Apexification of immature teeth with calcium hydroxide or mineral trioxide aggregate: systematic review and meta-analysis

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Objective. The aim of this study was to conduct a quantitative systematic review, including published data, comparing the efficacy of mineral trioxide aggregate and calcium hydroxide as material used for the endodontic management of immature teeth.

Study design. Relevant studies published through November 2009 were identified through literature searches using Pubmed (Medline) and Scopus databases. Controlled trials in which calcium hydroxide versus mineral trioxide aggregate were used for the apexification of immature permanent teeth were selected for this study. The evaluation included clinical outcome and apical barrier formation. The principal measure of treatment effect was risk difference. The overall effect was tested by using $Z$ score. Heterogeneity was tested by using the $\chi^2$ statistic and I square ($I^2$). A fixed-effect model was used when the studies in the subgroup were sufficiently similar. A random-effects model was used in the summary analysis when there was heterogeneity between the subgroups.

Results. Based on reduction of relative risk with 95% confidence intervals we found that the rate of clinical success ($P = .29$) and apical barrier formation ($P = .76$) of the 2 interventions had no perceivable discrepancy. Regarding success and apical barrier formation, either calcium hydroxide or mineral trioxide aggregate may be used for the apexification of immature teeth. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:e36-e42)

In 1999, Torabinejad and Chivian recommended the use of mineral trioxide aggregate (MTA) as an artificial apical barrier. It has since become the material of choice in artificial apical barrier procedures. MTA’s popularity as an artificial apical barrier can be attributed to several factors. The shorter treatment time with MTA seems to be the most attractive. Some data suggest that MTA appears to be more predictable with consistent hard tissue formation based on in vivo studies in dogs. The clinical success of this treatment has been reported by many studies. The purpose of the present study was to compare the efficacy of calcium hydroxide and MTA for root-end induction in immature roots and the relative effectiveness of these 2 materials regarding clinical success. Thus, the main objective was to address the choices (calcium hydroxide or MTA) that clinicians face in dental practice regarding the endodontic treatment of immature teeth.

MATERIALS AND METHODS

Data sources

We initiated this quantitative systematic review by performing a comprehensive computer search of the English- and French-language dental literature by using the Pubmed Medline (1966 through November 2009) and Scopus (1966 through November 2009) databases to identify controlled trials in which calcium hydroxide versus mineral trioxide aggregate were used for the
apexification of immature permanent teeth. The search strategy was based on the following Medical Subject Heading terms in different combination strategy: apexification, dental pulp necroses, root canal therapy, MTA cement, MTA, calcium hydroxide.

The title and abstract of all potentially relevant studies were identified for their relevance before retrieval of full articles. Full articles were also scrutinized for relevance if the title and abstract were ambiguous.

Additional hand searching was done for the volumes and issues of the identified key journals to manually search through indexes, bibliographies, and special issues. Reference lists from identified articles were scanned to identify other potentially relevant articles.

**Review process**

Research forms were designed and piloted for the purpose of this review. Two authors evaluated abstracts and full text. Disagreement among authors was resolved in consensus meetings.

**Inclusion and exclusion criteria**

The inclusion criteria were as follows:

1. The apexification was performed in immature permanent teeth with unformed apices for irreversible pulp disease or chronic apical periodontitis.
2. The study compared calcium hydroxide versus MTA.
3. The outcome was evaluated by clinical symptoms and radiographic evidence.
4. The formation of apical barrier was recorded.

The exclusion criteria included the following:

1. Studies were carried out in vitro.
2. Experimental studies, because their generalizability and comparability with field studies is uncertain.

**Definitions for success and failure**

The primary measure was clinical and radiographic outcome. The secondary measure was apical barrier formation.

The following parameters were used to assess success:

1. Clinically: no pain, tenderness to percussion, root fracture, or intraoral sinus tract.
2. Radiographically: normal periapical area and completion of lamina dura, and no radiographic evidence of root resorption.

A favorable outcome was assigned if the tooth was asymptomatic with a normal periapical area.

The osteoinductive properties of these 2 materials were also evaluated. Therefore in this study, 2 variables were recorded: success and apical barrier formation.

The null hypotheses were:

1. There is no difference in the proportion of teeth exhibiting clinical and radiologic signs of failure after the 2 types of treatment.
2. MTA apical barriers can achieve results similar to long-term Ca(OH)₂ treatment for inducing an apical barrier.

