

Original Article

Clinical and Radiographic Outcomes of Traumatized Immature Permanent Necrotic Teeth after Revascularization/Revitalization Therapy

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ABSTRACT

Introduction: Revascularization treatment is rapidly becoming an accepted treatment alternative for the management of endodontic pathology in immature permanent teeth with necrotic dental pulps. However, the success and timing of clinical resolution of symptoms, and radiographic outcomes of interest, such as continued hard tissue deposition within the root, are largely unknown.

Methods: In this prospective cohort study, 20 teeth were treated with a standardized revascularization treatment protocol and monitored for clinical and radiographic changes for 1 year. Standardized radiographs were collected at regular intervals, and radiographic changes were quantified.

Results: All 20 treated teeth survived during the 12-month follow-up period, and all 20 also met the clinical criteria for success at 12 months. As a group, the treated teeth showed a statistically significant increase in radiographic root width and length and a decrease in apical diameter, although the changes in many cases were quite small (such that the clinical significance is unclear). The within-case percent change in apical diameter after 3 months was 16% and had increased to 79% by 12 months, with 55% (11/20) showing complete apical closure. The within-case percent change in root length averaged less than 1% at 3 months and increased to 5% at 12 months. The within-case percent change in root thickness averaged 3% at 3 months and 21% at 12 months.

Conclusions: Although clinical success was highly predictable with this procedure, clinically meaningful radiographic root thickening and lengthening are less predictable after 1-year of follow-up. Apical closure is the most consistent radiographic finding. (J Endod 2014;40:1946–1952).

Keywords: Clinical outcomes, clinical research, endodontic outcomes, prospective cohort study, radiographic outcomes, regenerative endodontics, revascularization, revitalization

INTRODUCTION

Since the first case of revascularization of an immature permanent tooth with apical periodontitis and a sinus tract was reported by Iwaya et al in 2001 ⁽¹⁾, many more case reports and case series of such treatments have been published ⁽²⁾. Unlike apexification therapy, thickening of the

canal walls and continued root maturation are sometimes observed after revascularization/revitalization therapy ^(3, 4); therefore, the treatment procedure is currently widely accepted for the management of endodontic pathology when treating immature permanent necrotic teeth. Although there are multiple possible etiologies for pulp necrosis and/or apical periodontitis in immature permanent teeth, it appears traumatic injury is the most frequent contributory etiology leading to revascularization/revitalization therapy ⁽²⁾. Although several studies have attempted to predict the timing of periapical wound healing, increased thickening of the canal walls, and continued root lengthening of immature permanent necrotic teeth after revascularization/endodontic treatment, the expected rate of these outcomes remains unknown ^(3–11).

Infection can damage the pulp and, if not controlled, can lead to total pulpal necrosis and apical periodontitis as well as root resorption and/or arrested root development of immature permanent teeth. Traumatic injury to the tooth also can cause

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pulpal necrosis and arrested root development, even when the coronal dentin and enamel remain intact, most likely by damaging the periapical vasculature and Hertwig's epithelial root sheath^(12,13). It is not yet clear how trauma as an etiology for pulpal necrosis influences the clinical outcomes of revascularization/revitalization therapy, especially continued root development. In this prospective study, the time to resolution of clinical symptoms, radiographic periapical healing, and radiographic changes in root dimension were investigated in a cohort of patients receiving standardized revascularization/revitalization therapy in traumatized anterior teeth.

MATERIALS AND METHODS

Subjects

This study was approved by the Institutional Review Board of Alexandria University Faculty of Dentistry. A single operator (T.M.A.S.) completed all procedures at the Alexandria University Faculty Practice.

A total of 17 subjects with 1 or more immature permanent anterior teeth (N = 20 cases) met the study criteria and were recruited as subjects into this prospective cohort study. No subjects dropped out of the study during the 1-year follow-up period. The inclusion criteria for the study were subjects with 1 or more anterior teeth with non-vital pulp and immature root. The exclusion criteria for the study were as follows:

1. Teeth with radiographic signs of internal or external resorption
2. Teeth with a root fracture
3. Alveolar fracture
4. Presence of periodontal disease
5. Subjects with chronic systemic illness
6. Uncooperative subjects
7. Subjects with poor oral hygiene

The subjects included in this study represent a convenience sample of the patients who presented to the university faculty practice during the time of study enrollment and met the inclusion/exclusion criteria.

