Radiographic and Clinical Outcomes of the Treatment of Immature Permanent Teeth by Revascularization or Apexification: A Pilot Retrospective Cohort Study

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Abstract

Introduction: This retrospective cohort study compared clinical and radiographic outcomes of endodontic treatment performed in immature nonvital permanent teeth by apexification (calcium hydroxide or apical barrier with mineral trioxide aggregate) versus revascularization. Methods: A comprehensive chart review was performed to obtain a cohort of previously completed cases with recalls. Clinical and radiographic data were collected for 31 treated teeth (19 revascularization and 12 apexification) with an average follow-up time of 17 months and a recall rate of 63%. Tooth survival, success rate, and adverse events were analyzed. Changes in radiographic root length, width, and area were quantified. Results: The majority of treated teeth survived throughout the study period, with 30 of 31 (97%) teeth surviving (18/19 [95%] revascularization and 12/12 apexification). Most cases were also clinically successful, with 27 of 31 (87%) meeting criteria for success (15/19 [78%] revascularization and 12/12 apexification; nonsignificant difference). A greater incidence of adverse events was observed in the revascularization group (8/19 [42%] vs 1/12 [11%] in apexification) (risk ratio = 5.1; P = .04; 95% confidence interval, 0.719–35.48). Although more revascularization cases than apexification cases showed an increase in radiographic root area and width, the effect was not statistically significant. Conclusions: In this study, revascularization was not superior to other apexification techniques in either clinical or radiographic outcomes. Studies with large subject cohorts and long follow-up periods are needed to evaluate outcomes of revascularization and apexification while accounting for important covariants relevant to clinical success.

Key Words

Apexification, clinical outcomes, clinical success, endodontics, maturogenesis, radiographic outcomes, radiographic root area, regenerative endodontics, revascularization

The treatment of infected immature permanent teeth is one of the more challenging procedures in endodontics (1, 2). Such teeth normally have very wide canals, thin dentinal walls, and open apices, which present difficulty to the clinician in instrumentation, working length determination, and control of irrigants and obturation materials. Importantly, immature teeth are more prone to fracture, so even cases with ideal endodontic treatment have a poor long-term prognosis (1–3). Long-term application of intracanal calcium hydroxide (Ca(OH)2) was historically the treatment of choice for necrotic teeth with open apices (4). However, this treatment option requires patients to attend multiple clinic visits over an extended period of time, with treatments regularly extending over 6 months (5, 6). Also, the long-term use of Ca(OH)2 may change the physical properties of dentin and ultimately reduces the root strength (5). An alternative to apexification with Ca(OH)2 is placement of an apical barrier using a material such as mineral trioxide aggregate (MTA) (7, 8). Treatment with MTA apexification produces comparably favorable outcomes to long-term Ca(OH)2 treatment regarding the resolution of symptoms and periapical pathology (9–12). Despite the advantage of fewer visits, MTA apexification does not appear to improve root strength or produce thickening or lengthening of root canal walls (5).

More recently, a clinical protocol for revascularization was introduced in which, after a modified disinfection technique, bleeding is stimulated from the periradicular tissues and a blood clot is formed within the canal. This is hypothesized to provide a scaffold, growth factors, and possibly stem cells that support continued root formation via the growth of tissues into the canal space (13–17). Multiple case reports and case series have shown increased root width and/or length after some variation of a revascularization treatment procedure (13, 14, 18–23). Animal studies (24–26) have shown that the nature of hard tissues formed in the canal of vascularized immature teeth is heterogeneous mineralized tissue resembling cementum or bone, whereas soft tissues appear more similar to periodontal ligament than pulp. On the other hand, some human studies (27, 28) have shown pulp-like tissue after revascularization procedures. However, others (29–31) have shown cementum-, bone-, and/or periodontal ligament–like tissue. The reason for the variability in intracanal tissues formed is not understood at this point, but it may relate to the unpredictable survival of apical pulp tissues, apical papilla, or the Hertwig epithelial root sheath in the setting of inflammation and trauma.