**Data extraction**

Studies that fulfilled the inclusion criteria were processed for data extraction. The data on apexification in terms of clinical signs, symptoms, and apical barrier formation were extracted from each study independently and entered into a computerized database. The extracted information of each study also included the name of the first author, year of publication, number of cases, number of control subjects, and number of follow-ups.

Overall methodologic quality was assessed with the use of the 5-point Jadad score, which evaluates the quality of randomization, blinding, and reasons for withdrawal. The methodologic quality of each included investigation was evaluated by 2 of the authors. A consensus meeting was conducted to confirm agreement and to resolve disagreement between reviewers about this issue.

**Data analysis**

Meta-analysis was conducted with the help of the Review Manager computer program, version 5.0. (Cochrane Collaboration, Copenhagen, The Netherlands).

The principal measure of treatment effect was risk difference, which was defined as the risk in the experimental group (MTA) minus the risk in the control group (calcium hydroxide) with 95% confidence intervals (CIs). For the purpose of this study, it is given as the difference in clinical success rates and apical barrier formation between groups treated with calcium hydroxide or MTA. Risk difference is a measure of the impact of the treatment on the number of events (clinical success and apical barrier formation), because it takes into account the prevalence of the event, i.e., how common it is.

The overall effect was tested with the use of Z score, with significance set at $P < .05$. Heterogeneity was tested by using the $\chi^2$ statistic and I² square (I²), with significance set at $P < .1$. Because the test is poor at detecting true heterogeneity, a nonsignificant result cannot be taken as evidence of homogeneity. Using a cutoff of 10% for significance ameliorates this problem. Possible sources of heterogeneity were to be
assessed by sensitivity and subgroup analyses. A fixed-effect model was used when the studies in the subgroup were sufficiently similar ($P > .10$; $I^2 < 50\%$). A random-effects model was used in the summary analysis when there was heterogeneity between the subgroups.

RESULTS

Study selection and data summary
The majority of relevant studies were conducted using calcium hydroxide or MTA. Two studies comparing the 2 materials with a total of 50 teeth met inclusion criteria (Fig. 1).15-16

Designs of included studies
The included studies had control groups. The experimental group was the group that received apexification with MTA and the control the group that received apexification with calcium hydroxide.

Characteristics of included studies
One study was conducted in Egypt15 and 1 in India.16 Both studies were conducted in a university teaching hospital environment. Both studies reported the use of rubber dam for isolating teeth during the provision of treatment.

Characteristics of the participants in included studies are presented in Table I. In the study by Pradhan et al. (2006)16 the number of included teeth with periapical radiolucencies was stated, but in the study by El-Meligy and Avery (2006)15 the number of included teeth with radioluencies was not stated.

Both studies compared calcium hydroxide with mineral trioxide aggregate in the apexification of immature teeth. In both studies MTA was applied after calcium hydroxide disinfection for 1 week.

Technique for apical barrier detection
In the calcium hydroxide group, the method used to detect apical barrier formation was almost the same in both studies and was based on the tactile sensation felt by the operator to detect an apical stop. Radiographs were used as an adjunct to the clinical technique in the study by El-Meligy and Avery.15

In the MTA group, the apical barrier formation was assessed radiographically by evaluating the radiopaque
bridge apically over the MTA plug, because reentry is impossible.

**Complications and failures**

In the study by El Meligy and Avery,\(^1\) 2 of the 15 teeth in the group treated with Ca(OH)\(_2\) complained of tenderness to percussion after 6 and 12 months and were considered to be clinical failures.

In the study by Pradhan et al.,\(^2\) 3 of the 10 teeth treated with MTA were unsuccessful, because apical barrier was not formed when assessed radiographically.

**Materials and techniques used for final root canal obturation**

Final obturation was done using gutta-percha and sealer in both studies.

The total time taken for the management of teeth from the start to GP root canal filling was 7 ± 2.5 months in the study by Pradhan et al. and not specified in the study by El Meligy and Avery. No matrix material was used in either of included studies for the MTA cases.

In the study by Pradhan et al., the teeth in both groups were assessed every 4 weeks clinically and radiographically up to 11 months. In the study by El Meligy and Avery, the children were recalled for clinical and radiographic evaluation after 3, 6, and 12 months.