Study Procedures

Baseline examinations included clinical examinations with standard endodontic diagnostic procedures, clinical photographs, and imaging of teeth with periapical radiographs. Pulp sensibility testing was completed using both thermal and electric stimulation. Sensibility to cold was tested by the application of a cotton pellet saturated with Endo Frost (Roeko, Langenau, Germany). Sensibility to heat was tested by the application of a heated gutta-percha stick applied to the tooth. Sensibility to electrical stimulation was evaluated using the Digitest Pulp Tester

(Parkell Inc, Edgewood, NY). For electrical stimulation testing, teeth were isolated with cotton rolls and dried. Tooth paste was used as a conduction medium, and the probe was applied to the incisal one third of the labial surface. Radiographs were taken of all teeth using custom-made bite registration and a paralleling device to standardize all radiographic images in the study. Radiographs were scanned and saved on the computer in a JPEG format.

All 20 teeth were treated following a clinical protocol based on the publication by Banchs and Trope⁽¹⁴⁾. At the first appointment, the tooth was isolated with a rubber dam. The crown of the involved tooth and the surrounding rubber dam were disinfected by swabbing the area with 30% hydrogen peroxide followed by Betadine (Tizaro Suppl Limited, London, UK) for 1 minute each. The canal was accessed with a carbide no. 4 round bur. The pulp chamber was irrigated with 2.5% sodium hypochlorite solution (Clorox; Nobel Wax Factories for Chemicals, Cairo, Egypt). The length of the canal was estimated using the preoperative radiograph, and the canal was gently debrided with a K-file using a push and pull motion in order to remove any necrotic pulp tissue. The canal was then irrigated with copious amounts of 2.5% sodium hypochlorite followed by a sterile saline solution. The canal was dried with sterile paper points. A triple antibiotic paste was used that was made from tablets of antibiotics. After removing any coating, the tablets were crushed into a powder, combined in a 1:1:1 ratio, and mixed with sterile saline to form a pastelike consistency (ciprofloxacin [Ciprofloxazine 200 mg; European Egyptian Pharm Ind, Alexandria, Egypt]; metronidazole [Flagyl 500 mg; Amriya Pharm Ind]; and minocycline [Minocin 100 mg; Wyeth Pharmaceuticals, Ghagzhou, China]). The antibiotic paste was delivered into the apical third of the canal using a Lentulo spiral. A sterile cotton pellet was placed into the canal below the cemento-enamel junction (CEJ), and the access cavity was sealed with intermediate restorative material (Dentsply DeTrey, Konstanz, Germany).

At the second appointment, 2 weeks after the first visit, if the clinical signs/symptoms persisted, the first appointment treatment procedures were repeated. If symptoms were resolved, the tooth was isolated with a rubber dam swabbed with disinfectant. The intermediate restorative material and cotton pellet were removed from the access cavity. The paste was removed from the canal by irrigation with sterile saline solution, and the canal was dried with sterile paper points. A pre-curved K-file was introduced into the canal and extruded 2 mm past the apical foramen in order to induce bleeding into the canal to the level of the CEJ by rotating the file. A sterile cotton pellet was placed over the bleeding for 3–4 minutes to allow blood clot formation. Mineral trioxide aggregate (ProRoot MTA; Dentsply Tulsa Dental Specialties, Tulsa, OK) was mixed with sterile saline solution according to

manufacturer's instructions and placed over the blood clot, just below the level of the CEJ. The access cavity was restored with a light-cured composite resin (Ice composite; Southern Dental Industries, Melbourne, Australia.). The patient was followed up at 1, 3, 6, 9, and 12 months after the completion of revascularization/ revitalization therapy. Follow-up visits assessed for any subjective patient report of pain or discomfort, the integrity of restoration, pulp sensibility testing, tenderness to palpation and percussion, mobility, sinus tract, swelling, periodontal pocket depth measurements, and acquisition of a periapical radiograph.

The clinical outcomes of survival and success were evaluated throughout the study period. 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 showed no signs of endodontic pathology including tenderness to percussion or palpation, a swelling or sinus tract, or spontaneous pain.

Radiographic Analysis

The width of the apical foramen, thickness of the canal walls, and length of the root were measured from images obtained preoperatively and at each follow-up study visit using the open source software Image J (National Institutes of Health, Bethesda, MD). The TurboReg plug-in (Biomedical Imaging Group, Swiss Federal Institute of Technology, Lausanne, VD, Switzerland) was used to minimize distortions in angulation between compared radiographs. The methodology used by Bose et al. was modified and applied in the present study. Briefly, the image with the least visible distortion was chosen as the source image, whereas the other images were designated as target images. Three stable landmarks that were easily identifiable in the compared images were selected on the source and target images. Images were calibrated by using the 'set scale' option in Image J to measure the distance between 2 stable reference points on the source image and that measurement was used to set the scale of the adjusted target image. This calibration process allowed for the measurement of radiographic changes on a millimeter scale.

