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ORIGINAL ARTICLE

Comparison of mineral trioxide aggregate and calcium hydroxide for apexification of immature permanent teeth: A systematic review and meta-analysis

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KEYWORDS
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Background/purpose: Calcium hydroxide and mineral trioxide aggregate (MTA) are used for inducing a calcific barrier at an open tooth root (apexification). The purpose of this study was to compare the efficacy of calcium hydroxide and MTA for apexification of immature permanent teeth.
Methods: Medline, Cochrane, EMBASE, and Google Scholar were searched until November 24, 2015, using the keywords apexification, permanent teeth, MTA, and calcium hydroxide.
Results: Of 216 studies identified, four studies were included. There were no differences in the clinical success rate [pooled odds ratio (OR) = 3.03, 95% confidence interval (CI): 0.42–21.72, p = 0.271], radiographic success rate (pooled OR = 4.30, 95% CI: 0.45–41.36, $p = 0.206$), or apical barrier formation rate (pooled OR = 1.71, 95% CI: 0.59–4.96, p = 0.322) between calcium hydroxide and MTA groups. The time required for apical barrier formation was significantly less in the MTA group (pooled difference in means = −3.58, 95% CI: from −4.91 to −2.25, $p < 0.001$).
Conclusion: While both materials provide similar success rates, the shorter treatment time with MTA may translate into higher overall success rates because of better patient compliance.

Conflicts of interest: All authors declare that no conflicts of interest exist.

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Introduction

Apical periodontitis can lead to pulpal necrosis and arrest of root development, and is especially challenging to treat in immature permanent teeth in children.[1] Untimely or incorrect management can result in loss of permanent teeth, disorders of mandibular growth and masticatory function, and even speech disorders and facial cosmetic impairment.[1,2] Thus, correct treatment to prevent any loss of these teeth is vitally important. Apexification is a nonsurgical method of inducing a calcific barrier at the open root apex of nonvital teeth.[1,2] The barrier prevents toxins and bacteria from entering periradicular tissue, and facilitates placement of a root canal sealant and filling material.[3] However, an ideal apexification material has yet to be determined.

Calcium hydroxide is commonly used for apexification as it has no adverse periapical reactions, predictable results, and can be mixed with a number of different substances (camphorated mono chlorophenol, distilled water, saline, anesthetic solutions, chlorhexidine, and cresatin) to induce apical closure.[1,2] However, calcium hydroxide has a number of limitations including variable treatment time ranging from 5 months to 20 months, apical closure in relationship to treatment time is unpredictable, an increased risk of tooth fracture, and poor patient compliance with follow-up due to the extended treatment time, all of which can affect treatment outcomes.[1,2]

Mineral trioxide aggregate (MTA) is used as an apical barrier for teeth with immature apices, repair of root perforations, root-end filling, pulp capping, and pulpotomy procedures.[4] MTA has a number of favorable characteristics including biocompatibility, antimicrobial activity and prevention of bacterial leakage, no cytotoxicity, and can stimulate cytokine release from bone cells to promote hard tissue formation.[5,6] It also has a shorter treatment time compared with calcium hydroxide, and a more predictable time to apical closure.[5,6] However, MTA has some limitations such as nonreinforcement of root canal dentin and a higher cost than calcium hydroxide.[5,6] In addition, there are few studies examining the long-term efficacy of MTA for endodontic treatment in primary teeth.[4]

Few high-quality studies have directly compared the outcomes of calcium hydroxide and MTA for apexification, and thus there is no consensus as to which may be associated with superior outcomes. Thus, the purpose of the current study is to perform a meta-analysis comparing the outcomes of calcium hydroxide and MTA for the apexification of immature permanent teeth.

Methods

Strategy of literature search

PRISMA guidelines were used when conducting this systematic review and meta-analysis.[7] Medline, Cochrane, EMBASE, and Google Scholar were searched from inception until November 24, 2015, using combinations of the keywords apexification, permanent teeth, MTA, and calcium hydroxide. Searches were performed by two independent reviewers to identify potentially relevant articles, and the reference lists of potentially relevant articles were also hand-searched. A third reviewer was consulted where there was uncertainty regarding eligibility, and a decision arrived at by consensus.

