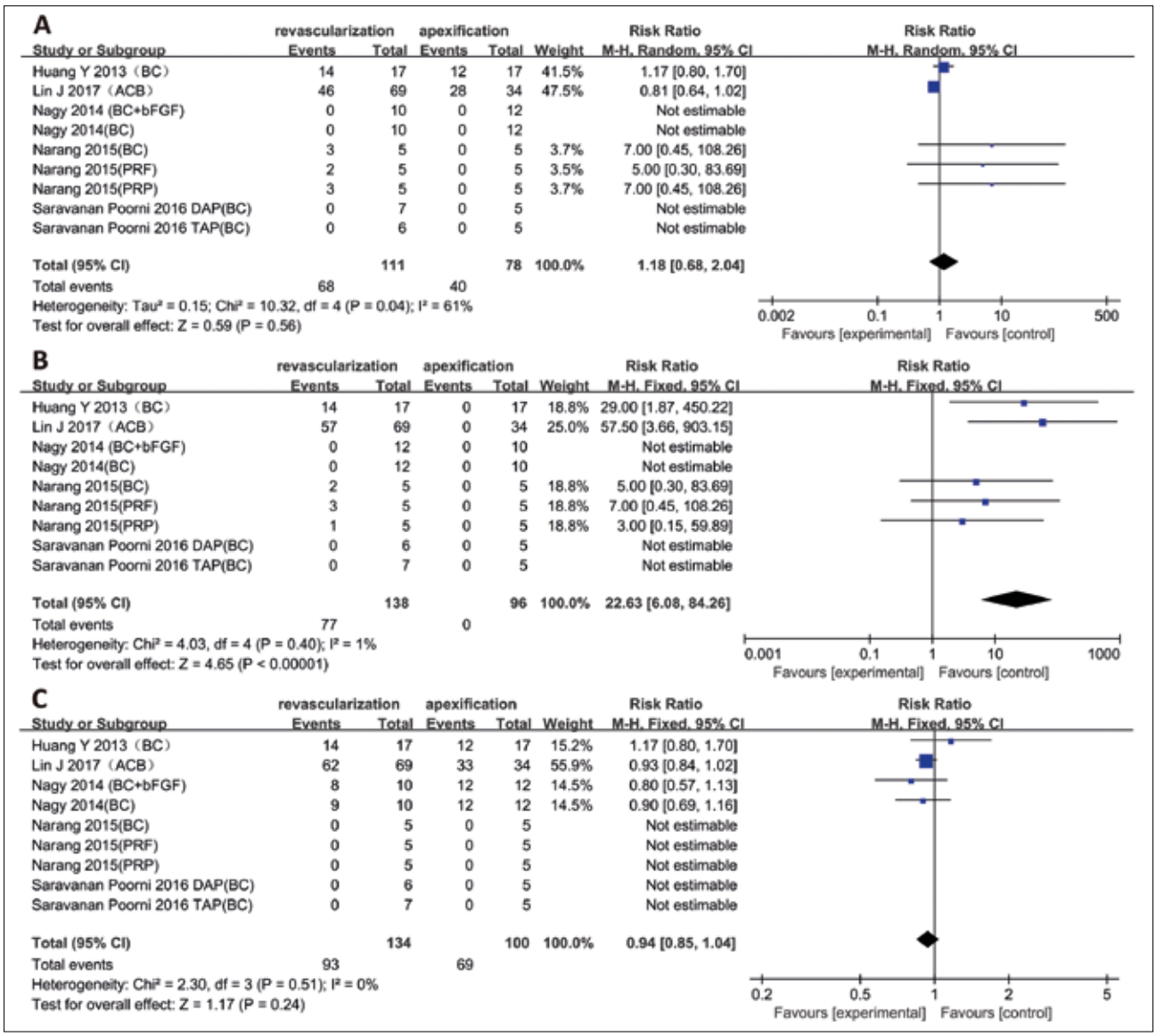


FIG. 5 A: Forest plot for the meta-analysis of apical closure. B: Forest plot for the meta-analysis of root thickness. C: Forest plot for the meta-analysis of effective rate.