After image standardization, root length, dentinal wall thickness at the apical third, and the apical foramen diameter were measured by using Image J. The root length was measured as a straight line from the CEJ or alveolar crest to the radiographic apex of the tooth. The dentinal wall thickness was measured at the level of the apical one third. The root canal width and the pulp space were measured at this level, and the remaining dentin thickness was calculated by subtracting the pulp space from the root canal width. The apical diameter was measured as a straight line across the radiographic apical foramen. Radiographs were also assessed for the presence or absence of periapical radiolucency as well as the apical foramen

being open or closed.

Statistical analysis

The McNemar test was used to compare the proportion of cases with and without periapical radiolucency present and with or without closure of the apical foramen at the 3-, 6-, 9-, and 12-month follow-ups versus the baseline proportion of cases. The repeated measures analysis of variance test was used to test for significant changes in root length and thickness of the canal walls (mm) at the 3-, 6-, 9-, and 12-month follow-up examinations versus baseline. $P \leq .05$ was considered statistically significant. Statistical analyses were performed using Stata 11.2 for Mac (Stata Corp LP, College Station, TX). Graphs were generated using GraphPad Prism 5 for Mac OS X (Graph Pad Software Inc, La Jolla, CA).

RESULTS

Baseline Study Population Characteristics

The characteristics of the study population are summarized in table 1. The majority of the subjects were male (70%), and the average age was 11.3 years. All treated teeth were anterior teeth with a nonvital pulpal sensibility testing preoperatively and showed either radiographic periapical pathology and/or periapical symptomatology. Most cases had radiographic evidence of a periapical lesion (85%), and half had active swelling or sinus tract. The etiology of the endodontic pathology for all teeth was trauma, and most teeth had some degree of coronal fracture (Table 1).

Table 1: Patient Demographics and Baseline Characteristics

Variable	Revascularization cases (n = 20)
Male sex, no (%)*	14 (70)
Female sex, no (%)	6 (30)
Age (y)	11.3 $\pm$ 1.9
Anterior tooth	20 (100)
Maxillary	18 (90)
Mandibular	2 (10)
Etiology	
Trauma	20 (100)
Enamel/dentin/pulp fracture	16 (80)
Enamel/dentin fracture	2 (10)
No loss of tooth structure	2 (10)
Periapical radiolucency present	17 (85)
Preoperative pain	12 (60)
Swelling or sinus tract	10 (50)
Preoperative negative pulp sensibility	20 (100)
Pulpal necrosis	15 (75)
Previously initiated randomized controlled trial	5 (25)

Continuous and ordinal variables presented as mean $\pm$ standard deviation. Frequency of all categorical variables presented as number (no) and percentage (%).

* Each tooth is treated as an individual case for analysis. However, some patients had multiple teeth included in the study.

Clinical Outcomes

All 20 revascularization/revitalization cases were followed for a total of 12 months, with follow-up examinations taking place every 3 months. All 20 treated teeth survived during the 12-month follow-up period, and all met the study criteria for clinical success (tooth survival without clinical symptoms including tenderness to percussion or palpation, swelling or sinus tract, or spontaneous pain) at 12 months. No teeth required additional endodontic treatment beyond the initial treatment. For all cases, any symptoms or sign of active infection were resolved by the 3-month follow-up visit. None of the teeth regained responsiveness to pulpal sensibility tests (cold, heat, and electrical) during the 1-year follow-up period.

Radiographic Outcomes

The proportion of cases with radiographic evidence of a periapical radiolucency (PARL) had significantly decreased by the 6-month follow-up visit (Figure 1). Ninety percent of cases (18/20) had complete resolution of radiographic periapical lesions at the 12-month follow-up visit. The remaining 2 cases still had evidence of a PARL but had no clinical symptoms, so they still met the clinical criteria for success in this study. The earliest time point when radiographic evidence for complete apical closure was observed was at 6 months after treatment (3 cases), with the proportion of cases with apical closure differing significantly from baseline at the 9-month visit (Figure 1). Fifty-five percent of cases (11/20) had complete radiographic apical closure 12 months after treatment.

By quantifying the actual distance of the apical opening in millimeters at each follow-up time, we found that the average apical diameter of the population decreased throughout the follow-up period and became significantly different from baseline at the 6-month time point, at which point the mean apical diameter had decreased by 0.65 mm (Figure 2A, 1-way repeated measures analysis of variance [ANOVA], $P < .0001$; Dunnett multiple comparison test baseline vs 6 months, $P < .001$). Comparison of the amount of change in the apical diameter within individual cases showed that on average the apical diameter at 3 months had decreased by 16% and by 12 months had decreased to 79% the size observed in the preoperative radiographs. Many teeth had complete apical closure (Figure 2B). Assuming a 20% change as a cutoff for a clinically meaningful change in apical diameter, all 20 cases had achieved this measure by 9 months.

