Regenerative Endodontics: Clinical Review and Case Reports

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Regenerative Endodontics: Clinical Review and Case Reports

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Learning Objectives: After reading this article, the individual will learn: (1) principles of regenerative endodontics in the treatment of immature necrotic permanent teeth, and (2) clinical protocol for treating immature necrotic permanent teeth with regenerative endodontics.

About the Author

Dr. Short graduated from Morris Brown College in 1995 as valedictorian with a BS degree. He attended the Medical College of Georgia School of Dentistry to attain a DMD degree in 1999. In 2002, he earned his postdoctorate degree in endodontics from Nova Southeastern University. Dr. Short became a board-certified endodontist in 2009, a status which only 25% of endodontists achieve. He is a Diplomate of the American Board of Endodontics, and his private practice, Apex Endodontics PC, is located in Smyrna, Ga. He is an expert consultant to the Georgia Board of Dentistry and an assistant clinical professor at the Georgia Regents University School of Dentistry. In addition, he has lectured nationally. Dr. Short has received several prestigious awards and accolades throughout his career and volunteers at various nonprofit organizations in his community, such as The Ben Massell Dental Clinic, which provides free dental care to those in need. Dr. Short has authored a book, Getting to the Root of Your Problem: 365 Days of Inspirational Thinking. As an Affordable Care Act (ACA) correspondent in oral healthcare, Dr. Short is currently part of a panel that corresponds with White House government officials dealing with healthcare issues and the ACA. He was also recognized as one of the Top 40 Dentists Under 40 in America by Incisal Edge Magazine. He can be reached at (678) 503-0790 or via email at dr.short@yahoo.com.

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Regenerative endodontic procedures (REPs) represent a paradigm shift for the treatment of necrotic pulps in immature permanent teeth, ranging from traditional barrier formation utilizing calcium hydroxide or mineral trioxide aggregate (MTA), to a biologically based treatment for root maturation. REPs capture the ability to use stem cells that reside naturally in and around the tooth to extend the life of the tooth. In particular, periradicular tissues of immature teeth are rich in blood supply and contain stem cells that have the potential for tissue regeneration. These stem cells may be the next breakthrough technology which may allow clinicians to grow human teeth in the foreseeable future. In fact, a Harvard-led team in May 2014 successfully used low-powered lasers to activate stem cells and stimulate the growth of teeth in rats and human dental tissue in a laboratory setting. The results were published in the journal Science Translational Medicine. Titanium dental implants may one day be considered “archaic,” such as silver cones or retrograde amalgams are now considered out of date by many clinicians, teachers, and researchers.

WHAT IS REGENERATIVE ENDOdontICS?

Regeneration is the process of renewal, restoration, and growth
that makes genomes, cells, or organisms resilient to natural fluctuations or events that cause disturbance or damage. Every species, from bacteria to humans, is capable of regeneration. Regeneration can either be complete where the new tissue is the same as the lost tissue, or incomplete where fibrosis occurs after the necrotic tissue is removed. In regenerative endodontics, the goal is for the pulp to “revitalize” or “regenerate” new tissue so that root maturation can occur in the absence of disease and the patient’s tooth can return to function, form, and aesthetics.

The management of immature permanent teeth with pulpal disease can be very challenging for the clinician. For example, it is difficult to properly debride, clean, and shape thin dentinal walls, which can result in cervical fracture. An extraction or fracture will present a restorative and aesthetic problem, especially if the patient is young, due to the fact that the bone is too immature for an implant.

Regenerative endodontics in its original state began with Ostby in 1961 with limited success. During the last decade, it has been redefined as “biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex.” Another term many use to describe regenerative endodontics is revascularization, which can result in thickening of dentinal walls and continued root development in immature teeth with necrotic pulps.
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When Should Regenerative Endodontics be Considered?

1. Necrotic pulp and immature or open apex
2. Young patient
3. Very thin dentinal walls
4. Cannot achieve a predictable apical seal with conventional endodontics
5. Presence of pathology with very large apical foramen.

What are the Key Components of Regenerative Endodontics?

In order for the regenerative endodontic technique to be effective, the following 3 key components are needed:

1. Stem cells
2. Scaffolds

Stem cells are undifferentiated cells that continuously divide. There are 2 main types: embryonic and postnatal (adult). An adult stem cell can divide and create another identical cell, but the capacity for differentiation into other cell types is limited. There are several types of adult stem cells that have been isolated from teeth: (1) dental pulp stem cells, (2) stem cells from human deciduous teeth, (3) periodontal ligament stem cells, (4) dental follicle progenitor stem cells, and (5) stem cells from apical papilla (SCAPs). The most current stem cells used in REPs are the SCAPs due to their location in Hertwig’s epithelial root sheath.