**Methodologic quality assessment of included studies**

Methodologic quality was assessed with the use of a scale developed and validated by Jadad et al.\(^3\) Based on these criteria, study quality scores were 1 for the study by Pradhan et al. and 3 for the study by El-Meligy and Avery (Table II).

**Meta-analysis**

The outcome measure was based on binary data (success/failure, barrier formation/absence of barrier formation).

**Assessment of clinical success (Table III).** According to \(\chi^2\) statistic and \(I^2\), the results of the 2 studies showed no apparent statistical heterogeneity (\(P = .30; I^2 = 8\%\)). A graphical informal test (Forest plot) also confirmed the homogeneity. Therefore, fixed-effect methods for combining study estimates were used and overall estimate produced. After synthesizing the results, we found that the rate of clinical success of the 2 interventions had no significant difference (risk difference \(-0.08 [95\% \text{ CI } -0.23 \text{ to } 0.07]; P = .29 [>.05]\)). Based on these data, the difference in clinical success between the 2 treatment regimens was not statistically significant (\(P = .29\)).

**Assessment of apical barrier formation (Table IV).** According to \(\chi^2\) statistic and \(I^2\), the results of the 2 studies showed apparent statistical heterogeneity (\(P = .02; I^2 = 83\%\)). So we used a random-effects model for meta-analysis. After synthesizing the results, we found that the rates of radiologic success of the 2 interventions had no significant difference (risk difference 0.07 [95\% CI -0.37 to 0.50]; \(P = .76 [>.05]\)). Based on these data, the difference in apical barrier formation between the 2 treatment regimens was not statistically significant (\(P = .76\)).

Radiographic success regarding the periapical healing was not possible to calculate, because of the lack of information regarding the number of teeth with periapical radiolocencies included in the study by El-Meligy and Avery.

**DISCUSSION**

This investigation compared the outcome of endodontic treatment of immature teeth with calcium hydroxide and MTA regarding success and apical barrier formation. The main results show that the difference between these 2 treatment regimens was not statistically significant. However, 2 small studies

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### Table I. Characteristics of participants in each study

<table>
<thead>
<tr>
<th></th>
<th>No. of participants</th>
<th>No. of teeth</th>
<th>Age range (y)</th>
<th>Type of teeth</th>
<th>Cause of necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Meligy and Avery (2006)</td>
<td>15</td>
<td>30</td>
<td>6-12</td>
<td>24 central incisor, 6 lateral incisor</td>
<td>24 previous trauma, 6 caries</td>
</tr>
<tr>
<td>Pradhan et al. (2006)</td>
<td>16</td>
<td>20</td>
<td>8-15</td>
<td>19 central incisor, 1 lateral incisor</td>
<td>20 previous trauma</td>
</tr>
</tbody>
</table>

### Table II. Methodologic quality assessment (points) of included studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Double-blinding</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dropouts</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total score</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

are not strong evidence for making clinical decisions. Neither of the papers reported their rationale for the sample size. This demonstrates an important limitation. The proper sample size should be calculated before trial.\textsuperscript{17} El-Meligy and Avery (2006)\textsuperscript{15} mentioned the randomization method in the distribution of cases, but did not stress concealment during allocation. Pradhan et al. (2006)\textsuperscript{16} described alternate distribution of patients. Inadequate allocation concealment leads to exaggerated estimates of treatment effect, on average, but with scope for bias in either direction.\textsuperscript{18} Randomization, as well as blinding, make groups comparable and minimizes bias and confounding factors (19, 20). Double-blinding of the treatment provided was impossible in each included study, because of the nature of intervention; however, outcome assessor blinding was possible. El-Meligy and Avery reported blinding in outcome evaluation. However, Pradhan et al. stated that although 3 examiners assessed the radiographic outcome, they were aware of the groups they were evaluating, because it was obvious from the radiograph, with MTA being more radiopaque than Ca(OH)\textsubscript{2}.

Another potential source of bias is differences in characteristics of subjects between the 2 studies. El-Meligy and Avery included traumatized and carious necrotic teeth; Pradhan et al. included only traumatized teeth. In clinical studies, these differences always exist, but imbalances in factors that are not prognostic cannot fairly be considered to be sources of bias.\textsuperscript{21} In root canal treatment, there is only 1 consensual preoperative prognostic factor, i.e., a radiographically detectable lesion or the presence of apical periodontitis.\textsuperscript{22} In the study by El-Meligy and Avery,\textsuperscript{15} the number of included teeth with apical radiolucency was not stated. Both studies used ≤1 year as a cutoff point, which might appear to be a shortcoming in cases where the lesion had not completely healed. One-year follow-up time is the soonest possible to determine whether or not the lesion has healed.\textsuperscript{23} Operators in the 2 studies were experienced practitioners; therefore, extrapolation of the results of this review to general practitioners may not be entirely appropriate.