Significant changes from baseline in the average root length (mm) of the population (Figure 2C, 1-way repeated measures ANOVA, $P < .0001$; Dunnett

multiple comparison test baseline vs 6 months, $P < .01$) were also observed after 6 months of follow-up. The within-case percent change in root length averaged less than 1% at 3 months and increased to only 5% at 12 months (Figure 2D). The within-case percent change in root width averaged 3% at 3 months and 21% at 12 months. Assuming a 20% cutoff for a clinically meaningful radiographic change, it is interesting to note that no cases met this criteria for root length measurements, but 9 cases met this criteria for root width measurements at the 12-month time point. When considering the clinical significance of these findings, it is important to note that although many cases showed a measurable increase in root width or length, on a case-by-case basis, many of these changes would not be discernable by visual examination and would not have been detectable without using software to quantify the radiographic changes.

The final radiographic outcome assessed was hard tissue bridge formation that occurred within the canal and not at the apex. Three teeth showed hard tissue bridge formation in the coronal third, and 2 teeth showed formation in the middle third of the root (Figures 3A–F and 4A and B).

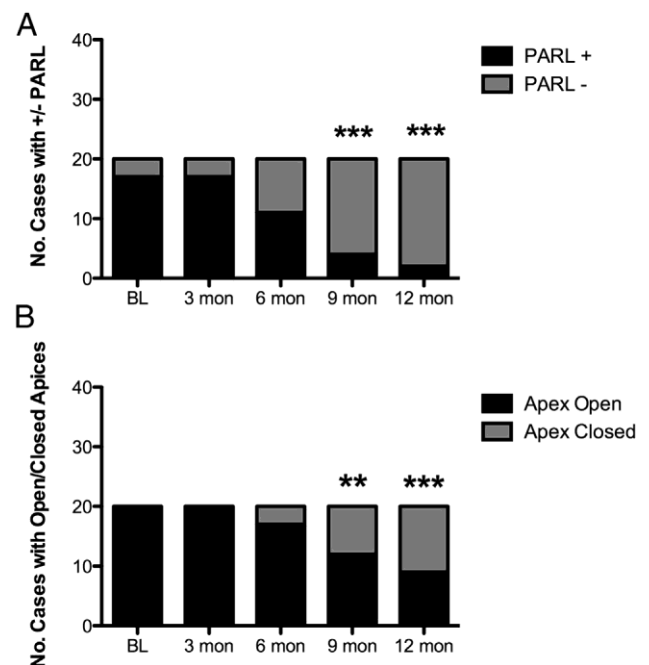


Figure 1. Radiographic findings regarding the proportion of subjects with periapical radiolucencies and open apices at various time points of the study. The proportion of teeth with a periapical radiolucency decreased throughout the study period and became significantly different from baseline after 9 months (McNemar χ^2 test, 6 months: $P = .06$; 9 and 12 months: $P < .0001$). (B) The proportion of subjects with an open apex began to decrease after 6 months and became significantly different from baseline at 9 months (McNemar χ^2 test, 9 months: $P < .05$; 12 months: $P < .001$).

