ORIGINAL RESEARCH PAPER

Endodontics

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REGENERATIVE ENDODONTICS – A REVIEW

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ABSTRACT

Regenerative endodontic procedure is a biologically based management for necrotic pulp in developing permanent teeth. The main goals of regenerative endodontics are regeneration of the pulp and dentin complex, increased teeth lifetime and to establish normal function. Regenerative endodontics aims to maintain the tooth's life and sensitivity while preventing necrosis it tries to regenerate the injured 'pulp-like' tissue .This review summarizes the methods created for pulp regeneration and complications based on recent biologic foundation and current clinical guidelines used in regenerative endodontics and discusses future strategies for pulp regeneration.

INTRODUCTION

Regenerative endodontic procedures (REPs) are biologically based treatments for replacing injured tooth tissues like dentin and root structures, as well as pulp and dentin complex cells. Traditional/ conventional methods for apexification and apical barrier techniques use materials like calcium hydroxide and MTA for managing immature teeth with pulp necrosis.[1] Though these methods are advantageous, high risk of reinfection and tooth breakage occurred due to reduced mechanical strength of dentin, immune responses, and somatic sensory functions.[2] To overcome these problems, regenerative endodontic procedures are utilized.

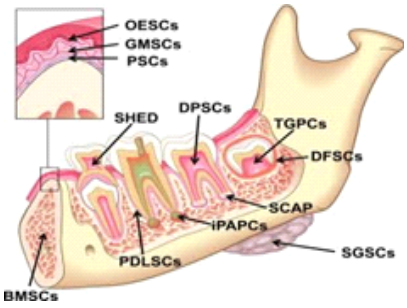
The aim of regenerative endodontics is to replace the damaged pulp and dentin complex, to promote root development and to strengthen the dentinal cells to prevent tooth fracture.[3] Moreover, it promotes apical closure of developing enduring teeth with apical periodontitis and thickening of canal walls. For the management of juvenile patients having necrotic permanent teeth with incomplete root formation, it is thus recommended as an alternative to standard apexification.[4] Patients who are compliant and not allergic to medicaments or antibiotics can be treated with REPs. On the other hand, REPs are not indicated in immediately replanted teeth after avulsion, cases with inadequate tooth isolation, teeth with extensive loss of coronal tissue requiring a post restoration or teeth with endodontic-periodontal lesions. The three main techniques used in regenerative endodontics are stem cell placement, growth factors and scaffold. Among these, stem cell transplantation has successfully regenerated pulp tissue in clinical practice. This article aims to review the effectiveness of various regenerative procedures used in clinical dentistry.

STEM CELLS IN REGENERATIVE ENDODONTICS

The stem cells that have been utilized to develop into odontoblast-like cells are

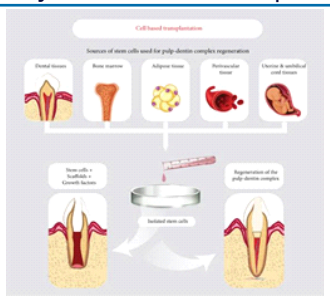
- DentalPulp Stem Cells (DPSCs),
- Stem Cells of the Apical Papilla (SCAPs),
- Periodontal Ligament Stem Cells (PDLSCs),
- Inflammatory Periapical Progenitor Cells (iPAPSCs), and
- Bone Marrow Stem Cells (BMSCs) [2][5]