Table 2. Regenerative Endodontic Technique

<table>
<thead>
<tr>
<th>First Appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Diagnose case properly (necrotic pulp with open or immature apex)</td>
</tr>
<tr>
<td>● Local anesthesia (with or without vasoconstrictor), rubber dam isolation, access</td>
</tr>
<tr>
<td>● Copious, gentle irrigation with 20 mL 3% sodium hypochlorite with side-vented syringe 2 mm from the apex</td>
</tr>
<tr>
<td>● Rinse with 5 mL of sterile saline</td>
</tr>
<tr>
<td>● Irrigate with 10 mL 0.12% chlorhexidine gluconate with sided-vented syringe</td>
</tr>
<tr>
<td>● Dry canal with large paper point</td>
</tr>
<tr>
<td>● Place calcium hydroxide (injectable) inside canal with sterile cotton pellet</td>
</tr>
<tr>
<td>● Seal with cotton pellet and 3 to 4 mm of temporary restorative material (such as Cavit Temporary Filling Material Refill [3M ESPE])</td>
</tr>
<tr>
<td>● Dismiss patient for 4 weeks to allow the calcium hydroxide time to disinfect the canal</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Second Appointment</th>
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<tbody>
<tr>
<td>● Assess response from patient from initial treatment; no signs or symptoms of remaining infection</td>
</tr>
<tr>
<td>● If swelling or sinus tract remains, repeat the first appointment procedure</td>
</tr>
<tr>
<td>● If patient is asymptomatic, anesthetize with 3% mepivacaine without vasoconstrictor, rubber dam isolation, access</td>
</tr>
<tr>
<td>● Copious, gentle irrigation with 20 mL 17% ethylenediaminetetraacetic acid with side-vented syringe followed by sterile saline</td>
</tr>
<tr>
<td>● Dry canal with large paper point</td>
</tr>
<tr>
<td>● Create bleeding into the canal space by over-instrumenting or poking the bone with a sterile endodontic file (this forms the blood clot, which acts as a scaffold to bring the stem cells up into the canal space)</td>
</tr>
<tr>
<td>● Stop bleeding 3 mm from cemento-enamel junction with sterile cotton pellet and remove the cotton pellet</td>
</tr>
<tr>
<td>● Place 3 to 4 mm of EndoSequence Root Repair Material (Brasseler USA), or white mineral trioxide aggregate (MTA) (DENTSPLY Tulsa Dental Specialties) on top of blood clot very lightly (note: MTA is now known to create a discolored tooth in this technique, which is discussed later in this article)</td>
</tr>
<tr>
<td>● Restore with composite or glass ionomer</td>
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<table>
<thead>
<tr>
<th>Follow-Up Evaluation</th>
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<tbody>
<tr>
<td>● First follow-up in one month</td>
</tr>
<tr>
<td>● Tooth should be asymptomatic and functional</td>
</tr>
<tr>
<td>● The 6- to 12-month follow-up: radiographic evaluation (resolution of periapical radiolucency starting and may see increased dentinal wall thickness)</td>
</tr>
<tr>
<td>● The 12- to 24-month follow-up: radiographic evaluation (increased dentinal wall thickness, radiographic healing more evident, and increased root length and width)</td>
</tr>
</tbody>
</table>
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CASE 1

Figure 2a. A 9-year-old male with a necrotic pulp, large periapical lesion, and immature root with blunderbuss apex on tooth No. 20. No history of trauma. Possible case of dens evaginatus. There is no conventional endodontic therapy that will cause the root to continue to form in length, width, and strength. These cases will require the regenerative endodontic procedure for a better outcome than apexification.

Figure 2b. Anesthetize, access, irrigate, dry, and place calcium hydroxide (injectable UltraCal XS Calcium Hydroxide Paste [Ultradent Products]) according to first appointment treatment protocol (see Table 2). Temporize with Cavit. No endodontic files are involved for cleaning and shaping.

Figure 2c. Clinical view of tooth No. 20 with Cavit in place. Note normal color of enamel at this point.

Figure 2d. One-month recall showing positive healing with some calcium hydroxide still in place.

Figure 2e. Completion on tooth No. 20 after one month with white MTA and composite following second appointment treatment protocol (see Table 2). A file is used to poke the bone and stimulate a blood clot to bring the stem cells up into the once-necrotic pulp chamber. The MTA is used as a barrier, not as an obturation material.

Figure 2f. The 8-month recall on tooth No. 20 showing root elongation and apical closure starting to occur.