Study selection criteria and data extraction

Study inclusion criteria were: (1) randomized controlled trials, prospective and retrospective studies, and case series; (2) patients had permanent immature teeth for which apexification was indicated; (3) compared calcium hydroxide versus MTA; and (4) reported quantitative clinical or radiographic outcomes. Letters, comments, editorials, case reports, proceedings, and personal communications were excluded. Studies that were performed *in vitro* and those that did not report a quantitative primary outcome were also excluded. The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and sex, intervention, and clinical outcomes.

Quality assessment

The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).[8] Briefly, six domains are evaluated: (1) random sequence generation; (2) allocation concealment; (3) blinding of patients and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; and (6) selective reporting risk. Risks of bias figures were generated using Cochrane RevMan version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Outcome measures and data analysis

The primary outcome was the clinical success rate. Secondary outcomes were radiographic success rate, apical barrier formation rate, and the time required for apical barrier formation.

Pooled odds ratios (ORs) were calculated for the clinical success rate, radiographic success rate, and apical barrier formation rate, and compared between the calcium hydroxide and MTA groups. Differences in means for the time required for apical barrier formation were calculated and compared between the two groups. The Cochran Q and the I^2 statistic were used to assess heterogeneity among studies. A value of $p < 0.10$ of the Q statistic was considered to indicate statistically significant heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability due to heterogeneity rather than chance, and a value $> 50\%$ was considered to indicate significant heterogeneity. If either the Q statistic or I^2 statistic indicated heterogeneity was present, a random-effects model of analysis was used (DerSimonian—Laird method). If no heterogeneity was present, a fixed-effects model (Mantel—Haenszel method) was used. Sensitivity of the meta-analysis was assessed using the leave-one-out approach. A two-sided p value < 0.05 was considered to indicate statistical

significance. If there were five or less studies, publication bias was not assessed because more than five studies are required to detect funnel plot asymmetry.[9] All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Study characteristics

A flow diagram of the study selection is shown in Figure 1. A total of 216 studies were identified in the database search, and 201 nonrelevant studies were excluded. The full texts of 15 articles were examined for eligibility and 10 were excluded, the reasons for which are shown in Figure 1. Thus, four studies were included in the meta-analysis.[10–13]

A total of 80 teeth were included in the four studies, and a summary of the characteristics and outcomes of the four studies are shown in Table 1. The total number of teeth in the MTA groups ranged from 10 to 15, the total number of teeth in the calcium hydroxide group ranged from 10 to 15, and the patient ages ranged from 6 years to 12 years. The clinical success rate ranged from 93% to 100% in the MTA groups, and from 87% to 100% in the calcium hydroxide groups. The radiographic success rate was 100% in the MTA groups and ranged from 87% to 93% in the calcium hydroxide groups. The number of teeth with apical barrier formation ranged from seven to 18 in the MTA groups, and from 10 to 13 in the calcium hydroxide groups, while the time required for apical barrier formation ranged from 3.0 months to