Despite the seemingly clear potential benefit of continued root development, there is currently not sufficient evidence to support the claim that revascularization treatment...
has superior clinical outcomes relative to traditional apexification or to measure the success rate of achieving continued root development after revascularization. The purpose of this pilot retrospective cohort study was to evaluate and compare the clinical and radiographic outcomes of apexification (Ca(OH)\textsubscript{2} and MTA apical barrier) and revascularization treatment of immature nonvital permanent teeth and to begin to identify patient factors that may be important to achieving successful outcomes in these cases.

**Materials and Methods**

**Subjects**

The study protocol was approved by the Institutional Review Board at the New York University (NYU) School of Medicine, New York, NY (approved August 20, 2012). A query of the Dentrix database at NYU College of Dentistry was performed to identify dental charts of pediatric patients aged 6–16 years who received endodontic treatment between September 2008 and September 2011. Because of inconsistencies in treatment codes used for revascularization and apexification procedures, we queried for all endodontic treatment codes including unspecified endodontic procedures (D3999), codes relating to apexification (D3351, D3352, D3353), and codes related to standard nonsurgical endodontic procedures (D3330, D3320, D3310). Codes related to pulpal regeneration had not been instituted and were not queried. A total of 338 potential cases were identified for screening (Fig. 1).

The clinical records identified in the database query were reviewed for eligibility using specific inclusion and exclusion criteria. To be eligible for the study, the subject must have been between the ages of 6 and 16 years at the time of treatment with a permanent tooth in need of endodontic treatment that could be classified as calcium hydroxide apexification, MTA apexification, or revascularization; the tooth should also have been immature at the time of treatment (stage 1–4 according to Cvek’s criteria [2]). Finally, the endodontic treatment must have been completed and the final restoration placed and at least a 3-month recall should have been documented in the patient’s records. Exclusion criteria included missing or grossly incomplete clinical records.

**Data Extraction**

Cases identified that met the inclusion/exclusion criteria were assigned a research subject number, and data were extracted from the clinical record. Data collection was accomplished using a standardized electronic form designed to collect information related to subject demographic features, contributory etiology (including history and type of trauma), preoperative signs and symptoms, number of clinical visits, details on clinical treatment, follow-up visits and treatments, and any other treatment rendered on the treated tooth. The final data set was exported to Excel (Microsoft, Redmond, WA) and saved on a secure server for analysis. All radiographs related to study cases were collected and stored in a digital format on a secure server.

**Clinical Outcomes**

The primary outcomes of clinical treatment evaluated were survival, clinical success, and adverse events. Survival was defined as the tooth remaining present in the arch throughout the study period. Clinical success was defined as a tooth that survived and also did not require another endodontic intervention during the recall period. Although healing of periapical radiolucencies was assessed, we did not include radiographic outcomes as part of the definition of clinical success because of the inherent difficulty in assessing periapical pathology radiographically in immature teeth.

Adverse events were defined as any event involving the treated tooth during treatment or during the follow-up period that would negatively impact the patient or guardian or require additional clinical visits. We specifically looked for documentation of intraoperative or postoperative pain, flare-ups, staining and/or internal bleaching, reinfection, and fracture. We characterized adverse events as follows:

1. **Mild**: No need for additional endodontic treatment
2. **Moderate**: Further endodontic treatment indicated after an event (eg, pain, swelling, or sinus tract) was present
3. **Severe**: Tooth was or needed to be extracted

**Radiographic Outcomes and Analysis**

Preoperative radiographs were evaluated by study investigators for the presence or absence of periapical radiolucency, stage of root development, and signs of resorption. The assessment of periapical pathology is challenging in immature teeth. However, the cases were reviewed by independent investigators (A.S.A. and J.L.G.), and consensus was obtained on questionable cases with the help of an additional study investigator (L.M.L.). Postoperative radiographs were assessed for the presence or absence of periapical radiolucency, signs of resorption, intracanal calcification, and apical calcification. In cases when a periapical radiolucency was present preoperatively, the postoperative images were assessed to determine if the radiolucency appeared larger or smaller on follow-up images.

For the quantification of changes in radiographic root dimensions, we measured changes in the radiographic root area, root length, and root width. First, the preoperative and postoperative images of digitized radiographs were opened in the ImageJ software program (National Institutes of Health, Bethesda, MD). Preoperative and final recall radiographs were aligned using the TurboReg plugin to minimize any dimensional changes that occurred as a result of angulation differences at the time the images were taken. In some cases, the differences in angulation made quantification of radiographic changes impossible.
In these instances, the case was either dropped or an alternative film (usually an earlier follow-up radiograph) that was better aligned was used in the analysis.