Figure 2g. Dark staining of crown after 8-month recall on tooth No. 20 due to the white MTA. (EndoSequence Root Repair Material [Bras-seler USA] can be used as a barrier and will not stain the crown.)

Figure 2h. Clinical view of tooth No. 20 with dark color staining after 8-month recall using MTA and composite.

Figure 2i. One-year recall showing complete apical closure and an intact periodontal ligament on tooth No. 20.

Figure 2j. The 2-year recall on tooth No. 20 showing absence of pathology and intact periodontal ligament.

Scaffolds are “ladders” that provide support for cell organization, proliferation, and vascularization. Dentin, blood clots, and platelet-rich plasma have been used to provide scaffolds in REPs. However, there are many other types of natural or synthetic materials available. The most common and readily available scaffold is the blood clot that is formed during the REPs.

Growth factors are proteins that bind to receptors on the cell and act as signals to induce cellular proliferation and/or differentiation. Examples in the pulp and dentin complex are bone morphogenic protein, transforming growth factor-beta, and fibroblastic growth factor. Current REPs utilize growth factors already found in platelets from the blood and dentin.

Regenerative Endodontic Therapy Versus Apexification
In the past, long-term calcium hydroxide was used to induce apexification of the immature tooth with pulpal necrosis. Once an apical barrier was formed, obturation material such as warm gutta-percha or MTA would be placed in the root canal system. While the success rate of calcium hydroxide was approximately 95%, there were several problems associated
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CASE 2

with this technique. These included the following:

1. Multiple appointments needed to replace calcium hydroxide due to wash-out
2. The time required to form a calcified barrier (3 to 24 months)
3. The long-term deleterious effects of calcium hydroxide on the dentin.

MTA offers an alternative to calcium hydroxide. However, it does not contribute to further root development; therefore, immature teeth remain subject to cervical root fractures. In contrast, REPs offer increased root development (length and width) which confers a better long-term prognosis (Figure 1).

Regenerative Endodontics Treatment Protocol

1. Informed consent prior to treatment (Table 1).
2. REP and follow-up guidelines (Table 2).
3. ADA CDT codes for pulpal regeneration procedures (Table 3).

CASE REPORTS

Case Report No. 1: Tooth No. 20
Case report No. 1 is demonstrated in Figure 2.

Case Report No. 2: Tooth No. 24
Case report No. 2 is demonstrated in Figure 3.
DISCUSSION

The success rate of regenerative endodontics is relatively high if the procedure is done properly and the patient is compliant. Some studies show a success rate of up to 90%. The majority of human case studies have shown good clinical outcomes for immature permanent teeth with pulpal necrosis in addition, a positive response to cold and/or electric pulp tests have occurred in some cases. The rate of root maturation is variable because of unique individual immune systems. A resorbable matrix such as CollaCote (Zimmer Dental) could be placed over the blood clot so material can lay against it, but is not essential for repair.

The 3 most important treatment factors in regenerative endodontics are: (1) disinfection of the root canal canal, (2) establishing bleeding to create a blood clot to carry the stem cells inside the canal, and (3) a bacteria-tight seal of the access opening. One of the main disinfectant agents in regenerative
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therapy is sodium hypochlorite, due to its ability to remove necrotic and organic tissue from the root canal.\textsuperscript{11} It is diluted to 3\% in order to reduce toxicity to the stem cells.\textsuperscript{20} When irrigating, the side-vented needle should be introduced into the root canal to a point 2 mm short of the apical foramen, very slowly to prevent a sodium hypochlorite accident in the peri-apical tissue. Initial sodium hypochlorite irrigation is followed by 5 mL of sterile saline to prevent possible interaction with chlorhexidine. Chlorhexidine is recommended because of its antimicrobial activity and long-term substantiveness interacting with dentin. It should not be used alone because it has no tissue dissolution capabilities.

Historically, research with antibiotics showed that a combination of metronidazole, minocycline, and ciprofloxacin could be effective against common endodontic pathogens (also known as triple antibiotic paste).\textsuperscript{17} However, minocycline can cause staining of the dentin which can create an aesthetic issue as reported by Kim et al.,\textsuperscript{21} and triple antibiotic paste can be toxic to living tissue in such a high concentration.\textsuperscript{22} Furthermore, if a patient does not know he or she is allergic to any of these antibiotics, there is a potential for anaphylactic shock.

Latest research has shown that calcium hydroxide can be used as the intracanal medicament, which will properly disinfect the canal space and stimulate proliferation of SCAPS without causing any severe allergic reactions or staining.\textsuperscript{22} Calcium hydroxide also acts as a physiochemical barrier, which prevents proliferation of residual micro-organisms inside the canal and helps to prevent reinfection of micro-organisms from the oral cavity.\textsuperscript{20} Calcium hydroxide should not be placed with a lentulo spiral. Instead, it should be placed with a syringe-tip carrier and then tamped down gently with a moistened cotton pellet.

