

Clinical Aspects of Regenerative Endodontic Procedures - A Review

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ABSTRACT

The concept of regenerative endodontics has gained much attention in endodontics in the past decade. The endodontic management of permanent immature teeth remains with challenges. Although treatment modalities for vital pulp therapy in these teeth provide long-term favorable outcome, the treatment of teeth with pulpal necrosis and apical periodontitis are significantly less predictable. Immature teeth diagnosed with pulpal necrosis have been traditionally treated with apexification or apexogenesis approaches. Unfortunately, these procedures provide little to no benefit in attaining continued root development. Regenerative endodontic procedures have evolved as an important alternative in treating teeth with otherwise questionable long-term prognosis because of thin, fragile dentinal walls. These procedures rely heavily on chemical disinfection of the root canal system. This review summarizes the current literature supporting a biological rationale for considering regenerative endodontic treatment procedures in treating the immature permanent tooth with pulpal necrosis.

INTRODUCTION

When a young permanent tooth faces Endodontic infection or physical trauma, it may cause pulpal necrosis and results in incompletely formed roots with wide open apices, reduced root length, and thin root dentinal walls.

Once the source of infection is removed in an affected site, it results in a programmed wound healing. The ideal wound healing is to recreate what occurs during embryonic tissue or organ development (1) and to reconstitute the original biological status structurally and functionally - a process defined as regeneration (2). It is by regeneration and repair a wound healing takes place (3). However if parenchymal cells of an organ is injured completely for e.g. pulpal necrosis, wound healing takes place only by repair and not regeneration (3).

These teeth can be treated with apexification procedures by using either calcium hydroxide treatment (4) or mineral trioxide aggregate (MTA) as an apical plug (5). Though these procedures results in the resolution of signs and symptoms of pathosis, it provides little or no benefit for continued root development (6). Regenerative endodontic procedures (REPs), attempts to restore normal pulpal physiologic functions including continued root development, immunocompetency, and normal nociception in addition to the resolution of symptoms(7).

Regenerative endodontic procedures can be defined as biologically based procedures designed to create and deliver tissues to replace diseased, missing and traumatized pulp-dentin complex. Dr. BW Hermann reported the usage of calcium hydroxide for vital pulp therapy cases [8]. Presently, non-vital infected teeth with immature apex can be treated by - regeneration of pulp dentin complex (tissue engineering technology), and the other in which the formation of new tissue is expected to occur from the structures within the tooth itself, allowing continued root development (revascularization). Thus:

- Pulp revascularization is the process of induction of angiogenesis in an endodontically treated root canal.
- Pulp regeneration is pulpal revascularization plus the restoration of functional odontoblasts and/or nerve fibers.

STEM CELLS

They are the undifferentiated cells that are capable of both self renewal and multilineage differentiation and hence defined as clonogenic. They differentiate into one daughter stem cell and one progenitor cell. It is of two types.

- Embryonic stem cells - they are present within the blastocyst stage of development.
- Postnatal stem cells - they can be isolated from bone marrow, neural tissue, dental pulp and periodontal ligament.

Stem cells can be differentiated from their source as:

- Autologous stem cells - they are harvested from the same individual to whom it will be implanted.
- Allogeneic stem cells - they are from a donor of the same species.
- Xenogeneic cells - it will be from individuals of another species.

For endodontic regeneration, autologous stem cells hold good because of less immune rejection when compared to other group of stem cells. Cells from dental stem structures will have more odontogenic properties in comparison to non dental stem cell population like bone marrow stromal stem cells.

