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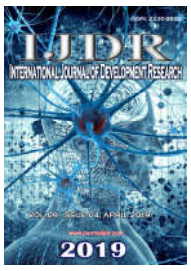

REVIEW ARTICLE OPEN ACCESS

AN OVERVIEW IN REGENERATIVE ENDODONTICS – CURRENT CONCEPT

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ABSTRACT

The management of immature permanent teeth with pulpal disease can be very challenging for the clinician. Regeneration is the process of renewal, restoration, and growththat 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.

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INTRODUCTION

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 (Wei, 2013). 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 (Ikeda, 2009). 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 (Wu, 2013). The rationale of revascularization is that if a sterile tissue matrix is provided in which new cells can grow, pulp vitality can be re-established. A newly created blood clot formed as a result of deliberately induced bleeding into the canal space provides that matrix. Growth factors like platelet derived growth factor, vascular endothelial growth factor and tissue growth factor are present in the clot and can stimulate the differentiation of undifferentiated cell types. The scaffold provides a physico-chemical and biological three-dimensional micro environment for cell growth and differentiation, promoting cell adhesion and migration. Stem cells and progenitor cells from the pulp

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(DPSC) and orperiodontium (SCAP) contribute to continued root development as shown in (Figure 1) (Polezhaev, 1972).

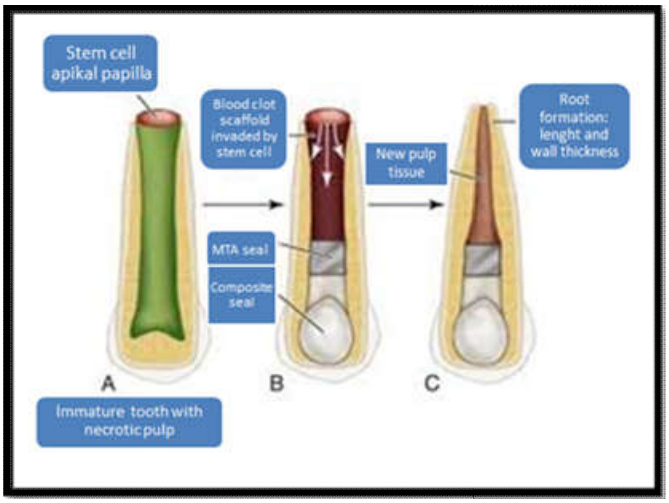

Figure 1. Showing revascularization

REPs capture the ability to use stem cells that residenaturally in and around the tooth to extend the life of the tooth.In particular, periradiculartissues of immature teeth are rich inblood supply and contain stem cells that have the potential fortissue regeneration. These stem cells may be the next breakthroughtechnology which may allow clinicians to grow humanteeth in the foreseeable future. In fact, a Harvard-led team in May 2014 successfully used low-powered lasers to activate stem cellsand stimulate the growth of teeth in rats and human dentaltissue in a laboratory setting. The results were published in thejournal Science Translational Medicine. Titanium dental implantsmay one day be considered "archaic," such as silver cones orretrograde amalgams are now considered out of date by manyclinicians, teachers, and researchers (Ostby, 1961). Regenerative endodontic procedures (REPs) represent aparadigm shift for the treatment of necrotic pulps inimmature permanent teeth, ranging from traditionalbarrier formation utilizing calcium hydroxide or mineral trioxideaggregate (MTA), to a biologically based treatment for rootmaturation.

According to the American Association of Endodontists (AAE) recommendation for the endodontic management of the permanent immature tooth with an open apex, the patient should fulfil the following criteria (Rule, 1966)

- Tooth with necrotic pulp and an immature apex.
- Pulp space not needed for post/core, final restoration.
- Compliant patient/parent.
- Patients not allergic to medicaments and antibiotics necessary to complete procedure

WHEN SHOULD REGENERATIVE ENDODONTICS BE CONSIDERED? (Nygaard-Østby, 1971)

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

WHAT ARE THE KEY COMPONENTS OF REGENERATIVE ENDODONTICS? (Ham, 1972)

- In order for the regenerative endodontic technique to be effective, the following 3 key components are needed as shown in (Figure 2):
- Stem cells
- Scaffolds
- Growth factors

