Clinical Evidence for Regenerative Endodontic Procedures: Immediate versus Delayed Induction?

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Abstract

Clinicians face many challenges when treating immature permanent teeth in young patients. Immediate blood clot induction can be a successful option as described by some case reports. No experimental studies or clinical trials have addressed this question. We have designed a clinical trial in which we hypothesized that there is no difference in success between immediate or delayed induction protocols. After confirmation of pulpal necrosis, patients were randomized. In the delayed group, 15 teeth were treated following the American Association of Endodontists guidelines, and calcium hydroxide was used as the intracanal medication. In the immediate group, 13 teeth had a blood clot inducted at the first appointment. The teeth were evaluated after 1, 3, and 12 months. Three independent evaluators assessed the periapical healing. The Pearson chi-square test or the Fisher exact test was used to compare the success rates between the 2 groups. Currently, of the 25 recruited patients (28 teeth), 19 have completed their 12-month follow-up. The group with delayed induction had a 71% success rate, and the group with immediate induction had a 33% success rate. In most cases (79%), trauma was the etiology. All successful cases started at stage 9 of root development (Nolla), and the majority showed healing type 2. Determination of the stage of root formation and etiology are possible critical factors for any therapeutic decision. In summary, it is early to conclude or suggest any of the protocols. Clearly, much more data are needed before sample size requirements can be met. *(J Endod 2017;43:S75–S81)*

Key Words

Calcium hydroxide, immature necrotic teeth, regenerative endodontics, revascularization, single visit

Significance

Randomized clinical trials are fundamental studies to support evidence-based practice in regenerative endodontics. This report presents preliminary data from an ongoing clinical randomized trial to support if immediate induction is feasible for immature teeth.

For over a decade, the American Association of Endodontists (AAE) has promoted regenerative endodontic procedures (REP). This has been possible because of the collaborative work and research support by the Regenerative Endodontic Committee, the AAE Foundation, and the endodontic community. The number and impact of regenerative endodontic publications have increased rapidly in recent years. In recognition, the *Journal of Endodontics* has added a subheading of "Regenerative Endodontics" to its table of contents. Although the research in this area is looking for high levels of evidence, many clinicians have used published case reports to develop their regenerative procedures. Immature necrotic teeth can be successfully treated by REPs in the short-term, but the long-term outcome is still missing. Many questions remain unanswered. Can an REP be effectively applied in 1 appointment? Are interappointment intracanal medicaments needed? Are treated teeth more brittle? Can treated teeth be moved orthodontically? What kind of tissue is formed when pulps heal? What are the criteria for case selection? Higher levels of evidence are needed. Randomized clinical trials are required to provide plausible answers to these questions.

The AAE provides clinical recommendations for REPs, which are based on successful case reports and *in vitro* studies (1). Although several case series and pilot studies have been published, the protocol used varies on important factors such as the concentration and type of intracanal irrigation (sodium hypochlorite, calcium hydroxide [$Ca(OH)_2$], or chlorhexidine), the type of interappointment medication (Ca $[OH]_2$ or triple or double antibiotic paste), the capping material (gray or white mineral trioxide aggregate [MTA]), and the incorporation or lack of scaffold material (collagen or platelet-rich plasma) (2–9). Even the outcome expected varies as shown by prospective and retrospective case series studies. Outcomes were categorized as survival or success based on subjective evaluation of periapical healing and the increase in root width and root length (10, 11). Others have then categorized their outcome by the assessment of qualitative periapical healing and quantitative root width and length (12). For example, Chen et al (4) classified their outcome by 5 types of possible healing ranging from normal root continuation to severe calcification and hard tissue formation. This leads us to the conclusion that, despite several efforts to develop clinical guidelines, there are many variables to consider when we select a

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protocol and design a clinical study. Only a few clinical trials have been reported, and several are ongoing although no data have been published thus far (Table 1).