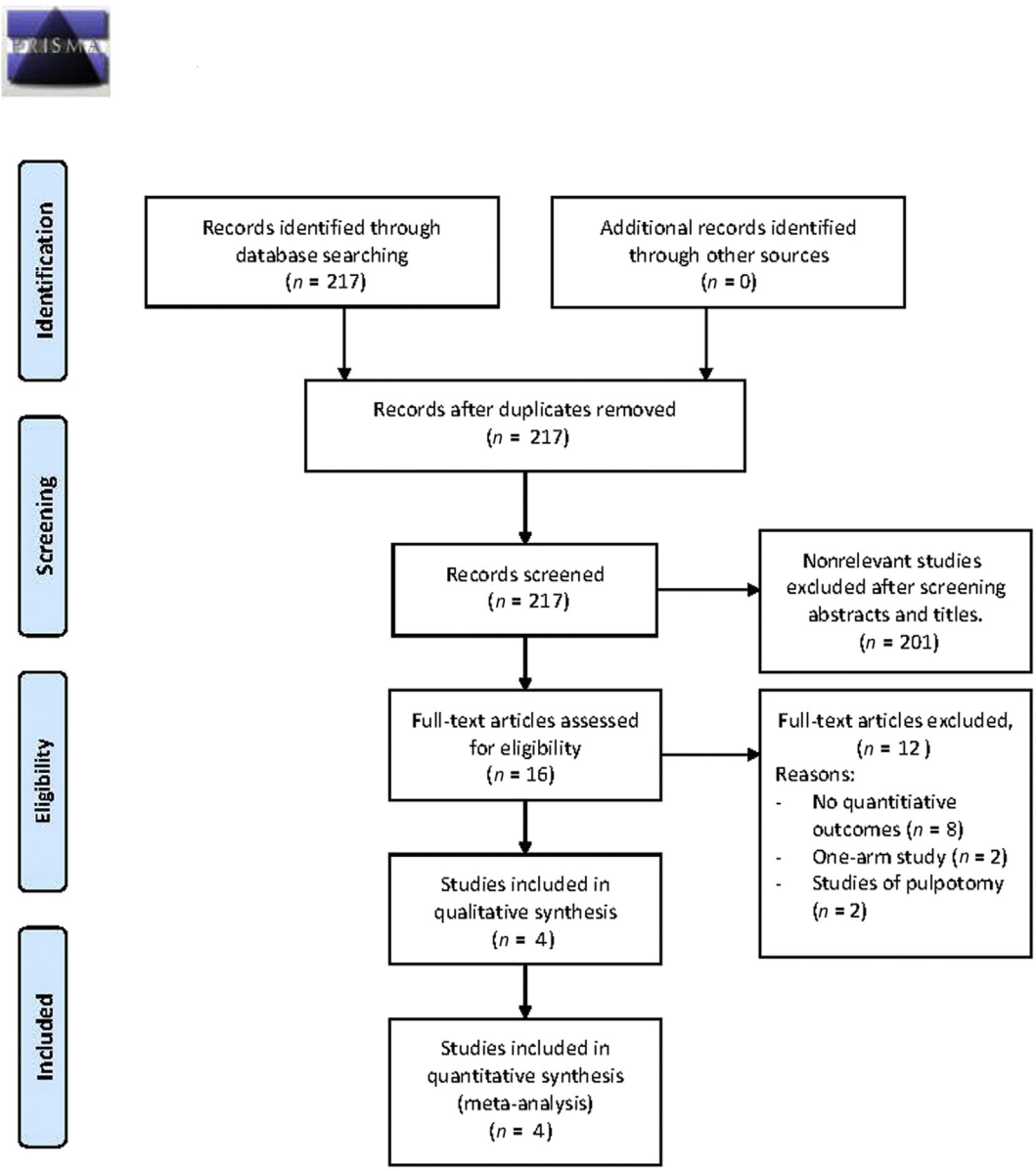

Figure 1 Flow diagram of the study selection.

Table 1 Basic characteristics of studies included in the meta-analysis.

Study (y)	No. of patients	No. of teeth	Intervention	Age (y)	Male (%)	No tenderness to percussion	Clinical success (%)	Radiographic success (%)	Apical barrier formation	Time required for apical barrier formation (mo)[a]
Bonte et al[10] (2015)	17	NR	MTA	10.2 (2.8)[a]	47	16/17	NR	NR	13	NR
	16	NR	Calcium hydroxide	10.9 (3.6)[a]	63	15/16	NR	NR	8	NR
Damle et al[11] (2012)	15	15	MTA	Range: 8–12	NR	15/15	100	100	13	4.5 (1.56), $n = 14$
	15	15	Calcium hydroxide		NR	15/15	93.3	93.3	13	7.93 (2.53), $n = 14$
El Meligy & Avery[12] (2006)	15	15	MTA	Range: 6–12	NR	15/15	100	100	15	NR
		15	Calcium hydroxide		NR	15/15	87	87	13	NR
Pradhan et al[13] (2006)	NR	10	MTA	NR	NR	NR	100	NR	7	3.0 (2.9), $n = 7$
	NR	10	Calcium hydroxide	NR	NR	NR	100	NR	10	7.0 (2.5), $n = 10$