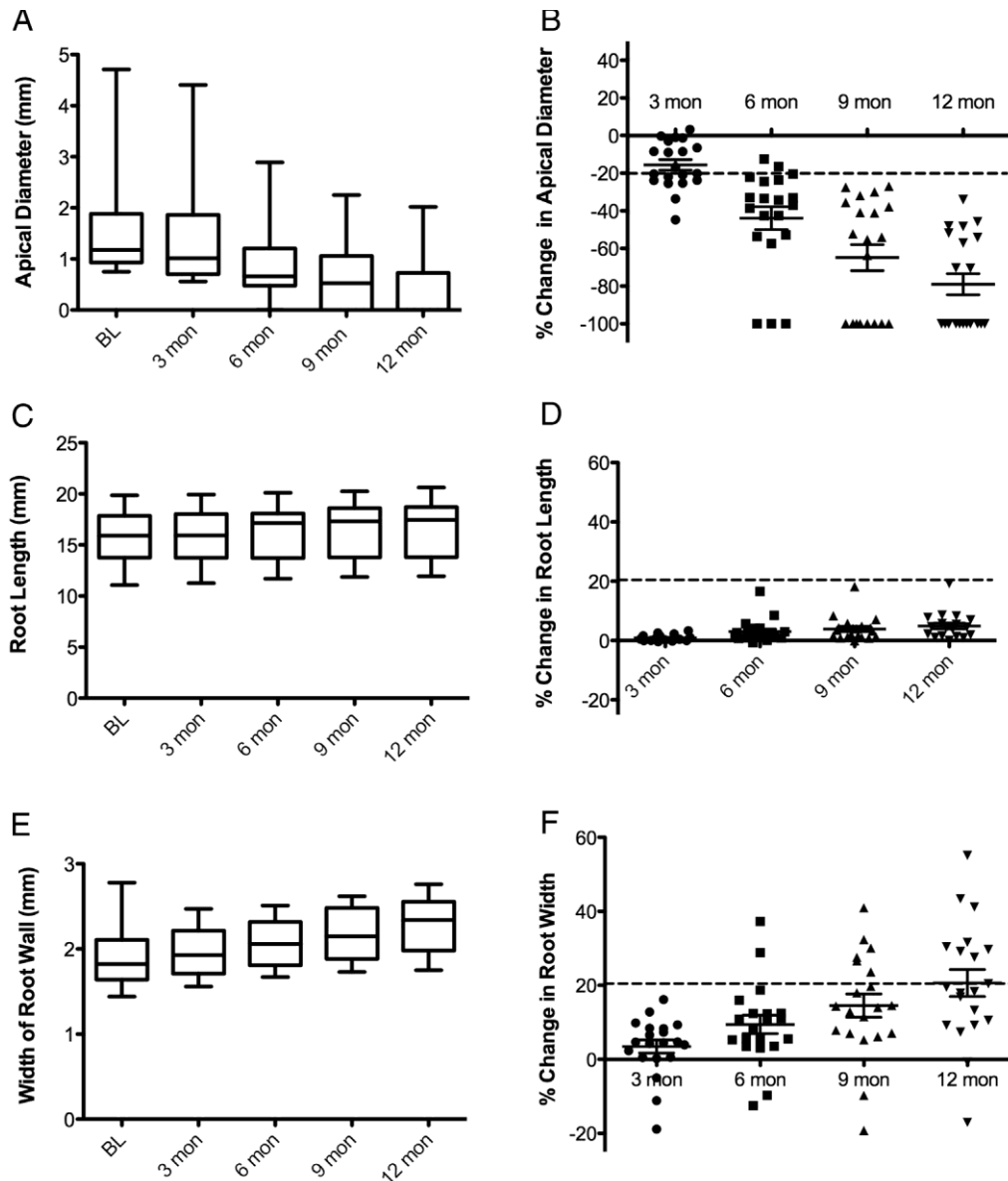


Figure 2: Radiographic changes in the apical diameter, root length, and root width over the study period. (A) A box and whisker plot of apical diameter (mm) measured at 3-month intervals. The band inside the box represents the median. The lower chamber of the box contains the first quartile, and the upper chamber of the box contains the third quartile. The upper and lower boundaries of the whiskers represent the minimum and maximum values of the population. The change was highly significant when analyzed using repeated measures ANOVA. (B) A scatter plot of the calculated percent change from baseline in the apical diameter for each case measured at each follow-up visit. The error bars represent the mean standard error of the mean. The horizontal line represents an arbitrary cutoff of 20% change, representing a clinically significant finding. (C) A box and whisker plot of the root length (mm) measured at 3-month intervals. The change was highly significant when analyzed using repeated measures ANOVA. (D) A scatter plot of the calculated percent change from baseline in the root length for each case measured at each follow-up visit. (E) A box and whisker plot of the width of the root wall (mm) measured at 3-month intervals. The change was highly significant when analyzed using repeated measures ANOVA. (F) A scatter plot of the calculated percent change from baseline in the root width for each case measured at each follow-up visit.

DISCUSSION

This study provides unique insights into the temporal nature of clinical and radiographic outcomes of revascularization/revitalization treatment. First, this was a prospective study with all treatments being completed by a single practitioner using a standardized protocol. Thus, case to case variability in treatment protocols was minimized. Also, the radiographs were collected in a standardized manner at predetermined time points using a bite registration and paralleling device, allowing for accurate quantification of radiographic changes. Collectively, the design of this study provided an optimal opportunity to assess temporal aspects of hard tissue deposition, resolutions of symptoms, and resolution of radiographic periapical pathology after revascularization / revitalization treatment.