Various sources for postnatal dental stem cells have been successfully studied:

Permanent teeth - Dental pulp stem cells (DPSC): derived from third molar.[9]

- Deciduous teeth - Stem cells from human-exfoliated deciduous teeth (SHED): stem cells are present within the pulp tissue of deciduous teeth. [10]

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- Periodontal ligament - Periodontal ligament stem cells (PDLSC). [11]
- Stem Cells from apical papilla (SCAP). [12]
- Stem cells from supernumerary tooth – Mesiodens. [13]
- Stem cells from teeth extracted for orthodontic purposes. [14]
- Dental follicle progenitor cells. [15]
- Stem cells from human natal dental pulp- (hNDP). [16]

SCAFFOLD

It should provide a framework for cell growth, differentiation and organization at a local site. In addition it should be porous to allow for placement of cells and also be biocompatible and biodegradable with host tissue. [17, 18]. It should be effective for transport of nutrients and waste. [19]

Materials for scaffold can be natural (collagen, dentin, fibrin, silk, alginate) or synthetic (various polymers like PLA, PGA, etc.). Synthetic polymers are degraded by simple hydrolysis and natural polymers are degraded enzymatically. Collagen is the most widely studied natural scaffold. Polymer hydrogel is a soft three-dimensional scaffold matrix, which can receive an engineered pulp tissue [20]. It can be injected at the site (injectable scaffold delivery). Hydrogels have high water content, soft and rubbery consistency and low interfacial tension with water or biological fluids. Hydrogels can be either photo-polymerizable [21] or self-hardening e.g., silanized hydroxypropyl-methylcellulose, they form rigid structures once they are implanted into the tissue sites. Another injectable scaffold is β -tricalcium phosphate which is alginate in gel phase and forms beads in solid phase. Treated dentin matrix also provides suitable environment for regeneration of dental tissue [22]. Enamel matrix derivatives (Emdogain), whose major component is amelogenins, have also been used as potential scaffolds.

GROWTH FACTORS

These are proteins that bind to receptors on the cell and induce cellular proliferation and/or differentiation. Growth factors stimulate cellular division in numerous cell types, while others are more cells specific. Many events in pulp dentin regeneration are signaled by growth factors. Growth factors that play a vital role are; transforming growth factor (TGF) and bone morphogenetic protein (BMP). TGF- β 1 and β 3 are important in cellular signaling for odontoblast differentiation and stimulation of dentin matrix secretion.

In a dentin matrix, odontoblasts secrete growth factors which will be protected in an active form through the interaction with other components (23). By addition of purified dentin protein fractions, it stimulates the tertiary dentin matrix secretion through the action of TGF- β 1. These growth factors are also involved in injury signaling and tooth-healing reaction. Unlike calcium hydroxide,

BMPs induce higher quantity and more homogeneous reparatory dentin. BMP-2, BMP-4 and BMP-7 have been shown to direct the stem cell differentiation into odontoblasts that result in dentin formation making the BMP family the most likely candidate as growth factors.

REVASCULARIZATION

It is the regeneration of cells from tissue within. The body tissue is composed of two components: cells and the surrounding environment. The first attempt was made in 1971 in a young permanent infected tooth with open apex [24] but it was not successful due to limitations in technology, material and instruments available in those times. Presently several case reports documented the revascularization of necrotic root canal systems by disinfection which is followed by establishing bleeding into the canal system via over instrumentation. In this method the root canal space has been disinfected and that the formation of blood clot yields a matrix (e.g., fibrin) that traps the cells capable of initiating new tissue formation. It is different from apexification not only by the closure of root and also results in increased root dentin thickness. The revascularization studies have established following prerequisites:

- Most commonly Revascularization occurs in teeth with open apices and necrotic pulp.
- Open apex.
- Disinfection by triple antibiotic paste consisting of ciprofloxacin, metronidazole and minocycline [25], Calcium hydroxide, [27]
- Effective coronal seal.
- Matrix into which new tissue can grow.
- Young patients.
- Use of anesthetic without a vasoconstrictor when trying to induce bleeding [28]
- No instrumentation of the canals.
- Use of sodium hypochlorite as an irrigant.

The growth of tissue occurs through the formation of a blood clot which serves as a natural protein scaffold. Continued thickening of the dentinal walls and subsequent apical closure was commonly observed in several case reports. The root length is increased by the growth of cementum with the ingress of connective tissue similar to periodontal ligament in the canal space was found [29]. The success of revascularization therapy mainly depends on the immature tooth which has an open apex, short root and intact but necrotic pulp tissue hence, the new tissues are easily accessible to the root canal system with a relatively short distance for proliferation to reach the coronal pulp horn. Minimum instrumentation helps to preserve viable pulp tissue which contributes to further development of open apex root and also the young patients have higher healing potential and more stem cell regenerative capacity.