Discussion

The endodontic treatment of immature necrotic teeth with incomplete root formation is extremely challenging. A large apical diameter and uncoordinated crown-to-root ratio increase the difficulty of pulp treatment and later repair, which may lead to a low retention rate. RET, as a new treatment with good efficacy in promoting continued root development, has been reported in many clinical trials [Bonte et al., 2015; Holden et al., 2008]. However, several studies have also shown that RET was not superior to other AP techniques, as more adverse events and a lower success rates were observed with RET [Nagy et al., 2014]. The lack of systematic analysis creates obstacle in the promotion of new technologies and the selection of treatment options. As no consensus has been reached with respect to the use of AP or RET, the purpose of this research was to carry out a meta-analysis that provides a reference for the scientific choice of treatment.

Once pulp necrosis occurs, young permanent teeth with wide apical foramina may spread throughout the tissue following an infection and extend into the periapical tissues, creating an environment that is not conducive to healing. The control of periapical inflammation is an important factor affecting the success of the treatment. Two studies with four groups qualitatively reported the healing of periapical periodontitis [Lin et al., 2017; Narang et al., 2015]. The effective rate in the treatment of periapical periodontitis in the RET groups ranged from 60% to 100%. However, in the AP groups, it was 100% in both studies. Possible reasons for this difference are residual bacteria [Fouad, 2011; Verma et al., 2017] and instability of the scaffold [Piva et al., 2014]. In most AP cases, following chemo-mechanical disinfection of the root canal space, an inductor material with antibacterial properties CH or MTA was placed [Damle et al., 2012]. Thus, if residual bacteria are left behind, their numbers are thought to be minimal, and root filling is thought to minimise their

access to sustain the periapical lesion, creating an environment conducive to healing [Fabricius et al., 2006; Refaei et al., 2020]. Conversely, in RET cases, intracanal medication was removed when preparing to induce bleeding or inject scaffolds. At the regeneration stage, leaving the root canal unfilled as the regenerative tissue develops may be conducive to bacterial proliferation if residual bacteria remain. As a result, the RET group was more likely to fail in the treatment of periapical inflammation than the AP group. The efficacy of pulp regeneration in the healing of periapical periodontitis requires a higher level of disinfection. Root canal irrigation and intracranial medication protocols are two crucial components of regenerative endodontic therapy [Fouad, 2011]. All of the included RET groups were irrigated with sodium hypochlorite solution and medicated with TAP. However, the blood clot group showed the worst periapical healing outcomes. Injecting stable scaffolds may sustain a disinfecting feature for an extended period to allow for more predictable repair of periodontal tissue [Piva et al., 2014]. The curative effect of periapical periodontitis was improved with the application of scaffolds. Pooled data from the included studies showed no significant difference in the periapical healing rate between the RET and AP groups.

