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REGENERATIVE ENDODONTICS – A REVIEW

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INTRODUCTION

Immature permanent teeth with necrotic pulp/apical periodontitis are traditionally treated with apexification procedure using either calcium hydroxide to induce apical hard tissuebarrier formation or apical MTA plug before root canal filling (Frank 1966, Heithersay 1975, Rafter 2005). Apexification procedure with calcium hydroxide usually takes multiple treatmentvisits over an extended period of time (Rafter 2005). The immature permanent teeth when exposed to prolonged calcium hydroxide dressing, show increased risk of root fracture (Andreasen et al. 2002). An apical MTA plug shortens the treatment time (Rafter 2005). The treatment outcome of calcium hydroxide apexification and apical MTA plug appears to be similar (Rafter 2005, Chala et al. 2011). However, an apexification procedure does not have potential to restore the vitality of damaged tissue in the canal space and promote rootmaturation of immature permanent teeth with necrotic pulp. A new treatment option termed 'revascularization' was introduced in endodontics in the year 2001 to manage an immature permanent tooth with apical periodontitis and sinus tract (Iwaya et al. 2001).

The term 'revascularization' was first used in the year 2001 by Iwaya et al. Later, revitalization instead of revascularization was proposed as a more applicable term as hard and soft tissues were also regenerated in the canal space along with blood vessels (Huang & Lin 2008a). Based on tissue engineering concept, the term 'regenerative endodontics' was adopted by the American Association of Endodontists in 2007 (Murray et al. 2007). Regenerative endodontics comprises of tissue engineering, stem cells, biomimetic scaffold, and bioactive growth factors in the canal space to regenerate the pulp tissue damaged by infection, trauma or

developmental anomalies (Nakashima 2005). In the endodontic literature, revascularization, revitalization, and regenerative endodontics have been used synonymously and interchangeably.

Regenerative endodontics has been defined as "biologically based procedures designed to replace damaged tooth structures, including dentine and root structures, as well as cells of the pulp-dentine complex" (Murray et al. 2007). Based on this definition, regenerative endodontic therapy (RET) is aimed to regenerate the pulp-dentine complex damaged by infection, trauma or developmental anomaly of immature permanent teeth with necrotic pulp.

Tissue engineering is the field of functional restoration of tissue structure and physiology of impaired or damaged tissues because of cancer, diseases and trauma.[1] Revascularization refers to the re-establishment of vascularity in the pulp space post-injury to the original vascularity of the pulp of a traumatized immature tooth. Revitalization, on the other hand, describes non-specific vital tissues rather than just blood vessels.[2] For immature teeth with non-vital pulp, such revascularization/ revitalization treatment induces apexogenesis, which thus results in tissue regeneration. The strength of the root and long-term retention of the tooth is increased by restoring root development and reinforcing dentinal walls. Such treatment modality has proven to be an efficient alternative to conventional apexification procedures.[3]

The tooth is a complex organ that is formed by highly organized mineralized tissues encasing the dental pulp. Different mineralized tissues have different regenerative capabilities. Ameloblasts are derived from ectoderm and produce enamel after being stimulated by the odontoblasts. These cells do not have regenerative capacity and undergo apoptosis after the formation of enamel matrix.[4] Odontoblasts and cementoblasts are derived from ectomesenchyme and lead to the formation of dentin and cementum respectively. These cells have limited regenerative capacity. In mild injuries, progenitor cells derived from pulp produce tertiary dentin at the pulp-dentin interface.[5] Tertiary dentin helps in maintaining the pulp vitality by separating the damaged tooth structure from pulp. Similar to dentin, cellular cementum is also laid down throughout life at the root apex to compensate for passive eruption of the tooth.[6]

The components of tissue engineering include stem cells, scaffolds and growth factors.[7] Although these three components are important, they cannot yield successful results without

the fourth major component - a conducive environment.[8]

STEM CELLS

Stem cell biology is one of the fundamental components of regenerative medicine. Stem cells help in tracking back the origin of any tissue. Stem cells exhibit two properties- self renewal and plasticity. These cells can be classified based on their origin as be embryonic stem cells (ES) or postnatal stem cells and based on their plasticity as pluripotent (capacity of maturing into cells belonging to any of the three germ layers) or multipotent (capacity to differentiate only into cells of the tissues from which they are derived).[9] Further, these cells could either be autogenous, allogeneic or xenogeneic. A stem cell niche, identified in several connective tissues, is the microenvironment in which the stem cells reside and represents as little as 1% of total population. Mesenchymal stem cells constitute the majority of the stem cells of orofacial region.