After alignment, the area, length, and width were measured. The polygon tool was used to measure the total root area using the mesial and distal cementoenamel junction (CEJ) as the most coronal aspect of the outline. The total canal area was measured using the most coronal aspect of the canal area at the level of the CEJ. A modified protocol was used to measure posterior teeth in which only the distal canal was quantified. The “straight-line” tool of TurboReg was used to measure the root length. The measurements were performed as a straight line from the CEJ to the midpoint of the apex of the root from both the mesial and distal points, and then both measurements were averaged to obtain the total root length. Width was measured at 5 levels of the root that were determined relative to the previously determined length (50%, 66%, and 80%). The measurements obtained at each of the widths were averaged to determine the overall percentage change in width. Every measurement was completed in duplicate and averaged.

Clinical Protocol

Although the American Association of Endodontists has recently published clinical guidelines for revascularization (32), there is little evidence available to support specific aspects of treatment including medicaments and irrigants used. Because this was a retrospective study spanning a number of years, a specific clinical protocol was not implemented before performing the treatments. Residents under the supervision of endodontic faculty performed all cases. Revascularization cases were performed in multiple visits (2–5). In all cases, the first appointment consisted of local anesthesia, rubber dam isolation, access cavity preparation, working length determination, and irrigation with varying concentrations of sodium hypochlorite, chlorhexidine, and/or EDTA with minimal or no instrumentation. Intracanal medicaments (triple antibiotic [ciprofloxacin, metronidazole, and minocycline], double antibiotic [ciprofloxacin and metronidazole], and/or Ca(OH)₂) were used for varying durations. The last appointment before completion of revascularization consisted of local anesthesia, rubber dam isolation, irrigation to remove the remaining intracanal medication, and laceration of the apical tissue in an attempt to induce bleeding into the canal, although this was not achieved in all cases. Finally, all cases used MTA placed at approximately the level of the CEJ followed by the placement of a resin-bonded restoration.

In the Ca(OH)₂ apification treatment, standard irrigants and instrumentation were used followed by the placement of Ca(OH)₂ in the canal, sometimes until an apical barrier formed, although not in all cases. The cases were ultimately obturated with gutta-percha and AH Plus Sealer (Dentsply, York, PA), and resin-bonded restoration was used to restore the tooth. Cases were always completed in multiple visits (3–5). For the MTA apification treatment, standard irrigants and instrumentation were used, and Ca(OH)₂ was used as an intracanal medication between visits for varying durations. All cases were completed in multiple visits (2–5). MTA was placed in the apical portion of the canal, and the remaining canal system was obturated with thermoplasticized gutta-percha and AH Plus Sealer.

Statistical Analysis

The data were imported from Excel into Stata (Stata/SE 11.2 for Mac; StataCorp, College Station, TX) for analysis. Appropriate descriptive statistics were calculated including the mean, median, and standard errors. In testing for differences between groups, a t test was used to evaluate continuous variables, whereas dichotomous variables were evaluated using the Fisher exact test and ordinal variables were tested using the Mann-Whitney U test. Risk measurements were made by calculating either risk ratios or risk differences. Statistical significance was set at $P \leq .05$.

Results

An initial query of the NYU College of Dentistry clinical database system resulted in a total of 338 charts identifying endodontic procedures completed in children ages 6–16 years over a 3-year period. After applying the inclusion and exclusion criteria, only 49 cases met the study criteria (Fig. 1). Of the possible 49 cases to be included, 18 cases did not have documentation of a recall visit (recall rate = 63%) and were excluded. Of the 31 cases with recall, 19 were treated with revascularization treatment (REVASC group), 7 with Ca(OH)₂ apification, and 5 with MTA apification. Because of the small number of cases in the apification groups (Ca(OH)₂ and MTA), we consolidated them into 1 group (APEX group) with 12 APEX cases.