Immature necrotic teeth with interrupted root development usually lead to a poor crown-to-root ratio, which compromises the long-term prognosis of the tooth. The formation of good apical closure and the promotion of root elongation and thickness are very important for the treatment of immature necrotic teeth. Nagy et al. [2014] found that the increase in length in the REG group (blood clot) and the FGF group (blood clot + injectable scaffold) was 1.2 ± 0.5 mm and 1.3 ± 0.12 mm, respectively. AP groups did not show any increase in length or thickness. Narang et al. [2015] observed a similar result in their study; there was no apical closure, root lengthening or thickening in AP groups. The RET groups achieved better increases in root length and width. Root lengthening was also found in 10 of 17 cases only in the RET groups according to Huang et al. [2013]. J Lin et al. [2017] conducted a quantitative and qualitative analysis of root elongation. According to their study, 81.16% of the cases in the RET group achieved valid results in terms of root lengthening, while only 9 cases (26.47%) were in the AP group. Moreover, the RET group exhibited a significant increase in root length in millimeters (1.64±1.43 mm vs 0.60±1.06 mm, $P<0.05$) compared with root length of the apexification group. The possible mechanism for this difference may be due to the increased thickness and length of the root being caused by the deposition of cementum-like tissue, which relies on the function of stem cells [Lei et al., 2015]. Current RET commonly uses provoked apical bleeding, which enables PDL stem cells, bone marrow mesenchymal stem cells, and the Hertwig epithelial root sheath to be transplanted into the canal space [Huang et al., 2008; Lovelace et al., 2011; Chen et al., 2012]. On the other hand, blood clots or biological scaffolds are considered storage factors that stimulate growth, differentiation and maturation of fibroblasts, odontoblasts, and cementoblasts from precursor cells [Huang et al., 2013; Ulusoy et al., 2019]. However, in AP groups, the root canal is filled with a dense material that does not contain growth factors, such as MTA and CH. In contrast, another study [Poorni et al., 2017] showed that the mean root length was increased in the RET (TAP) group but decreased in the RET (DAP) group, while it increased marginally in the AP group. Meta-analysis was performed to summarize the effects of the two operations on root development and showed that root length and root thickness were significantly increased in the RET group compared with the AP group. Adequate root length is a guarantee for later dental restoration. Root length should be considered when choosing the treatment plan. RET could be considered a first treatment option, especially for patients with obvious insufficient root length.

A clear definition of success and failure as an outcome in RET and AP is still lacking, and success and failure were assessed using different outcome measures [Jeeruphan et al., 2012; Kahler et al., 2014; Alobaid et al., 2014; Saoud et al., 2014]. Success was defined as patients with no signs of endodontic pathosis in several studies [Narang et al., 2015; Saoud et al., 2014]. However, for immature teeth with markedly deficient root development, even if the periapical inflammation is completely eliminated, it is still inevitable that the root will be removed if a certain length cannot be obtained in the later stage to meet the condition of repair. Other studies have suggested that success should be defined as an asymptomatic state and the disappearance of apical radiolucency with an increase in root length, a decrease in the apical foramen, or both [Lin et al., 2017]. If the follow-up time is short, this criterion tends to define AP as a failure due to its long treatment cycle. In the presented study, for the first time, we classified the comprehensive results into three types and suggest that the overall effective rate/valid rate are more appropriate when comparing the early efficacy of the two operations. Our systematic analysis did not support that RET is more likely to produce valid cases, both RET and AP provide similar overall effective rates.

The main adverse events were calcification and discolouration in the root canal. Calcification in the root canal may be related to the use of MTA [Masuda-Murakami et al., 2010], and it was found in 26 (37.7%) RET cases in the included study [Lin et al., 2017], while 30 (43.5%) RET cases showed discoloration. In the present study, minocycline, one of the triple pastes used to disinfect root canals, was found to cause tooth discolouration. Due to photoactivation, minocycline binds calcium ions to form insoluble complexes through chelation [Kim et al., 2010]. In an attempt to minimise these adverse events, some workhs have recommended the use of a biantibiotic paste omitting minocycline or replacing it with Arestin and amoxicillin [Thomson and Kahler, 2010; Trope, 2010]. One of the included studies [Poorni et al., 2017] used double antibiotic paste for the trial, though the results showed that the efficacy of double antibiotic in promoting root prolongation was not as good as that of triple paste. It is still necessary to explore drugs that can reduce adverse reactions without affecting the curative effect of root development.

Conclusion

Based on our meta-analysis, it can be concluded that both treatment protocols were effective options with regard to the healing of periapical periodontitis and the closure of open apices. RET is more effective for root elongation and thickening without higher risk of overall treatment invalid, suggesting that RET could be considered a first choice for the treatment of immature necrotic teeth with severe root maldevelopment. For patients with high aesthetic requirements, RET should be used with caution and the patient's intention should be considered in the treatment approach.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Acknowledgements

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Authorship

YL and JH conceived and designed the experiments, and participated in its design and coordination and helped to draft the manuscript and revise the manuscript. YX and FL performed the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

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