In the present study, 90% (18/20) of the revascularized cases had complete resolution of periapical lesions at the 12-month follow-up, and all cases were clinically successful, without signs or symptoms of active infection. Several clinical case series have been published using revascularization / revitalization procedures with follow up time ranging from 6 months to 3.5 years; they also reported high levels of clinical success (78%–100%) and resolution of radiographic periapical pathology (80%–100%) (7, 9–11). However, case series are not a useful study design for estimating rates of clinical success because the inclusion of treatment failures is at the discretion of the authors. Rather, cohort studies are needed with well-defined inclusion/exclusion criteria that take into account subjects lost during the follow-up period. Two retrospective cohort studies including about 20 revascularization/revitalization studies have also reported fairly high rates of clinical success (78% and 100%) and radiographic healing of periapical lesions subsequent to treatment (93% and 100%) (4, 15). Taken together, regenerative endodontic therapy appears to have a high clinical success rate in the initial 1–2 years after treatment completion. Studies with longer follow-up periods are still needed to better estimate the long-term success.

In the present study, complete apical closure occurred in 55% (11/20) of revascularized/revitalized treated teeth, with all cases showing at least a 20% decrease in apical diameter by the 1-year follow-up visit (Figure 2B). The average decrease in the apical diameter within individual cases from the preoperative radiograph to

the 1-year follow-up was 81%. This was the most robust and consistent radiographic change observed in the population treated in this study. Radiographic evidence of apical closure of revascularized teeth has been observed in other studies at various follow-up times (10, 15–17); however, the frequency and time course of the occurrence of apical closure after revascularization / revitalization treatment were not appreciated before this study.

The second most frequently observed radiographic finding in this study was thickening of the canal walls. Although all cases showed a measurable increase in canal thickness, in some cases this increase was quite small, such that it would not be detectable without quantitative assessment of the radiographic changes. In order to estimate the proportion of cases with a clinically meaningful change in root thickness, we applied a threshold of 20% change. Using this criteria, we found 9 cases (45%) met this criteria, with another 4 cases just missing the 20% cutoff at the 12-month follow-up visit (Figure 2F). Although the remaining 5 cases did still have a measurable increase in root width, the clinical significance of this increase in these cases is questionable. It is possible that with further follow-up time, the root walls will continue to thicken, strengthening the predictability of this radiographic outcome after revascularization. At 12 months, the average within-case percent change from the preoperative radiograph was 20%. This is comparable with what was observed in other cohort studies including Jeeruphan et al (4), who reported an average 27% increase with an average of a 21-month follow-up, and Alobaid et al (15), who saw a 10% increase with an average of a 15-month follow-up. Differences in within-case radiographic changes could be due to the fact that non standardized radiographs were used in the retrospective cohort studies, which often can reduce the accuracy in measuring the actual radiographic change. Another potentially important factor that could influence root growth is the contributing etiology in the different study populations, including the frequency of severe trauma (avulsions and intrusions) as the contributing etiology for pulpal necrosis in the study population. The cases in the Alobaid study were primarily caused by trauma including avulsions and luxation, whereas the Jeeruphan study was primarily caused by an etiology of dens evaginatus. Because severe trauma has the potential to produce damage to the Herwig epithelial root sheath and/or the apical papilla, traumatized teeth may be less likely to achieve clinically meaningful continued root development than treated immature teeth with pulpal necrosis caused by caries or dens evaginatus.