MTA = mineral trioxide aggregate; NR = not reported.
[a] Mean (standard deviation).

4.5 months in the MTA groups and from 7.0 months to 7.9 months in the calcium hydroxide groups.

Clinical success rate

There was no significant heterogeneity when data from the three studies reporting clinical success rate[11–13] were pooled (Q = 0.44, df = 2, $p = 0.801$, $I^2 = 0\%$); therefore, a fixed-effects model of analysis was used (Figure 2). The analysis revealed that there was no statistical difference in clinical success rate between the MTA group and calcium hydroxide group (pooled OR = 3.03, 95% CI: 0.42–21.72, Z = 1.10, $p = 0.271$).

Radiographic success rate

Only two studies[11,12] reported radiographic success rate data. There was no significant heterogeneity when data from the two studies were pooled (Q = 0.06, df = 1, $p = 0.810$, $I^2 = 0\%$); therefore, a fixed-effects model of analysis was used (Figure 3A). The analysis revealed there was no statistical difference in the radiographic success rate between the MTA group and the calcium hydroxide group (pooled OR = 4.30, 95% CI: 0.45–41.36, Z = 1.26, $p = 0.206$).

Apical barrier formation rate

All four studies provided apical barrier formation rate data and were included in the analysis.[10–13] There was no significant heterogeneity when data from the four studies were pooled (Q = 4.70, df = 3, $p = 0.195$, $I^2 = 36.20\%$); therefore, a fixed-effects model of analysis was used (Figure 3B). The analysis revealed there was no statistical difference in the apical barrier formation rate between the MTA group and the calcium hydroxide group (pooled OR = 1.71, 95% CI: 0.59–4.96, Z = 0.99, $p = 0.322$).

Time required for apical barrier formation

Two studies[11,13] reported the time required for apical barrier formation. There was no significant heterogeneity when data from the two studies were pooled (Q = 0.14, df = 1, $p = 0.711$, $I^2 = 0\%$); therefore, a fixed-effects model of analysis was used (Figure 3C). The time required

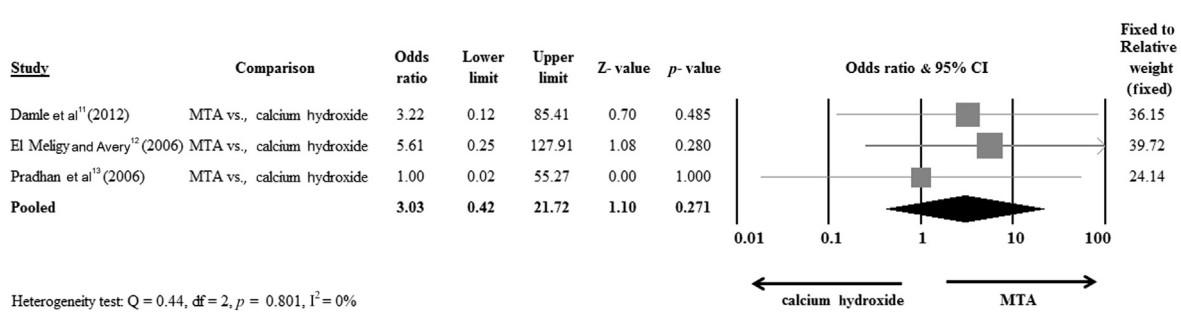

Figure 2 Forest plot for the meta-analysis of clinical success rate. CI = confidence interval; MTA = mineral trioxide aggregate.