The meta-analysis showed no statistically significant difference in success rate ($P = .29$) and apical barrier formation ($P = .76$) between the 2 treatment regimens.

### Table III. Table and forest plot of the risk difference of clinical success: calcium hydroxide versus MTA

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>MTA Events</th>
<th>Total</th>
<th>Calcium hydroxide Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk difference, $M - H$, fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Meligy and Avery (2006)</td>
<td>0</td>
<td>15</td>
<td>2</td>
<td>15</td>
<td>60.0%</td>
<td>$-0.13 (-0.33-0.06)$</td>
</tr>
<tr>
<td>Pradhan (2006)</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>40.0%</td>
<td>$0.00 (-0.17-0.17)$</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>100.0%</td>
<td>$-0.08 (-0.23-0.07)$</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.09; df = 1 (P = .30); I^2 = 8\%$
Test for overall effect: $Z = 1.06 (P = .29)$ Favors MTA Favors Ca(OH)\textsubscript{2}

### Table IV. Table and forest plot of the risk difference of apical barrier formation: calcium hydroxide versus MTA

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>MTA Events</th>
<th>Total</th>
<th>Calcium hydroxide Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk difference, $M - H$, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Meligy and Avery (2006)</td>
<td>0</td>
<td>15</td>
<td>2</td>
<td>15</td>
<td>60.0%</td>
<td>$-0.13 (-0.33-0.06)$</td>
</tr>
<tr>
<td>Pradhan (2006)</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>40.0%</td>
<td>$0.30 (-0.00-0.60)$</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>100.0%</td>
<td>$0.07 (-0.37-0.50)$</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.08; \chi^2 = 5.82; df = 1 (P = .02); I^2 = 83\%$
Test for overall effect: $Z = 0.31 (P = .76)$ Favors MTA Favors Ca(OH)\textsubscript{2}
The lower 95% CI of risk difference in clinical success rate was −0.23 in favor of MTA, indicating that if a larger trial were conducted, apexification with MTA may lead to a higher clinical success rate. The upper 95% CI of the risk difference in apical barrier formation was 0.5 in favor of calcium hydroxide.

However, when clinicians are faced with choices of which treatment regimen should be offered to patients, the central issues that should be considered are which regimen does more good than harm, which regimens are worth the effort, and the cost of using each of them.24

Traditionally, apexification with Ca(OH)$_2$ is undertaken to close the root end such that the filling materials can be contained within the root canal space.2 Filling the root canal is undertaken normally when the apical calcific barrier is formed. Without the barrier, there is nothing against which the traditional gutta-percha filling material can be condensed. MTA is used to fill the apical end without the need for calcific barrier formation. Using MTA for apexification may shorten the treatment period and improve patient compliance.9,16

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This expedient cleaning and shaping of the root canal system followed by its apical seal with MTA makes the rapid placement of a bonded restoration within the root canal possible,25,26 which may prevent potential fractures of immature teeth.27 Regarding therapeutic efficacy, the current study failed to demonstrate a difference between the 2 treatment regimens. On the other hand, in the era of tissue engineering, apexification may become less needed in years to come. However, as clinicians dealing with individual patients, we will strive for the best evidence available to manage immature teeth.

Limitations of this systematic review include:

1. We used only published studies in this meta-analysis; therefore, the results are weighted toward the findings of published trials.
2. The 2 studies were performed in teaching hospital schools, which makes extrapolation for general practitioners difficult.
3. Bias of publication was not calculated, because of the number of included studies.
4. The relatively small sample is a limitation, because the generalizability of the findings could be difficult. A larger sample size would definitely be desirable with longer follow-up to firmly establish the effect of this treatment in the periapical region. (Table III IV)

CONCLUSION

Calcium hydroxide and MTA may be suitable materials for the treatment of the immature teeth. However, more studies evaluating the factors influencing success and failure in teeth should be conducted.

REFERENCES

22. Sathorn C, Parashos P, Messer HH. Effectiveness of single versus multiple-visit endodontic treatment of teeth with apical

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