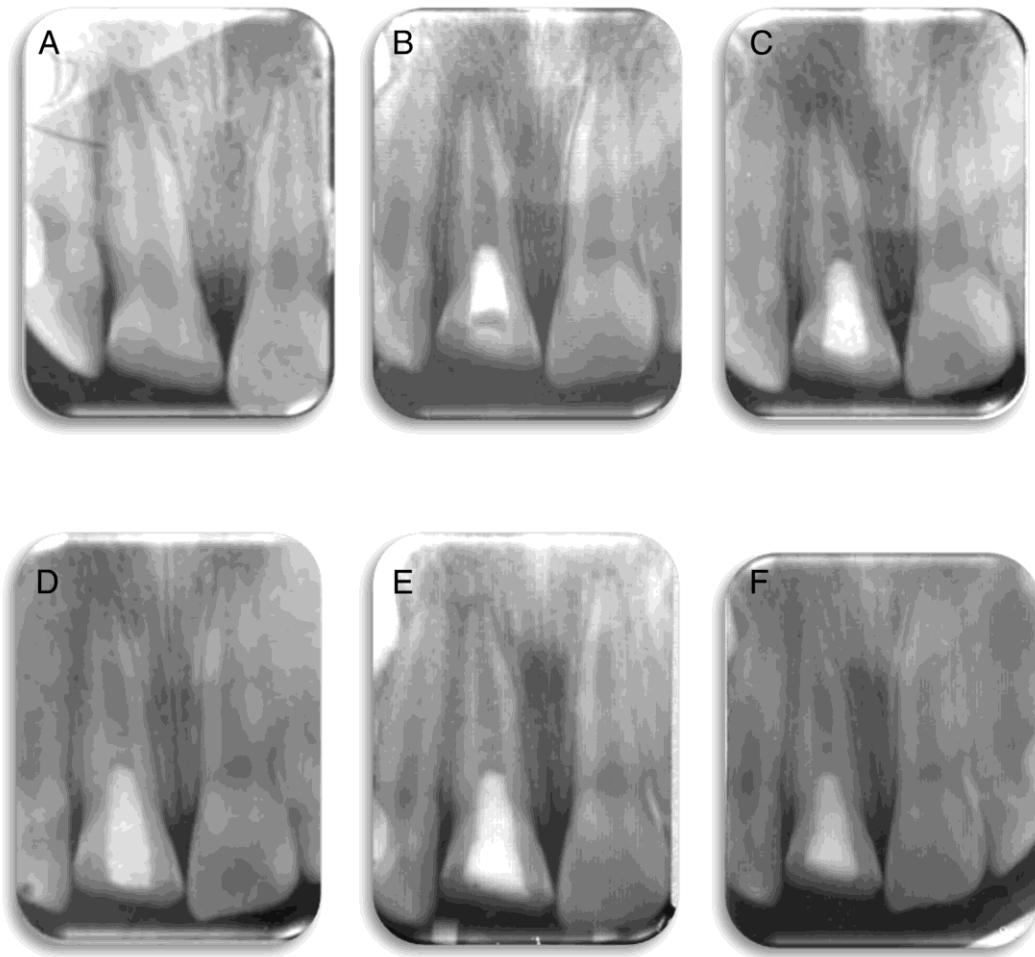


Figure 3: Immature, fractured tooth (#8) with an open apex and large periradicular radiolucency in a 11-year-old boy. Periapical radiographs: (A) a periapical radiolucent lesion with an open apex; (B) after the placement of mineral trioxide aggregate; (C) at the 3-month follow-up, partial regression of periapical radio- lucent lesion and partial closure of the root end; (D) at the 6-month follow-up, with marked reduction in periapical lesion with continued development of the root; (E) at the 9-month follow-up, nearly complete healing of periapical lesion with continued development of the root apex; and (F) at 1-year follow-up, complete maturation of the root apex with hard tissue bridge formation noted midroot.