Clinicians face many challenges when treating immature permanent teeth in young patients. These include patient behavior and anatomic features such as the lack of apical constriction and short and thin roots. Besides these challenges, the primary target of the latest regenerative clinical guidelines by the AAE includes the preservation of vitality of the apical papilla and its stem cells (1). In 2008, Huang et al (13) hypothesized that partial survival of the dental apical papilla after pulpal necrosis in immature permanent teeth is responsible for the successful outcomes. Lovelace et al (14) found a significant number of stem cells coming from the apical bleeding during the induction of a blood clot in immature teeth compared with the number in circulating blood. The cytotoxicity of the intracanal irrigants used for REP has consistently shown that chlorhexidine and sodium hypochlorite inhibit stem cell attachment to dentinal walls. On the other hand, EDTA promotes stem cell attachment and differentiation and does so even after prior use of chlorhexidine and sodium hypochlorite (15–18). The use of full-strength intracanal antibiotics inhibits stem cell growth and leads to cell death. Other advocated intracanal medicaments at high concentrations have also been questioned. Calcium hydroxide supports the induction of stem cell growth and is much more easily removed from dentinal walls than tetracycline-containing pastes (19, 20).

One possible strategy that may favor maintenance of the vitality of the apical papilla is to complete the treatment in a single appointment with immediate blood clot induction. This might also enhance patient compliance (7,21–23). However, there is little experimental evidence to support a single-appointment protocol, except for a single *in vivo* study in beagle dogs (24). In this study, their protocol included the use of 2.5% sodium hypochlorite (Endovac; Kerr, Orange, CA), minimal instrumentation, and immediate blood clot induction. The study showed a comparable outcome with the group in which the traditional 2-visit protocol was used. This traditional protocol included triple antibiotic paste with blood clot induction at a subsequent appointment (24). Some case reports do describe successful outcomes after an immediate blood clot induction, but no experimental studies or clinical trials have addressed this question (21–25). With this knowledge gap in the literature identified, we have designed a clinical trial in which we have hypothesized that there is no difference between immediate or delayed induction in terms of the successful outcome of periapical healing and the increase in root width and root length. Here we describe the designed clinical trial along with the preliminary findings.

Materials and Methods

Randomized Clinical Trial Design

The Institutional Review Board of the University of Michigan, Ann Arbor, MI, approved the research protocol, and the study has been conducted since 2012 at the Graduate Endodontic Clinic, School of Dentistry, University of Michigan. Nonpregnant, healthy, American Society of Anesthesiologists (ASA) physical status classification 1 and 2, and cooperative 6- to 25-year-old patients were screened for the study. Patients diagnosed with pulp necrosis on an immature permanent tooth or patients with at least 1 open apex of 1 mm or more in diameter were recruited. Selected teeth needed to be restorable and not periodontally involved (no periodontal probing >4 mm). Teeth with evidence of internal or external resorption, ankylosis, or root fracture were excluded from the study.

All potential participants were evaluated clinically and radiographically. The evaluation included assessment of pain, swelling, and/or

TABLE 1. Randomized Clinical Trials (clinicaltrial.gov)

Title	Sponsor	Sample	Time frame/status	Protocols
Comparison of Two Dental Techniques Used to Treat Teeth Which Have Become Infected of Painful Following Trauma Comparison	University of Liverpool, England	30	Completed February 2011–August 2015	1. Revitalization 2. MTA apexification
Regenerative Endodontic Procedure of Immature Permanent Teeth With L-PRF: a Pilot Controlled, Clinical Trial	Universitaire Ziekenhuizen Leuven Belgin	20	Collecting September 2014–September 2020	1. REP with L-PRF biological: stem and progenitor cells 2. REP
Regenerative Endodontic Procedure of Immature Permanent Teeth With PRF: A Pilot Randomized Controlled Trial	Fujian Medical University, China	50	Collecting May 2013–February 2017	1. REP (TAP)/PRF-MTA 2. REP (TAP)/MTA
Revitalization of Immature Permanent Teeth With Necrotic Pulps Using SHED Cells	Fourth Military Medical University, China	80	Collecting February 2013–October 2017	Scaffold-free SHED-deprived pellet single-group assignment
Regeneration of Pulp-Dentin Development in Teeth With Necrotic Pulps and Immature Roots	Loma Linda University University of North Carolina University of Texas Health Science Center at San Antonio	120	Collecting September 2014–November 2019	1. TAP/Emdogain (Institut Straumann AG, Basel, Switzerland)/MTA 2. TAP/Collaplug (Calcitek, Carlsbad, CA)/MTA 3. MTA apexification

L-PRF, leucocyte and platelet-rich fibrin; MTA, mineral trioxide aggregate; PRF, platelet-rich fibrin; REP, regenerative endodontic procedure; SHED, stem cells from human exfoliated deciduous teeth; TAP, triple antibiotic paste.