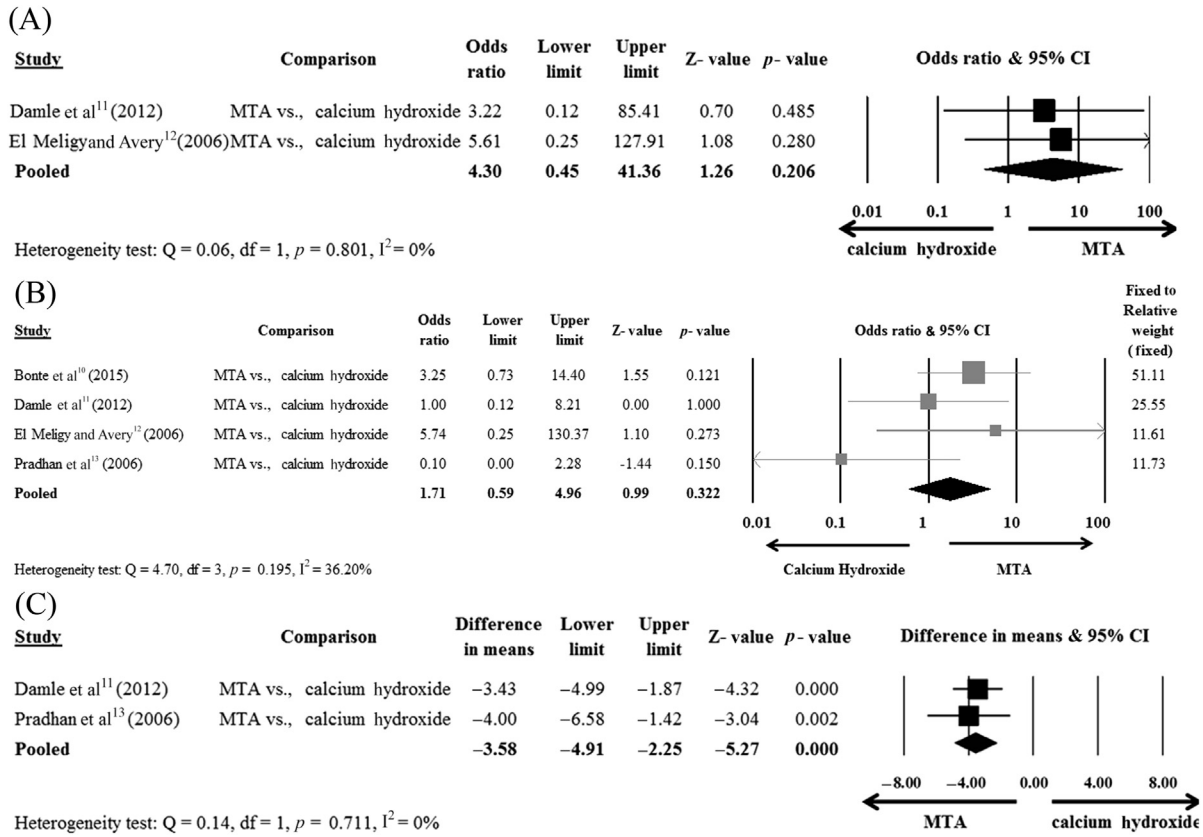

Figure 3 Forest plots for the meta-analysis of: (A) radiographic success rate; (B) apical barrier formation rate; (C) time required for apical barrier formation. CI = confidence interval; MTA = mineral trioxide aggregate.

for apical barrier formation was significantly less in the MTA group (pooled difference in means = −3.58, 95% CI: from −4.91 to −2.25, Z = −5.27, $p < 0.001$).

Sensitivity analysis

The results of meta-analysis using the leave-one-out approach to assess sensitivity are summarized in Figure 4. The direction and magnitude of the pooled estimates of clinical success rate did not vary considerably when individual studies were removed in turn, indicating that the meta-analysis had good reliability.