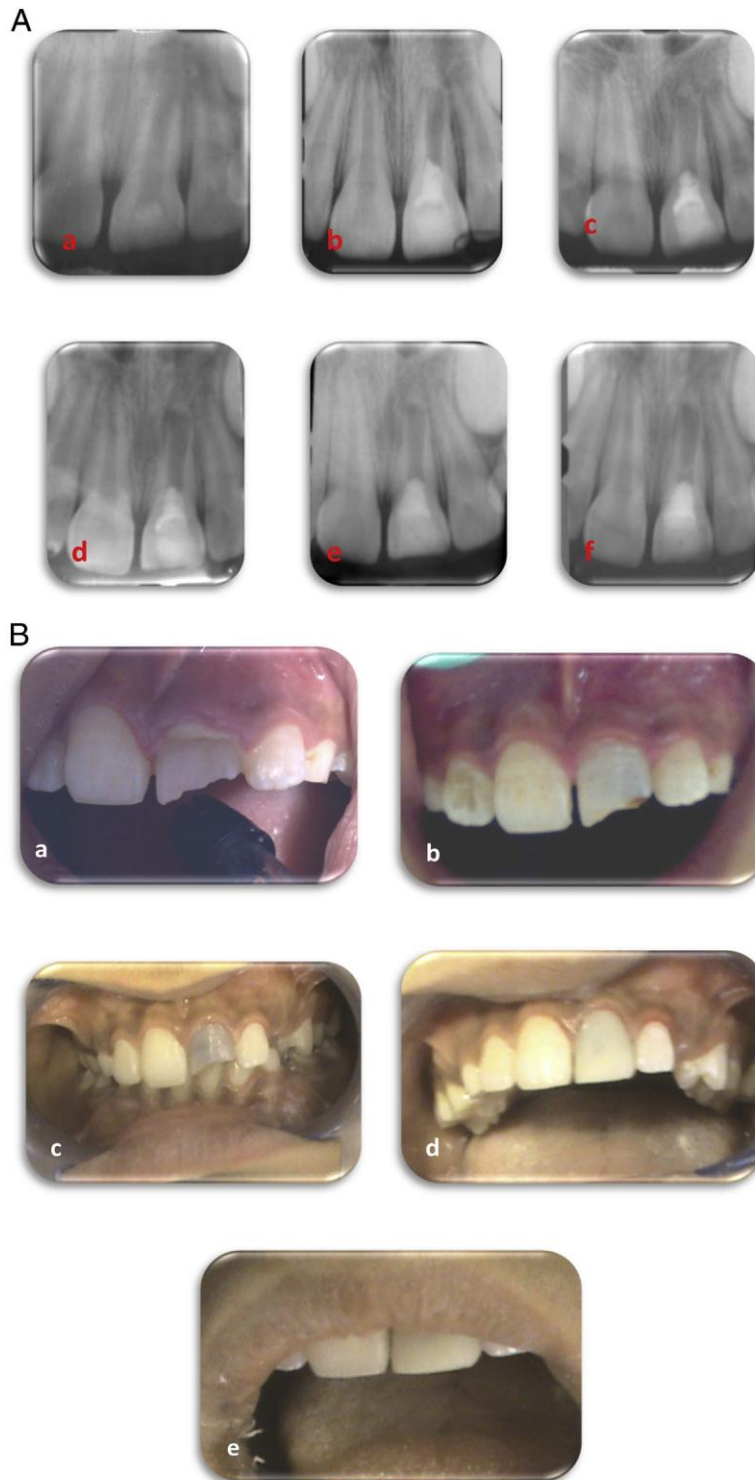


Figure 4: (A) A 12-year-old boy presented with labial swelling and cervical pus discharge over tooth #9. Intraoral periapical radiographs: (a) immature root with thin dentinal root walls associated with large periapical pathology; (b) after the placement of mineral trioxide aggregate; (c) at the 3-month follow-up, regression of periapical radiolucent lesion and hard tissue formation at the apex (minimal thickening and lengthening of the root noted); (d) at the 6-month follow-up, with marked reduction in the periapical lesion with some root thickening; (e) at the 9-month follow-up, nearly complete healing of the periapical lesion with continued development of the root apex; and (f) at the 1-year follow-up, midroot calcific bridge formation noted. (B) Clinical photographs: (a) preoperative clinical photograph showing labial swelling and cervical pus discharge over tooth #9 and (b) 3-week postoperative photograph showing complete healing of the swelling. (c) At the 3-month follow-up, normal gingival contour was observed. Significant coronal staining, likely from the triple antibiotic paste, was also noted. This was observed in many of the cases. (d and e) At the 1-year follow-up with final treatment with composite resin veneer.

Continued root lengthening was the least robust and consistent radiographic finding in this study. Although a statistically significant change in root length was observed in the study population over time, the clinical significance of the measured radiographic changes in root length is not clear. Again, using a 20% threshold for a clinically meaningful within-case change in radiographic root length, no cases met this criteria at 12 months, with only 1 case approaching the threshold (Figure 2D). Overall, at 12 months, there was a 5% average increase in root length across all the cases. Jeeruphan et al⁽⁴⁾ observed a 15% average change in root length, and Alobaid et al⁽¹⁵⁾ observed a 5% change. Thus, all 3 cohort studies support the finding that a greater amount of root thickening occurs than root lengthening after revascularization / revitalization treatment.

All revascularized/revitalized teeth in the present study did not respond to pulp sensibility tests (cold, heat, and electric current) at the end of the 12-month study. Based on histologic studies of animal and human revascularized/revitalized teeth, thickening of the canal walls is mainly caused by deposition of cementum like tissue without the tubular structure observed in dentin⁽¹⁸⁻²³⁾. Even if there was a regeneration of sensory nerve fibers adjacent to the newly formed hard tissue in the canal, these sensory nerve fibers probably would not be activated by sensibility tests relying on hydrodynamic mechanisms because there are no tubules present in the newly formed hard tissue. It is also important to point out that a positive response of revascularized /revitalized tooth to an electric pulp test^(7,11,16) does not necessarily imply that regeneration of pulplike tissue has occurred. This is because most vital tissues are innervated (including periodontal ligament and alveolar bone) because nerves play a critical role in immunologic defense mechanisms (via the release of neuropeptides), healing, and protection.

In conclusion, the findings reported here support the idea that revascularization/revitalization treatment has a high short-term clinical success rate. Apical closure was the most predictable and robust radiographic finding followed by thickening of the root wall, and only modest changes in root length were observed 1 year after treatment. The knowledge provided regarding the frequency and timing of radiographic hard tissue deposition will help clinicians to know when they might expect to observe these outcomes in their patients.

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