TABLE 1. Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Revascularization</th>
<th>Apexification</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, $n$ (%)</td>
<td>9 (47)</td>
<td>8 (73)</td>
<td>0.4</td>
</tr>
<tr>
<td>Age, y</td>
<td>8.8 ± 1.6</td>
<td>9.8 ± 2.0</td>
<td>.9</td>
</tr>
<tr>
<td>Anterior tooth, $n$ (%)</td>
<td>19 (100)</td>
<td>9 (75)</td>
<td>.06</td>
</tr>
<tr>
<td>Signs and symptoms of pain present, n/total n (%)</td>
<td>11/14 (78)</td>
<td>9/10 (90)</td>
<td>.06</td>
</tr>
<tr>
<td>Etiology, n/total n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>15/19 (79)</td>
<td>9/12 (75)</td>
<td>.4</td>
</tr>
<tr>
<td>Severe trauma</td>
<td>6/11 (55)</td>
<td>1/8 (13)</td>
<td>.1</td>
</tr>
<tr>
<td>Caries</td>
<td>1/19 (5)</td>
<td>3/12 (25)</td>
<td>.01</td>
</tr>
<tr>
<td>Anatomic</td>
<td>3/19 (16)</td>
<td>0/19</td>
<td>.6</td>
</tr>
<tr>
<td>Periapical radiolucency present, n/total n (%)</td>
<td>8/19 (42)</td>
<td>8/12 (67)</td>
<td>.06</td>
</tr>
<tr>
<td>Stage of root development</td>
<td>2.8 ± 1.0</td>
<td>3.9 ± 0.3</td>
<td>.001</td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>14.5 ± 8.5</td>
<td>21.8 ± 12.0</td>
<td>.06</td>
</tr>
</tbody>
</table>

Continuous and ordinal variables presented as mean ± standard deviation. Missing data reflected by the changing denominators. Continuous variables evaluated using the t test, and dichotomous variables evaluated using the Fisher exact test. Only $P$ values approaching statistical significance are shown.

*Each tooth is treated as an individual case for analysis. However, some patients had multiple teeth included in the study: 1 patient had 4 teeth, 1 patient had 5 teeth, and 2 patients had 2 teeth involved.

†Severe trauma category includes avulsion and intrusion. Other trauma (ie, not severe) includes enamel-dentin fracture, dentin-pulp fracture, and luxation. The denominator changed because of missing data about the type of trauma.

‡Trauma to primary teeth affected the development of permanent teeth.

§Statistically significant difference using the Mann-Whitney U test.
TABLE 2. Outcome Rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Revascularization n (19)</th>
<th>Apexification n (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival no. (%)</td>
<td>18 (95)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Clinical success no. (%)</td>
<td>15 (79)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>All adverse events no. (%)</td>
<td>8 (42)</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

Baseline Study Population Characteristics

The demographics and baseline clinical characteristics of the study population were evaluated to assess the comparability of the 2 groups (REVASC vs APEX). Age, sex, significant medical history, tooth type, etiology, preoperative signs and symptoms of pain, preoperative periapical radiolucency, and the follow-up period time were comparable between groups (Table 1). The stage of root development differed significantly between the REVASC and APEX groups, with more immature teeth in the revascularization group (Table 1). Trauma was by far the predominant contributory etiology in both groups, with 15 cases (78%) in the REVASC group and 9 cases (75%) in the APEX group. Although not significantly different, a greater proportion of cases of severe trauma, including avulsion and intrusion, occurred in the REVASC group. The average follow-up period was 15 and 22 months in the REVASC and APEX groups, respectively, with the study representing a total follow-up time of 44.6 patient years.

Clinical Outcomes

Because it is not known whether teeth treated by a revascularization procedure have comparable clinical outcomes with teeth treated by conventional apexification procedures, we assessed the frequency of survival, clinical success, and adverse events. During the follow-up period, most cases (30/31, 97%) survived (Table 2, 18/19 [95%] revascularization and 12/12 [100%] apexification). The extraction case was in the REVASC group when the child retraumatized the treated tooth and fractured it. (This case was previously published [30]). Most cases were also clinically successful during the follow-up period (27/31, 87%), with 15 successful cases (79%) in the REVASC group and 9 cases (75%) in the APEX group. Although not significantly different, a greater proportion of cases of severe trauma, including avulsion and intrusion, occurred in the REVASC group. The average follow-up period was 15 and 22 months in the REVASC and APEX groups, respectively, with the study representing a total follow-up time of 44.6 patient years.