The Dental Pulp derived Stem Cells (DPSC) are majorly used and are isolated from human pulp. They can regenerate odontoblast with mineralized tubules and fibrous tissue with blood vessels.[6] In a canine model, angiogenic and neurogenic potential of DPSC subpopulation with CD31- and CD105+ cells were found to be suitable for pulp regrowth. DPSC subpopulation Mobilized Dental Pulp Stem Cells (MDPSCs) with highest amount of CD105 can be mobilized by the use of Granulocyte Colony Stimulating Factor (G-CSF). These cells can also be used to regenerate pulp even in mature teeth with small apical foramen. [7] The Stem Cells extirpated from Exfoliated Deciduous teeth (SHED) has a greater capacity for extensive proliferation than DPSCs and Mesenchymal Stem Cells (MSCs) derived from bone marrow.[8] DPSCs are only present in wisdom tooth and do not regenerate after extraction like bone marrow and they typically lose their phenotypic characteristics[9]. Alternative stem cells have to be explored. In recent reports, mesenchymal stem cells with the ability to regenerate in injured pulp and in injured periapical tissue have been found.[10] Stem Cells from Apical Papilla (SCAP) originate in root canal from apical papilla when bleeding is provoked. They have greater potential than DPSCs. They are mainly used in apical periodontitis cases. Periodontal Ligament Stem Cells (PDLSCs) are derived after extraction of impacted teeth and for orthodontic purposes. They extricate into Periodontal ligament (PDL), cementum, alveolar bone. If they are derived from older patients they exhibit compromised regeneration.[7][10]



Non dental stem cells

DPSCs or Stem cells from apical papilla (SCAP) are hopeful cells for pulp regeneration; there aren't many autologous sources, especially in matured teeth. Bonemarrow Mesenchymal Stem Cells (BMSCs) or Adipose Tissue Stem Cells (ADSCs) are tested for their potential to regenerate pulp and dentin in dog they form pulp tissues in dog. [11][12] Notably, MSCs from the Umbilical Cord (UC - MSCs) has just recently been documented with favorable clinical results, such as elimination of infection, recovery of disease, maintenance of radiographic root development, restoration of vascularity and responses to sensitivity testing.[13]



GROWTH FACTORS

Theoretically, tissue regeneration, progenitor cell recruitment, proliferation, and differentiation are all facilitated by growth factors generated from dentin.[14] For instance, the growth factors Transforming Growth Factor (TGF-ß1) and Fibroblast Growth Factor (FGF-2) encourage cell migration and multiplication. A vital part in regulating growth of cells and vasculogenesis is played by Vascular Endothelial Growth Factor (VEGF), whereas Bone Morphogenetic Protein (BMP) and FGF2 facilitate the signaling in development of dentinal tissues. Non Collagenous Protein (NCPs), such as dentin matrix protein and dentin phosphoprotein, may play a role in odontogenesis.[15] [16]

Synthetic growth factors also been utilized to provide a synergic impact in REPs when paired with autologous growth factors. Human Recombinant Platelet-Derived Growth Factor (rPDGF) has been utilized to successfully encourage root formation in an juvenile tooth with necrosed pulp using collagen scaffolds. A clinical experiment has shown the ability of inject able hydro gel scaffolds incorporated with Basic Fibroblast Growth Factor (bFGF) to encourage root development and apical healing in pulp necrosed teeth.[17]

SCAFFOLDS / BIOMATERIALS

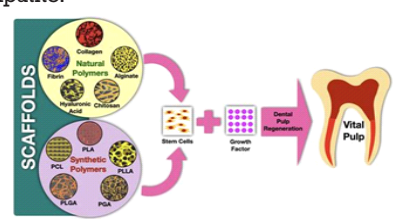
Scaffolds which are porous, biodegradable can be inserted to create a three - dimensional framework. An ideal qualities of scaffolds includes porosity to aid in diffusion, biocompatibility, capacity to support cell growth and differentiation, and adequate physical and mechanical strength. It can function as either natural or synthetic. Stem cells, growth factors, and scaffolds are also mixed.[18]

Host - derived / natural / autologous scaffolds:

In modern regenerative endodontics, Platelet - Rich Plasma (PRP) or intracanal blood clot are often used to create host - derived scaffolds. Their usage has been hindered by the erratic nature of clot formation, difficulties in obtaining PRP. Several naturally - derived scaffolds have been created for distribution of SCAP to the root canal area and tissue regeneration as an alternative.[19]

Exogenous scaffolds / synthetic:

Polymers include Polyglycolic Acid (PGA), Polylactic Co-Glycolic Acid (PCGA) and PolyCaproLactone (PCL) are few examples. The degradation rate, microstructure, strength and porosity enable control of physiochemical characteristics. Osteoconductivity can be increased by using scaffolds that contain inorganic substances like tricalcium phosphate and hydroxyapatite.