The use of 17\% ethylenediaminetetraacetic acid (EDTA) is recommended at the second appointment to promote survival of the stem cells and assist with adhesion of the stem cells on the dentin.\textsuperscript{20} EDTA is a chelating agent and decalciﬁes the surface of the root canal dentin to expose its collagen fibers, promoting differentiation of the stem cells which is vital in the regenerative procedure.\textsuperscript{23}

Several studies have shown that white MTA can cause staining after REPs.\textsuperscript{24} Blood contamination was shown to exacerbate the color change using white MTA,\textsuperscript{25} which happens due to the blood clot which forms the scaffold of the regenerative procedure. In addition, the sodium hypochlorite contacts the bismuth oxide in the white MTA and causes dark brown, nearly black discoloration.\textsuperscript{26} A new root repair material by Brasseler USA called EndoSequence BC Root Repair Material Fast Set Putty has shown similar results as the MTA for root maturation with less staining and shortened set time. The putty is completely devoid of heavy metals such as bismuth oxide, which has been shown to cause discoloration.\textsuperscript{26} In addition, Biodentine by Septodont has shown similar efficacy as MTA for positive bioactivity and biocompatibility in promoting dental pulp stem cell proliferation,\textsuperscript{27} and can possibly be used in REPs.

CONCLUSION

Throughout decades, there have been significant changes in the clinical management of infected immature permanent teeth, dating back to the 1960s in work by Ostby.\textsuperscript{6} In the 2000s, Banchs and Trope\textsuperscript{17} reported an alternative treatment to revascularization by introducing the use of triple antibiotic pastes. Like all dental procedures, these procedures are subject to change as more research and case studies are published, including better materials and technology.

Regenerative endodontics is one of the most exciting developments in dentistry, and endodontics is at the cutting edge of the technology. Knowledge of pulp biology, intracanal medicaments, and dental trauma lays the framework in which this procedure should be understood in order to perform it properly and successfully. A working knowledge of biological and mechanical skill is required to attain the highest results in order to make regenerative endodontics a success in clinical practice.

Table 3. ADA Code on Dental Procedures and Nomenclature (CDT Codes) for Pulpal Regeneration Procedures

| First Phase of Treatment: D3351 (debridement and placement of antibacterial medication) |
| Interim Phase (repeat of first phase, if necessary): D3352 (interim medication replacement) |
| Final Phase: D3354 (pulpal regeneration [completion of regenerative treatment in an immature permanent tooth with a necrotic pulp]; does not include final restoration) |

References

6. Ostby BN. The role of the blood clot in endodontic therapy: an experimental histo-
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POST EXAMINATION QUESTIONS

1. Complete regeneration is where new tissue is the same as the lost tissue. Incomplete regeneration is where fibrosis occurs after necrotic tissue is removed.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.

2. Another term many use to describe regenerative endodontics is revascularization.
   a. True.
   b. False.

3. When should regenerative endodontics be considered?
   a. Necrotic pulp and immature or open apex.
   b. Young patient.
   c. Very thin dentinal walls.
   d. All of the above.

4. The key component(s) of regenerative endodontics is/are:
   a. Stem cells.
   b. Scaffolds.
   c. Growth factors.
   d. All of the above.

5. The most current type of stem cells used in regenerative endodontics is:
   a. Dental pulp stem cells.
   b. Stem cells from apical papilla.
   c. Stem cells from human deciduous teeth.
   d. Dental follicle progenitor stem cells.

6. The most common and readily available scaffold for use in regenerative endodontic procedures (REPs) is:
   a. Dentin.
   b. Platelet-rich plasma.
   c. Blood clot.
   d. None of the above.

7. Growth factors in the pulp and dentin complex include:
   a. Bone morphogenic protein.
   b. Transforming growth factor-beta.
   c. Fibroblastic growth factor.
   d. All of the above.

8. One of the main disinfectant agents in regenerative therapy is sodium hypochlorite. It is diluted to 6% in order to reduce toxicity to stem cells.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.
9. This chelating agent promotes differentiation of stem cells, which is vital in the regenerative procedure.
   a. MTA.
   b. Calcium hydroxide.
   c. 17% ethylenediaminetetraacetic acid.
   d. None of the above.

10. In REPs, calcium hydroxide acts as a physiochemical barrier against micro-organisms. It should be placed into the canal with a lentulo spiral.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.
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2. a b
3. a b c d
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6. a b c d
7. a b c d
8. a b c d
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