The between-group differences in survival and clinical success were nonsignificant (risk ratio = 5.1; \( P = .04 \)) and risk difference for non-survival = 0.05; 95% CI, 0.03–0.39), \( P = .09 \) and risk difference for non-clinical success = 0.21; 95% confidence interval [CI], 0.03–0.39), \( P = .09 \) and risk difference for non-clinical success = 0.21; 95% CI, −0.15 to 0.04, \( P = .4 \).

Because not much has been reported about adverse events in teeth treated by REVASC or APEX, we also determined the incidence of adverse events in this study population (Table 2). We found a greater incidence of adverse events in the REVASC group with 8 cases (42%) documenting adverse events versus 1 case (11%) in the APEX group. In the REVASC group, 4 of the cases (50%) were classified as mild, 3 cases (38%) as moderate, and 1 case (12%) as a severe adverse event (Table 3). The 1 adverse event case in the APEX group was classified as a mild adverse event. When comparing the risk for an adverse event occurrence, we found a slightly higher risk for an adverse event occurring after revascularization treatment than after apexification treatment (risk ratio = 5.1; \( P = .04 \); 95% CI, 0.719–35.48). It should be noted that teeth in which adverse events occurred had a more immature stage of root development than teeth without an adverse event incidence (Table 3).

Quantitative Radiographic Outcomes

To determine whether there was a difference in the radiographic measures of root area, length, and width between REVASC and APEX treatment cases, we quantified the radiographic changes between the preoperative radiograph and the last follow-up radiograph in each case. Because these radiographs were not collected in a standardized manner, they were occasionally not comparable despite attempting to correct discrepancies with software (ImageJ). Thus, 3 cases from the APEX group and 2 cases from the REVASC group were dropped. We also dropped 2 cases from the REVASC group because of extensive intracanal calcification, making measurements of root width and area impossible. Given these constraints, for radiographic outcomes, the average follow-up time was 15.4 ± 9.0 months (\( n = 8 \)) for the APEX group and 15.5 ± 10.4 months (\( n = 15 \)) for the REVASC group.

In terms of radiographic changes, the width measurement showed the largest difference between treatment groups (1.4% ± 3.2% for APEX vs 10.2% ± 4.0% for REVASC, Fig. 2). However, none of the measured radiographic outcomes (ie, width, length or radiographic root area [RRA]) were statistically different between groups using a \( t \) test. Cases treated by REVASC generally showed a greater absolute change and greater variability in the width and RRA measurements (again not statistically different) but not length (Fig. 3). In fact, 1 of the cases treated by APEX showed the largest increase in root length. Figure 3A–C shows an example of an APEX case treated by Ca(OH)\(_2\) that showed an increased root length after treatment. In terms of clinical significance, assuming a 20% increase in length or width is clinically meaningful; 3 of 15 (20%) REVASC cases would have met this threshold in RRA measurement, 1 of 8 (12.5%) APEX cases did in length measurement, and 3 of 15 (20%) REVASC cases would have met this threshold in width measurement. In total, the number of REVASC cases with a

TABLE 3. Type of Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Class</th>
<th>Root stage</th>
<th>Adverse event type</th>
<th>Time (mo)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVASC</td>
<td>Mild</td>
<td>2</td>
<td>Staining</td>
<td>15</td>
<td>Internal bleaching</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Staining</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Pain†</td>
<td>23</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Retraumatized</td>
<td>8</td>
<td>Restorative</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
<td>Reinfecion</td>
<td>9</td>
<td>Endodontic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Reinfecion</td>
<td>8</td>
<td>Endodontic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Reinfecion</td>
<td>37</td>
<td>Endodontic</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>4</td>
<td>Fracture</td>
<td>25</td>
<td>Extraction</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>4</td>
<td>Retraumatized</td>
<td>12</td>
<td>Restorative</td>
</tr>
</tbody>
</table>

APEx, apexification; REVASC, revascularization.

*Root stage was more immature in adverse event (AE) teeth than non-AE (\( P = .002 \) with Mann-Whitney U test).