Inflammation at implantation site is the main drawback for synthetic scaffolds.[20]

HISTOLOGICAL ASSESSMENT OF REPS

Majority of case studies and clinical research revealed that in growing teeth, REPs lengthened the roots, thickened the root walls, and reduced the opening of the apical foramen. When the teeth treated with Regenerative endodontic procedures (REPs) were histologically examined, it was discovered that the newly generated cells was really ectopic bone, cement, and Periodontal ligament (PDL) rather than dental tissue that seemed to be pulp. Animal research have been supported the aforementioned findings. According to Zhu et al., the development of cementum- and PDL-like tissues is caused by a deficiency in stem cells that are transported to the canal when blood is invoked in the root canal. The stem cells in the blood clot may not differentiate into odontoblast, according to Nosrat et al., as they may be recruited into the root canal from sources other than the apical papilla, such as bone marrow [21] Hence, several tissue engineering methods have been suggested in an effort to rebuild actual pulp cells, as well as the use of scaffolds coated with growth hormones, platelet-rich plasma (PRP), and a combination of dental pulp stem cells. [22] [23].

Results from immunohistochemical staining revealed that the expression of osteogenic markers was considerably greater in the mineralized tissue than it was elsewhere suggesting that REPs may promote repair rather than true regeneration. Regeneration is therefore aided by regenerative endodontic operations, which are described as the restoration of function and tissue continuity but with deformation of the normal architecture.

STEPS IN REGENERATIVE ENDODONTICS:

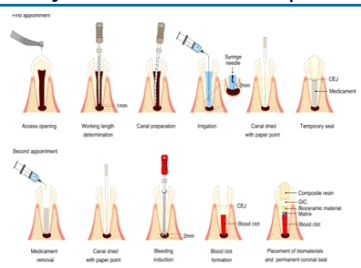
First consultation

- Local anaesthesia is given, dental dam isolation and access opening is performed.
- 20 ml NaOCl is irrigated liberally and gently using a system. To reduce tissue toxicity to stem cells, lower NaOCl concentrations are indicated with 1.5% Naocl.
- Paper points are used to dry the canal.
- CaOH or Triple Antibiotic Paste with a low concentration is placed. Ciprofloxacin, metronidazole, and minocycline are mixed in 1:1:1 ratio to a concentration of 0.1 mg/ml and is kept below CEJ.
- A temporary material with a thickness of 3–4 mm, such as cavit, IRM, or GIC is placed.

Second consultation (after 4 weeks)

- Analyze the treatment's initial response if there are indications or symptoms of an ongoing infection.
- Give 3% Mepivacaine anaesthesia without vasoconstrictor, rubber dam isolation
- Irrigation with 20 ml of 17% EDTA
- Use paper points, dry the canal.
- If the canal system is over-instrumented, it is possible to produce bleeding and have blood fill the canal all the way to the cemento-enamel junction. To do this, a pre-curved K-file is spun 2 mm beyond the apical foramen.
- Bleeding should stop when 3–4 mm of reparative material is possible.
- Use MTA/CaOH as a capping material and, if required, envelope the blood clot with a resorbable matrix, like CollaPlug, Collacote, CollaTape, or another substance.
- Above the capping material, a gentle flow of GIC is applied in a layer of 3 to 4 mm and exposed to light for 40 seconds. MTA has a reputation for causing discoloration.
- Alternatives to MTA, such as Biodentine®, should be considered in teeth where aesthetics are a concern.
- Try using Collatape/Collaplug and then repairing anterior and posterior teeth with 3 mm of Resin modified glass ionomer.