Considerations for Regeneration Procedures

Current considerations for REPs
<p>Case selection:</p> <ul style="list-style-type: none"> • Tooth with necrotic pulp and an immature apex • Pulp space not needed for post/core, final restoration • Compliant patient <p>Informed consent:</p> <ul style="list-style-type: none"> • Two (or more) appointments • Use of antimicrobial(s) • Possible adverse effects: staining of crown/root, lack of response to treatment, pain/infection • Alternatives: MTA apexification, no treatment, extraction (when deemed nonsalvageable) • Permission to enter information into AAE database (optional) <p>First appointment:</p> <ul style="list-style-type: none"> • Local anesthesia, rubber dam isolation, access • Copious, gentle irrigation with 20 mL NaOCl using an irrigation system that minimizes the possibility of extrusion of irrigants into the periapical space (eg, needle with closed end and side vents, or EndoVac). To minimize potential precipitate in the canal, use sterile water or saline between NaOCl; lower concentrations of NaOCl are advised, to minimize cytotoxicity to stem cells in the apical tissues. • Dry canals • Place antibiotic paste or calcium hydroxide. If the triple antibiotic paste is used: (1) consider sealing pulp chamber with a dentin bonding agent to minimize risk of staining, and (2) mix 1:1:1 ciprofloxacin/metronidazole/minocycline (or, if esthetics are crucial, then consider a 1:1 mixture of ciprofloxacin/metronidazole). • Deliver into canal system via lentulo spiral, MAP system, or Centrix syringe • If triple antibiotic paste is used, ensure that it remains below the CEJ (to minimize crown staining) • Seal with 3 to 4 mm of Cavit, followed by immediate restorative material, glass ionomer cement, or another temporary material • Dismiss patient for 3 to 4 weeks <p>Second appointment:</p> <ul style="list-style-type: none"> • Assess response to initial treatment. If there are signs/symptoms of persistent infection, consider additional treatment time with antimicrobial, or alternative antimicrobial. • Anesthesia with 3% mepivacaine without vasoconstrictor, rubber dam, isolation • Copious, gentle irrigation with 20 mL of ethylenediamine tetraacetic acid, followed by normal saline, using a similar closed-end needle • Dry with paper points • Create bleeding into canal system by overinstrumenting (endo file, endo explorer) • Stop bleeding 3 mm from CEJ • Place CollaPlug/CollaCote at the orifice, if necessary • Place 3 to 4 mm of white MTA and reinforced glass ionomer and place permanent restoration <p>Follow-up:</p> <p>Clinical and radiographic examination:</p> <ul style="list-style-type: none"> • No pain or soft tissue swelling (often observed between first and second appointments) • Resolution of apical radiolucency (often observed 6–12 months after treatment) • Increased width of root walls (this is generally observed before apparent increase in root length and often occurs 12–24 months after treatment) • Increased root length <p>Data from Available at: www.aae.org/Dental_Professionals/Considerations_for_Regenerative_Procedures.aspx.</p>

What Tissue is in the Canal?

Histology after REPs in dogs shows that the radiographic changes in the root may be from the deposition of cementum-like and bone-like tissues (30), suggesting in growth of periodontal ligament tissue versus the pulp tissue. It can be:

1. in growth of cementum and periodontal ligament (PDL)
2. in growth of cementum, PDL, and bone
3. in growth of bone and bone marrow

CONCLUSION

Revitalization therapy for immature permanent necrotic teeth with or without infected pulp has shown increased thickening of the canal walls and/or continued root development, it has become an alternative treatment choice alongside apexification therapy. Clinically, it was said that the pulp tissue was regenerated in the canal to promote maturation of the revitalized tooth. However, animal and human studies revealed that the tissues formed were cementum, or bone-like tissue and fibrous connective tissue similar to periodontal ligament. Future regenerative therapy in endodontics may involve the cleaning and shaping of root canals followed by the implantation of vital dental pulp tissue complex produced in the laboratory.

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