Publication bias

Publication bias was not assessed for these outcomes because more than five studies are required to detect funnel plot asymmetry.

Quality assessment

Results of the quality assessment of the studies are shown in Figures 5A and 5B. Three of the four included studies had low risk of bias in random sequence generation. All included studies had low risk of bias in incomplete outcome data and selective reporting. However, two of the four

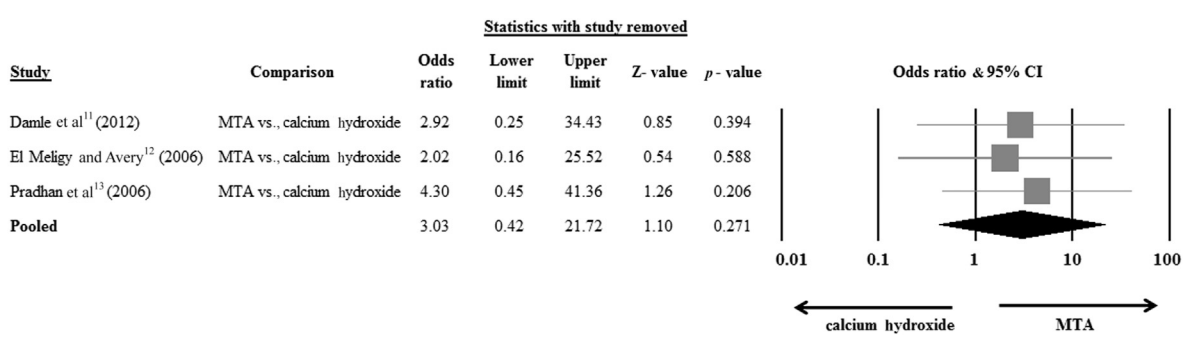

Figure 4 Results of the sensitivity analysis to examine the influence of individual studies on pooled estimates for clinical success rate using the leave-one-out approach. CI = confidence interval; MTA = mineral trioxide aggregate.