Follow-up There is no pain, soft tissue edema, or sinus congestion analyzing with radio graphically and clinically examination.[24]



CLINICAL OUTCOMES

The success criteria of REPs include elimination of symptoms, bony healing, increased root wall thickness and/or root length (desirable) and positive response to vitality testing. REPs can resolve the symptoms of infection and achieve periapical healing with a likelihood of 91%–94%. [25] [26] A wide range of 2.70-71.43% and 4.70-72.67% increase in root length and wall thickness have been observed. Around 50-60% of previous case studies have reported regain of positive response to pulp sensibility tests. The outcomes of REPs were assessed under three categories: patient centered, outcomes focused on the clinician, and outcomes focused on the histological findings. [27]

Patient-centered outcomes include the elimination of swelling, drainage, and discomfort, as well as the survival of the teeth's functional structure. From a clinician's perspective, the ideal REPs show radiographic signs of healing and root growth following the treatment, as well as favorable outcomes on pulp sensibility tests. Though the ultimate objective is to achieve full regeneration of treated tooth histologically, most teeth treated with REPs showed the newly formed dental tissue to be ectopic bone, cementum, and periodontal ligament instead of dental pulp or pulp-like tissue. Immunohistochemical staining results have shown that REPs may promote repair or partial regeneration of components of the pulp-dentin complex instead of inducing true regeneration. [28]

COMPLICATIONS

The common complications encountered after REPs are pain, tooth discoloration and intracanal calcification. Pain can be avoided by rubber dam isolation, correct working length determination, gentle and copious canal irrigation with NaOCl and EDTA, and placement with intracanal medicament. If the patient has severe pain, then effective dental drainage and root canal disinfection should be performed in time. If the pain is continuous, does not go away or is aggravated, then alternative treatments like apexification or tooth extraction should be considered. Tooth discoloration, another common complication of REPs, occurs due to blood clot formed inside the canal. This could be avoided by placing a resorbable matrix over the blood clot. Use of disinfectant pastes containing minocycline, or barrier materials containing iron, aluminum, magnesium oxides and particularly bismuth oxide can cause tooth discoloration as they can react due to contact with strong oxidizing agents, such as NaOCl or collagen.

Tooth discoloration can be minimized by keeping low concentration Triple Antibiotic Paste (TAP) below CEJ. Minocycline in TAP could be superseded with other antibiotics such as amoxicillin, clindamycin and cefaclor. Bismuth oxide is either removed or replaced with zirconium oxide in new bioceramic materials such as Biodentine®, and EndoSequence® BC RRM-Fast Set Putty to reduce tooth staining. Internal bleaching is a less invasive treatment option for treating tooth discoloration after REPs. In case of an unsuccessful outcome, more invasive interventions like ceramic restorations could be done.

Intracanal calcification, also defined as revascularization associated intracanal calcification (RAIC), is a common issue after REPs found in 62.1% of revascularization cases. The calcifications are categorized into calcific barrier (CB) which is precipitated along mid-root area or canal obliteration (CO) which is the complete obliteration of the canal lumen. Sometimes, bioactive materials like ProRootMTA and Biodentine can activate PDLSCs and BMSCs from alveolar bone leading to mineralization in the root canal space by significantly stimulating TGF- 1 release from the root dentin. Some cases without induced bleeding also presented intracanal calcification, leading to the conclusion that RAIC is likely a compound effect from multiple contributing factors, which remains uncertain. Treatment for RAIC is usually unnecessary unless the tooth is symptomatic. If symptoms are evident and could not be relieved, then RCT with guided access, microendodontic surgery, intentional reimplantation or tooth extraction followed by a proper rehabilitation procedure could be considered. [27] [28]

CONCLUSION

Regenerative Endodontics, a biologically based therapy, is presently regarded as the initial therapeutic choice for developing teeth with pulpal necrosis based upon the favorable outcome of multiple documented occurrences in the case reports. Our perception of clinical procedures has been improved in relation to the prevention of pulp infection, activation of stem cell potential in the canal, and release of growth factors adhere to the dentinal walls. Further research of stem cell based tissue engineering may enable appropriate regeneration and improved treatment results.

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