†Intraoperative pain.
clinically significant change (20% or greater) in any of the radiographic outcomes measured (RRA, width, or length) was 4 of 15 (27%) versus 1 of 15 in the APEX group. Two cases showed changes in both RRA and width. No significant difference was found between groups using the Fisher exact test.

Descriptive Radiographic Findings

Although the measurement of radiographic resolution of periapical pathology is difficult in immature permanent teeth, we performed this analysis as well. We only identified 1 case in the REVASC group with persistent periapical pathology at the final recall, which was larger than at the initiation of treatment. All other cases in the study were classified as healed or healing based on resolution or the smaller appearance of periapical radiolucencies. External resorption was noted in 4 cases, all in the REVASC group. In 3 of the 4 cases exhibiting resorption, the resorption appeared similar in the preoperative and follow-up radiographs. The remaining case only showed the development of resorption on the follow-up radiograph. Finally, we evaluated radiographic changes after the completion of treatment including apical calcification/closure, intracanal calcification, and canal obliteration. We found 6 REVASC cases and 1 APEX case showing apical calcification (Fig. 3A–C and G–I [tooth #9]). Only REVASC cases had the potential to show intracanal calcific barrier formation and canal obliteration, and we observed 3 cases and 2 cases of each, respectively.

Discussion

This retrospective cohort study found that the clinical success and survival of immature teeth receiving revascularization treatment was comparable with that of traditional apexification treatment with Ca(OH)₂ or MTA. The majority of data available on clinical outcomes in the literature come from case series and case reports; the exceptions were 1 retrospective cohort study and 1 prospective pilot cohort study (3, 33), both of which reported 100% clinical success after treatment by revascularization. The advantage of a cohort study versus a case series study is the implementation of measures in the study design to minimize the influence of bias in case selection. In our study, we performed a comprehensive chart review of all cases completed during a 3-year period, ultimately identifying a set of cases meeting our predetermined inclusion and exclusion criteria. Not all potentially eligible cases had a recall on file; our recall rate was 63%. It is possible that the 37% cases not included because of lack of recall could have differing outcomes from those reported here, which is a potential source of selection bias in this study. However, 63% is a fair recall rate for a retrospective study lacking incentives for patients to return for recall visits, and we believe the results of this study are valuable to understand clinical outcomes after endodontic treatment of immature permanent teeth.

Although our observed frequency of clinical success (79%) of REVASC treatment was not statistically different from that of APEX, it was not as high as existing reports of success from prospective and retrospective cohort studies (100%). There are several possible reasons for the difference in the success rate between this study and existing studies. First, our study had a very high rate of trauma as the contributory etiology, with 79% of revascularization cases having a primary contributory etiology of trauma. The retrospective study by Jeeruphan et al (3) had only 35% of REVASC cases with trauma as the etiology, and the prospective study by Jadhav et al (33) did not report the etiology. This difference in the rate of trauma could certainly contribute to differences in the clinical success rate. Also, how the study defined clinical success will influence the reported success rate. We defined clinical success as a tooth that survived and also did not require another endodontic intervention during the follow-up period. We decided not to include radiographic outcomes in our definition of success; although, if we had, the success rate would have most likely been lower.

There are several advantages and disadvantages of a retrospective study design. Two advantages are the study is less costly than a prospective study, and it is generally more feasible to quickly observe outcomes with longer follow-up periods because the follow-up has already occurred in the past. One of the major disadvantages is that there is no control over the frequency of potential confounding factors between study groups. In our study, most of the patient-specific factors were evenly distributed among the treatment groups, including age, sex, tooth type, preoperative symptoms, and preoperative periapical pathology. However, the REVASC group had a higher incidence of treated teeth

Figure 2. Scatterplots showing the percentage change in measured radiographic root dimensions. Each dot represents an individual treated tooth with closed circles from APEX cases and open squares from REVASC cases. The middle horizontal line represents the mean, and the error bars are the standard deviation. The dashed horizontal line denotes a 20% increase dimension, which represents an arbitrary cutoff point to represent a potentially clinically meaningful change. (A) A graph of the percentage change in RRA. Three REVASC cases had 20% or greater change in RRA. (B) A graph of the percentage change in length. One APEX case had a 20% increase or greater change in length. (C) A graph of the percentage change in width. Three REVASC cases had 20% or greater change in width.