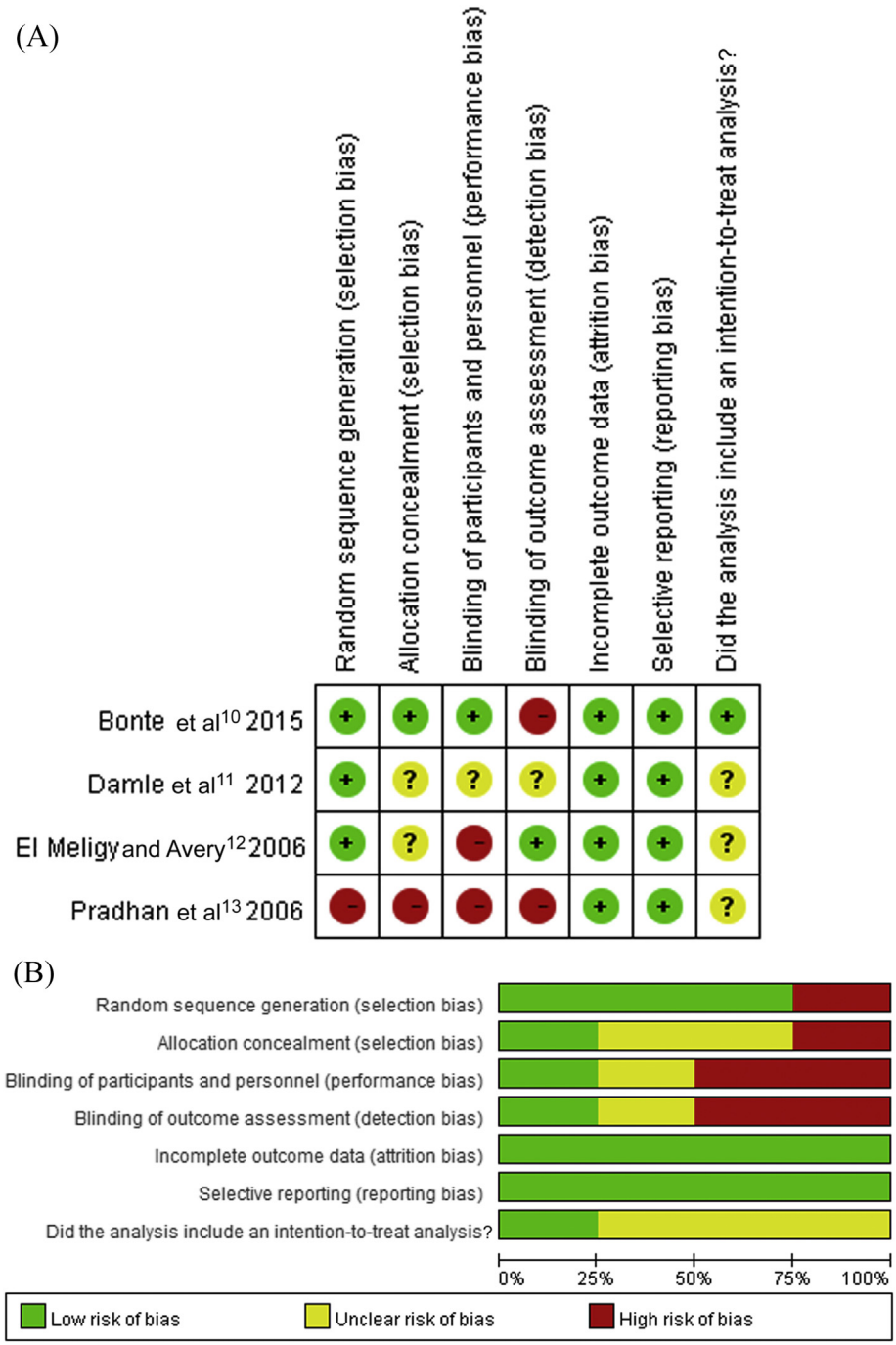

Figure 5 Quality assessment results using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0): (A) risk of bias summary; and (B) overall assessment of risk of bias.

studies had high risk of bias in blinding of participants and personnel, and three studies had an unclear risk of bias in intention-to-treat bias. Overall, the included studies had low risk in attrition bias and reporting bias, but had high risk in performance bias.

Discussion

The purpose of this meta-analysis was to determine whether calcium hydroxide or MTA provides better outcomes for the apexification of immature permanent teeth, as no consensus has been reached with respect to the use of these two materials and they both have unique advantages and drawbacks. The results showed that both materials had similar clinical success rates, radiographic success rates, and apical barrier formation rates. However, MTA was associated with a significantly shorter time to achieve apical barrier formation than the calcium hydroxide. This is of significance because many failures with calcium hydroxide are due to poor patient follow-up because of the extensive treatment time.

Calcium hydroxide has long been considered the method of choice for apexification, but its disadvantages including a prolonged treatment time have resulted in the search for new material.[1,2] MTA is a mixture of Portland cement and bismuth oxide that contains dicalcium silicate, tricalcium silicate, tricalcium aluminate, and tetracalcium aluminoferrite, as well as other mineral oxides.[14] The pH of 12.5 after setting is similar to that of calcium hydroxide.[14] MTA is unique in that it is the first material that has been shown to consistently allow for over growth of cementum and promote periodontal tissue regeneration.[6] While there are many animal studies that have examined MTA, high quality human studies comparing MTA and calcium hydroxide for apexification of immature teeth are few.