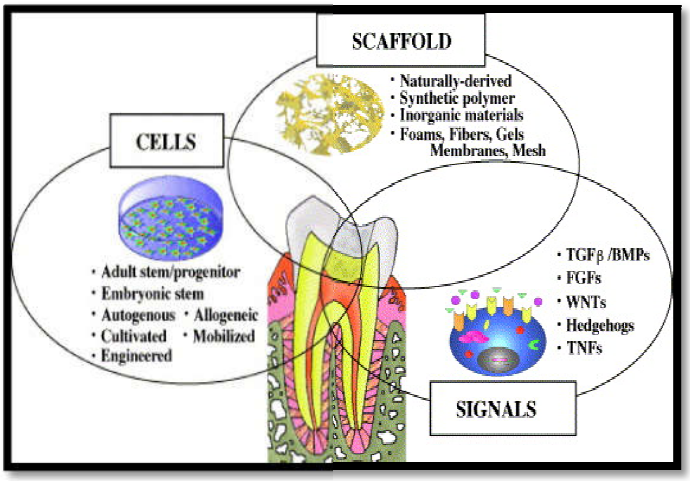

Figure 2. Showing key components of regenerative endodontics

Stem cells are undifferentiated cells that continuously divide.Thereare 2 main types: embryonic and postnatal (adult). Anadult stem cell can divide and create another identical cell, butthe capacity for differentiation into other cell types is limited.

There are several types of adult stem cells that have beenisolated from teeth:

(1) Dental pulp stem cells,
(2) Stem cellsfrom human deciduous teeth,
(3) Periodontal ligament stemcells,
(4) Dental follicle progenitor stem cells, and
(5) Stemcellsfrom apical papilla (scaps).

The most current stem cells usedin REPs are the SCAPs due to their location in Hertwig'sepithelial root sheath.[9] Scaffolds are "ladders" that provide support for cell organization, proliferation, and vascularization. Dentin, blood clots, and platelet-rich plasma,PRF,collaplugshave been used to provide scaffolds in REPs. Scaffolds act as carriers for specific cell types and they guide and support tissue regeneration. Scaffolds that have been commonly used for regenerative procedures are natural scaffolds such as collagen, chitosan, silk, fibrin, and synthetic scaffolds such as polyglycolide, polyglycerolsebacate etc. Blood clot, platelet-rich plasma as well as platelet rich fibrin have been recently tried as scaffolds in regenerative endodontics. Many other materials that include natural nanotoliths nanofibers with the microalga Spirulina bacterial cellulose nanocomposite nanofiber scaffold and various fibrin gels have been investigated as potential scaffolds. However, there are many other types of natural or synthetic materials available. The most common and readily available scaffold isthe blood clot that is formed during the REPs (Banchs, 2004). Growth factors are proteinsthat 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 plateletsfrom the blood and dentin. The major drawback in growth factors is that a different set of growth factors is required to induce stem cells from different sources to achieve specific differentiation. Along with this safety, quantity and time of delivery of the growth factors pose a significant challenge. This problem can be overcome by use of the bio-mimetic ECM embedded scaffold that can be produced in large quantities and are patient specific without complications of immune response and do not require any exogenous growth factor delivery (Murray, 2007). 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 REPs.In addition, a positive response to cold and/or electric pulp tests have occurred in some cases.The rate of root maturogenesis is variable because of unique individual immune systems.

The 3 most important treatment factors in regenerative endodontics are (Ikeda, 2008):

- Disinfection of the root canal canal,
- Establishing bleeding to create a blood clot to carry the stem cells inside the canal, and
- A bacteria-tight seal of the access opening.

Goals of 'regeneration' techniques

- Eliminate symptoms
- Space maintenance
- Bony healing
- Increase in root wall thickness
- Increase in root length
- Positive response to vitality tests

Ada code on dental procedures and nomenclature (cdt codes) for pulpal regeneration procedures (Ravindran, 2014)

- **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).