Stem cell population applied in REP include

Dental pulp stem cells (DPSC)

Dental pulp stem cells are isolated from human dental pulp and are capable of regenerating the mineralized tubules and fibrous tissues with blood vessels; very similar to the pulp-dentin complex of a normal human tooth.[10]

Stem cells from apical papilla (SCAP)

Stem cells from apical papilla are released in the root canal space from the apical papilla, when it is lacerated during the evoked-bleeding step of REP. They have greater capacity for dentin and tissue regeneration than DPSCs and high proliferative potential, reflected by higher telomerase activity.[11] These cells have high survival rate despite challenging conditions such as periapical infections.

SCAFFOLDS

Ideal properties of a scaffold include

- Scaffold porosity to facilitate diffusion,
- Biocompatibility and biodegradability,
- Effective transportation of oxygen and nutrients,
- Ability to support cell growth and differentiation,
- Nontoxicity and adequate physical and mechanical strength. (12)

Scaffolds can either be natural or synthetic.

Natural scaffolds

Natural scaffolds can be autologous or derived from natural substances. PRP and PRF and blood clot are autologous scaffolds. Collagen and glycosaminoglycan are derived from natural substances and provide excellent tensile strength to the tissues.

Synthetic scaffolds

Commercially available scaffolds are polymers such as polyglycolic acid (PGA), polylactic acid (PLA), polylactic co-glycolic acid (PLGA), polycaprolactone (PCL). They allow precise control of physiochemical features like degradation rate, microstructure, strength, porosity and undergo degeneration by hydrolysis. The major disadvantage associated with synthetic scaffolds is inflammation at the site of implantation.[13]

PROCEDURE

Informed Consent

- 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)

First Appointment

- Local anesthesia, dental dam isolation and access.
- Copious, gentle irrigation with 20ml NaOCl using an irrigation system that minimizes the possibility of extrusion of irrigants into the periapical space (e.g., needle with closed end and side-vents, or EndoVac™). Lower concentrations of NaOCl are advised [1.5% NaOCl (20mL/canal, 5 min) and then irrigated with saline or EDTA (20 mL/canal, 5 min), with irrigating needle positioned about 1 mm from root end, to minimize cytotoxicity to stem cells in the apical tissues.
- Dry canals with paper points.
- Place calcium hydroxide or low concentration of triple antibiotic paste. If the triple antibioticpaste 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 to a final concentration of 0.1-1.0 mg/ml. Triple antibiotic paste has been associated with tooth discoloration. Double antibiotic paste without minocycline paste or substitution of minocycline for other antibiotic (e.g., clindamycin; amoxicillin; cefaclor) is another possible alternative as root canal disinfectant.

- Deliver into canal system via syringe
- If triple antibiotic is used, ensure that it remains below CEJ (minimize crown staining).
- Seal with 3-4mm of a temporary restorative material such as Cavit™, IRM™, glassionomeror another temporary material.

Second Appointment (1-4 weeks after 1st visit)

- 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, dental dam isolation.
- Copious, gentle irrigation with 20ml of 17% EDTA.
- Dry with paper points.
- Create bleeding into canal system by over-instrumenting (endo file, endo explorer) (induce by rotating a pre-curved K-file at 2 mm past the apical foramen with the goal of having the entire canal filled with blood to the level of the cemento–enamel junction). An alternative to creating of a blood clot is the use of platelet-rich plasma (PRP), platelet rich fibrin (PRF) or autologous fibrin matrix (AFM).
- Stop bleeding at a level that allows for 3-4 mm of restorative material.
- Place a resorbable matrix such as CollaPlug™, Collacote™, CollaTape™ over the blood clot if necessary and white MTA as capping material.
- A 3–4 mm layer of glass ionomer (e.g. Fuji IX™, GC America, Alsip, IL) is flowed gently over the capping material and light-cured for 40 s. MTA has been associated with discoloration. Alternatives to MTA (such as bioceramics or tricalcium silicate cements [e.g., Biodentine®, Septodont, Lancasted, PA, USA]) should be considered in teeth where there is an esthetic concern.

o Anterior and Premolar teeth - Consider use of Collatape/Collaplug and restoring with 3mm of a nonstaining restorative material followed by bonding a filled composite to the

beveled enamel margin.

- Molar teeth or teeth with PFM crown - Consider use of Collatape/Collaplug and restoring with 3mm of MTA, followed by RMGI, composite or alloy.