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at a more immature stage of root development than the APEX group. More severe trauma cases were included in the REVASC group (6 vs 1), which could be clinically significant, even though the difference in the frequency of severe trauma between groups was not statistically significant. Because our sample size was small, we did not have sufficient power in the study to perform multivariate analyses that could control for these factors when assessing outcomes of APEX versus REVASC treatment (currently no other studies in this area have either). Because of this limitation, we cannot be sure that the trend toward a higher clinical failure rate and the observed significant increase in adverse event incidence was caused by the treatment modality or these uncontrolled factors. Future studies will involve expansion of the chart review over a longer period, which will increase our sample size and allow us to assess the influence of these other potentially important factors on clinical success and radiographic outcomes. The identification of predictive variables of clinical and radiographic outcomes in the treatment of immature permanent teeth is critical both for the clinical management of these patients and informed study design for future prospective cohort studies.

A surprising finding in this study was the low incidence of radiographic evidence for continued root development in the REVASC group. Statistically, there was no difference between teeth treated by REVASC and APEX in terms of root length, root width, and radiographic root area (Fig. 2). This is in contrast to almost all existing case reports, case series, and retrospective and prospective cohort studies. Although the statistical difference between groups was not significant, there were clearly individual cases in which REVASC treatment led to increased root width and total root area (although interestingly not length), but the frequency of this occurrence was much lower than what would be expected from the existing literature. There are several potential explanations for this discrepancy. First, many of the published case reports and case series may represent inadvertent biases toward choosing the best cases that show striking radiographic evidence of increased root length (selection bias). Also, existing studies that did not quantify the radiographic changes in root length and width but rather subjectively assessed changes in root dimensions are subject to interpretation bias. This is a problematic approach to assessing radiographic changes because retrospective studies typically use radiographs that were captured in a nonstandardized manner from children, leading to lots of variability in angulation between preoperative and follow-up films. It was our experience that variability in angulation would make the subjective assessment of these films almost impossible, without the benefit of image correction software.

Figure 3. Radiographs of representative clinical cases included in this retrospective cohort study. (A–C) This case involved an 8-year-old male who traumatized tooth #9, causing a fracture that involved the pulp. The case was treated with calcium hydroxide APEX: (A) preoperative radiograph, (B) postoperative radiograph, and (C) follow-up radiograph 19 months after treatment. The arrows point to the apex to show that this tooth demonstrated root lengthening after treatment as well as apical calcification. (D–F) This case involved a 9-year-old male with trauma to tooth #9, causing a fracture involving the pulp. The case was treated by MTA APEX: (D) preoperative radiograph, (E) postoperative radiograph, and (F) follow-up radiograph 10 months after treatment. (continued)
dimensions of teeth treated by REVASC. Because our study had variable follow-up times, some of the cases could still have the potential for root dimension changes. However, 10 of 15 REVASC cases included in the radiographic analyses had a greater than 12-month follow-up, which should be sufficient time to observe radiographic changes based on many case reports.

Trauma is clearly an important contributory factor to the incidence of immature permanent teeth with necrotic pulps because an estimated 22% of children suffer trauma to the permanent dentition, with an age range peaking between 7 and 10 years, more frequently in males, and most commonly involving the maxillary central and lateral incisors (35–37). The risk of the dental pulp becoming necrotic increases with the severity of the trauma, with intrusion having the highest incidence at 85% (38). In animal models, it was shown that damage to the Hertwig epithelial root sheath predicted whether root development continued in transplanted immature permanent teeth (39). It is also hypothesized that stem cells of the apical papilla are important to pulpal regeneration and continued root development. The effects of trauma and long-standing periapical infections subsequent to pulpal necrosis to the viability of the apical papilla and Hertwig epithelial root sheath are currently not known. More studies are needed to better understand the true incidence of continued root development after revascularization procedures and the influence of patient and tooth factors such as the etiology of pulpal necrosis (eg, trauma vs caries), age, size of apical foramen, presence, size and temporal persistence of periapical pathology, and so on.

The findings reported here suggest that revascularization treatment has comparable, but not superior, clinical and radiographic outcomes with traditional apexification procedures. More clinical research is needed with large subject numbers and long follow-up periods to better understand which cases are best suited for revascularization treatment.

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