Disinfection of the Root Canal

Lesion Sterilization and Tissue Repair: Lesion sterilization and tissue repair (LSTR) therapy is a technique that allows disinfection of dentinal, pulpal, and periradicular lesions using a combination of antibacterial drugs. LSTR concept was developed at the Cariology research unit, School of Dentistry, Niigata University, Japan, 2004 (Iwaya, 2001). LSTR 3Mix-MP is considered as the combination of metronidazole, minocycline, and ciprofloxacin (3Mix), and those three antibiotics mixed with macrogol and propylene glycol (MP) were proven to be able to penetrate efficiently through root canal and to disinfect the lesion of caries. Laboratory test showed that LSTR 3 Mix-MP could kill mixed bacteria in root canal more potent than that of Tempohore (Avital, 2002). Since LSTR 3Mix-MP was bactericidal in aerobic bacteria and in obligate anaerobic bacteria that are resistant, LSTR 3Mix-MP could eliminate bacteria from dental tissue infected in primary or permanent molar teeth. This assumption is that by eliminating bacteria, the infection, inflammation, and pain are also eliminated. Due to the polymicrobial nature of infected root canal, single empirical antibiotic is insufficient in disinfection of the root canal. Non specific antibiotic suppress most of the microbial flora and allow residual virulent micro-organisms to repopulate the root canal. Therefore it is essential to use combination of antibiotics to act against all endodontic pathogens and to prevent resistance. Besides the main root canal considering as capillary blood vessel that can be cleaned, there are also many additional root canal in primary molar teeth that cannot be cleaned with mechanic tools. Thus, good material are needed to deliver three-antibiotic mixture (3Mix) and create asepsis condition either in the main or in the additional root canal. Propylene glycol is solvent commonly used in industries, food, and daily goods. The penetration effect of propylene glycol into root dentin was investigated by Cruz et al. Lesion sterilization and tissue repair (LSTR), involves the use of antibacterials combined with a mixture of macrogol and propylene glycol (MP) as the efficient vehicle to carry the antibacterials within the tooth (Avital, 2002).

REGENERATIVE ENDODONTIC TECHNIQUE

First Appointment

- Diagnose case properly (necrotic pulp with open or immature apex)
- Local anesthesia (with or without vasoconstrictor), rubber dam isolation, Access
- Copious, gentle irrigation with 20 mL 3% sodium hypochlorite with side-vented syringe 2 mm short from the apex
- Rinse with 5 mL of sterile saline
- Dry canal with large paper point
- Place triple antibiotic paste inside canal with lentulospirals
- Seal with cotton pellet and 3 to 4 mm of temporary restorative material (such as Cavit Temporary Filling Material
- Dismiss patient for 21 days to allow the TPA to disinfect the canal.

Second Appointment

- Assess response from patient from initial treatment; no signs or symptoms of remaining infection
- If swelling or sinus tract remains, repeat the first appointment procedure
- If patient is asymptomatic, anesthetize with 3% mepivicaine without vasoconstrictor, rubber dam isolation
- Copious, gentle irrigation with 20 mL 17% ethylenediaminetetraacetic acid with side-vented syringe followed by sterile saline
- Dry canal with large paper point
- 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) (Figure 43)

- Stop bleeding 3 mm from cemento-enamel junction with sterile cotton pellet and remove the cotton pellet
- 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)
- Restore with composite or glass ionomer after 1 week.

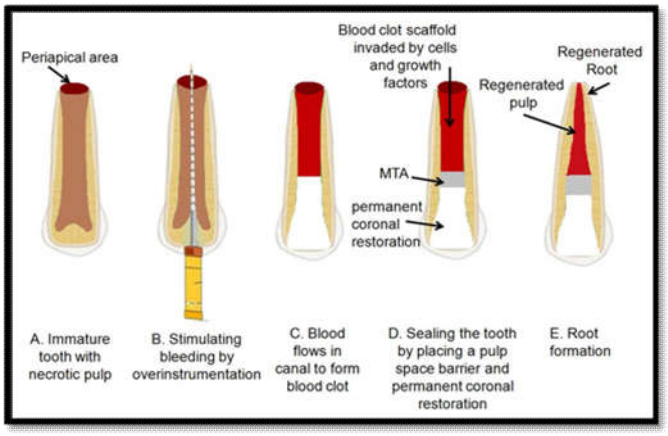

Figure 3. Revascularisation procedure

Conclusion

Regarding root canal temporarymedication, triple antibiotic paste used has good concentration that seems to be the most appropriate in order to avoid any problems associated with calcium di-hydroxide (weakening dentinal walls, inducing tissue necrosis, and decreasing effectiveness by infectious exudates). Indeed, the three antibiotics cover at best action spectra of root canal bacteria and showminimum stemcells cytotoxicity when used in adequate concentration (0.39 g/mL).[15]During the second step of the procedure, the addition of PRF in root canal may be beneficial. PRF provides an additional supply of blood components, such as growth factors and a more solid support (scaffold) allowing growth of the generated tissue.Biodentine would be proposed for root canal capping because it appears to have the necessary assets for this procedure (same mechanical properties as human dentine expand to entirely fill space by its plasticity that would increase crown-root tightness, absence of cervical area coloration, and very low cytotoxicity).For the final hermetic filling, the choice of material does not greatlymatter but it should be as airtight as possible and sustainable.

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