Follow-up

- Clinical and Radiographic exam
- No pain, soft tissue swelling or sinus tract (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.
- Positive Pulp vitality test response
- The degree of success of Regenerative Endodontic Procedures is largely measured by theextent to which it is possible to attain primary, secondary, and tertiary goals:
- Primary goal: The elimination of symptoms and the evidence of bony healing.
- Secondary goal: Increased root wall thickness and/or increased root length (desirable, but perhaps not essential)
- Tertiary goal: Positive response to vitality testing (which if achieved, could indicate a more organized vital pulp tissue)

The size of the apical foramen has been of significance when attempting regeneration in a permanent tooth with closed apex. Cells such as fibroblasts, osteoblasts, cementoblasts and endothelial cells migrate through the apical foramen into the canal to produce PDL, bone, cementum, blood vessels in the canal space. It is believed that these cells can easily migrate through an apical foramen of diameter lesser than 0.5 mm.[14] However, a study by Fang et al. showed that the highest success rate of REP is attained in apical diameters of 0.5-1 mm.[15] Further studies have to be done in this area to determine if the size of the apical foramen actually influences the outcome of REP in teeth with closed apex.

OUTCOME

Research demonstrates that regenerative endodontics is a viable treatment option which has been described as a ‘paradigm shift’ that allows for continued root development, a return of vitality and health in formerly necrotic immature teeth.[16]

Resolution of symptoms

When REPs and apexification procedures (MTA and Calcium hydroxide) were compared, REP and MTA plug apexification procedures were equally effective in resolving signs and symptoms of disease and survival over 18 months in 100% and 95% of all patients, respectively, whereas apexification procedures using calcium hydroxide were significantly less effective (77%).[3] However, a study by Alobiad et al. concluded that REPs promoted healing in 79% of patients treated, whereas apexification procedures promoted healing in 100% of the patients.[17]

Survival of tooth

From a patient's perspective, an ideal treatment should result in increased functional life of the tooth. This is especially important when survival of an immature permanent tooth is considered, since early loss of a permanent tooth will not only cause malocclusion, but also impair craniofacial development. As mentioned earlier, REP has shown greater survival rate than MTA.[3]

Esthetics

An important patient-centered outcome is preservation or restoration of esthetics. TAP or MTA when used as an intracanal medicament can cause coronal staining. This staining is believed to be caused by minocycline, a constituent of TAP.[18-20] However, use of a dentinal adhesive to block dentinal tubules or substituting minocycline with cefuroxime or Arestin can prevent the coronal staining.[21]

Clinician-based Outcomes

Clinicians base the success of treatment based on clinical and radiographic exam such as no pain, soft tissue swelling or sinus tract (between first and second appointments), resolution of apical radiolucency (6-12 months after treatment) and positive response to pulp sensitivity tests.

Radiographic signs

One of the primary clinician-centered outcomes is radiographic signs of resolution of apical lesion and continued root development. Increased width of root walls is generally observed before apparent increase in root length and often occurs 12-24 months after treatment. Several studies have concluded that although REPs predictably promote healing of apical periodontitis in more than 90% of the cases, radiographic root development is far less

predictable.[11]

Histology

Studies conducted by Torabinejad et al. and Nosrat et al. on human immature permanent teeth using PRP, showed that the tissues that grow into the root canals after regenerative endodontic procedures resemble periodontium, that is, fibrotic PDL, collagen fibres and cementum-like hard tissues.[22,23] However, no evidence of odontoblasts could be seen histologically. Nosrat et al. compared the histological sections of human immature permanent teeth using a novel hydroxyapatite scaffold and blood clot. All the specimens histologically showed dentin, dentin associated newly formed mineralized tissue, newly formed connective tissues and the PDL. However, none of the specimens showed pulp-like tissues.[24]

Vitality response

Positive response to pulp sensitivity test is considered to be a sign of pulp vitality.[25] Reestablishment of pain perception indicates the presence of vital, vascularized tissues with normal physiological response. Clinicians have noted positive response to cold or electric pulp sensitivity testing in 60% of published cases.[63]

CONCLUSION

Regenerative endodontic procedures have proven to be a successful alternative for the treatment of necrotic teeth with open apex, by permitting continued root development. Several studies have demonstrated root development with high rates of resolution of clinical and radiographic signs and symptoms upon treatment using REP. However, current clinical protocols of REP foster repair rather than regeneration. Moreover, the resemblance of the regenerated tissue to a healthy pulp-dentin complex is debatable. No matter how theoretically correct these clinical attempts are, their outcome will be variable due to multifactorial reasons like practitioner skill and variation, severity of the disease, patient's intrinsic response, and case selection.[27] Although regenerative endodontics has a promising potential to be an effective biological approach to restore the vitality of teeth, additional research and clinical trials are required to develop clinical applications and outline predictable outcomes for the procedure. Upon significant research, over time, regenerative endodontics may open doors to a wide range of possibilities of dental tissue regeneration.

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