Only one other systematic review has compared calcium hydroxide and MTA for the apexificaiton of immature permanent teeth. In a meta-analysis published in 2011 by Chala et al[15] comparing calcium hydroxide and MTA, 300 studies of interest were identified but based on strict criteria only two were included, and they were two studies that were included in the current analysis.[12,13] Based on those two studies, the authors concluded that the results of the two compounds were comparable. A 2010 review compared the use of formocresol and MTA in primary teeth pulpotomy, and considering the frequency of radiographic findings such as furcation involvement and the potential cytotoxicity of formocresol the authors concluded that MTA was preferable.[16]

Individually, the four studies included in the current meta-analysis support the use of MTA. El Meligy and Avery[12] performed apexification with calcium hydroxide or MTA in 15 children with at least two necrotic permanent teeth and performed clinical and radiographic evaluations at 3 months, 6 months, and 12 months after treatment. Persistent periradicular inflammation and tenderness to percussion was present at 6 months and 12 months in two of 15 teeth treated with calcium hydroxide and in none of the teeth treated with MTA. Pradhan et al[13] treated 20 nonvital permanent maxillary incisors with unformed apices with apexification with MTA or calcium hydroxide. The mean time taken for apical biological barrier formation for the MTA and calcium hydroxide groups were 3 ± 2.9 months and 7 ± 2.5 months, respectively, ($p = 0.008$), and the total treatment times for the two groups were 0.75 ± 0.49 months and 7 ± 2.5 months, respectively. Damle et al[11] treated 30 permanent incisors with necrotic pulps and open apices with either MTA or calcium hydroxide with follow-up at 12 months. The mean time to barrier formation in the two groups was 4.50 ± 1.56 months versus 7.93 ± 2.53 months, respectively ($p = 0.0002$) and the mean time to radiographic evidence of completion of lamina dura was 4.07 ± 1.49 months versus 6.43 ± 2.59 months, respectively ($p = 0.0067$). In the most recent study published in 2015, Bonte et al[10] randomized children with nonvital permanent incisors requiring apexification to receive treatment with calcium hydroxide or MTA. At 12 months, a mineralized barrier was observed in 50% of the children in the calcium hydroxide group and 82% in the MTA group ($p < 0.07$). Importantly, four of 15 teeth in the calcium hydroxide group developed root fractures compared with none in the MTA group.

Other studies that did not meet the inclusion criteria for this analysis support the use of MTA. Lee at al[17] divided 40 necrotic open-apex incisors in 40 children 6.5—10 years of age into four treatment groups: Group 1, ultrasonic filing and MTA placement; Group 2, ultrasonic filing and calcium hydroxide; Group 3, hand filing and MTA; and Group 4, hand filing and calcium hydroxide. Ultrasonic filing plus MTA had the shortest time for apical hard tissue barrier formation, whereas calcium hydroxide apexification was better than MTA with respect to elongation of apical root length. Qudeimat et al[18] randomly assigned 64 permanent first molars with carious pulp exposures in children to apexification with calcium hydroxide or MTA. With an average follow-up of 34.8 ± 4.4 months there was no statistical difference in the success rate of teeth treated with calcium hydroxide (91%) or MTA (93%) and a radiographic hard tissue barrier under calcium hydroxide was seen in 55% of teeth as compared with 64% of teeth under MTA ($p = 0.4$). Moretti et al[19] randomly assigned 45 primary mandibular molars with dental caries in 23 children aged between 5 years and 9 years to receive calcium hydroxide, MTA, or control treatment (zinc oxide-eugenol paste). With a follow-up period of 24 months, clinical and radiographic success was noted in all treated teeth in the control and MTA groups and dentine bridge formation was detected in 29% of the teeth treated with MTA. In teeth treated with calcium hydroxide, 64% of the teeth had clinical and radiographic failures during the follow-up period, and internal resorption was a frequent radiographic finding.

There are a number of limitations to this study. The number of studies was small, and their quality was not high. Results of apexification can be operator dependent. In addition, the definitions of clinical and radiographic success may have varied between the studies. We did not examine the outcomes of the two compounds with respect to their use for root fractures. These limitations suggest that future high-quality studies are needed to compare the results of the two treatments.

In summary, while both calcium hydroxide and MTA provide similar clinical success and radiographic success rates and apical barrier formation rates, MTA is associated with a significantly shorter time for apical barrier formation, thus shortening the treatment time. The shorter treatment time with MTA may translate into higher overall success rates because of better patient compliance with treatment completion.

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