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Regenerative Endodontics - A Paradigm Shift: A Review Article

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ABSTRACT

Regenerative endodontic treatment is an alternative approach for immature necrotic permanent teeth. This method, is based on disinfection of the root canal system and periapical region without damaging the existing cells. The aim is to assist in the formation of new tissue within the canal after the stem cells are transported to the root canal and to induce further root development. Studies on Stem cells, signalling molecules and scaffold which is triad of regenerative endodontic treatments concept are increasing nowadays thanks to intensive progress of regenerative medicine and tissue engineering. This review outlines the clinical protocols currently used and studies in regenerative endodontic procedures.

Keywords: Regenerative endodontic treatment, stem cells, scaffold, calcium hydroxide, immature teeth and pulp necrosis.

INTRODUCTION

Dentistry has traditionally been at forefront of regenerative medicine, commonly employing novel bioactive material to stimulate bone growth and regeneration Regenerative Endodontics also known as 'Tissue Engineering' is a discipline in dentistry which focuses on restoring native tissue structure and functionality to an afflicted tissue. These cells have the potential to improve physiologic activity and restore native tissue structure.

Regenerative procedures are among various options for treatment of immature teeth with necrotic pulps especially since further development of the root apex and increased thickness of root walls are expected[1]. Induced bleeding and blood clots are integral parts of these procedures as they provide an appropriate scaffold and sufficient stem cells[2]. Platelet-rich plasma (PRP) has also been recommended as a potential scaffold for regenerative endodontic treatments[3]. PRP releases growth factors rapidly within 7 to 14 hours, which then declines[4]. A second-generation platelet concentrate, platelet-rich fibrin (PRF), was developed by Choukroun et al[5]. PRF contains increased amounts of fibrin clot. PRF formation involves incorporation of higher concentration of cytokines into fibrins. Therefore, growth factors meshed in these fibrins are released more slowly between 7

and 14 days[4]. In this case series, a regenerative procedure using PRF was performed on 4 immature single-rooted teeth with pulp necrosis and then evaluated clinically and radiographically for up to 12 months.

HISTORY

The field of regenerative endodontics has dramatically evolved in the past decade. The initial case report of a revascularization in 2001[6] followed by another report in 2004. For the first time, successful clinical outcomes in teeth diagnosed with pulp necrosis were reported without the obturation of the root canal with an inert material (gutta-percha) or a bioceramic material (eg; mineral trioxide aggregate). This represented a departure from the classic philosophy that a root canal had to be sealed once debrided to achieve resolution of apical periodontitis and that reestablishment of physiologic pulp like responses was possible. This truly represented a paradigm shift introducing endodontics to the fields of regenerative [7].

Suddenly, a significant body of basic science research related to dentinogenesis, tooth development, and mesenchymal stem cell biology was adopted by this emerging field and provided a foundation for further advancements and translation into clinical practice. The goal of regenerative endodontics was the use of biologic-based procedures to arrest the disease process, preventing its recurrence while favoring the repair or replacement of damaged structures of the pulp-dentin complex. Although vital pulp therapies, such as direct and indirect pulp capping, and pulpotomy procedures aim to preserve and maintain pulpal health in teeth that have been exposed to trauma, caries, restorative procedures, and anatomic anomalies, non-vital therapies include procedures that aim to reestablish a new vital tissue to replace dental pulp lost to liquefaction necrosis following infection.

Several terms have been coined for these procedures that include “revascularization [6]”, “revitalization [8,9],”and “maturogenesis [10]” among others. The physiological development of roots is usually arrested when immature permanent teeth become infected and subsequently develop pulp necrosis and/or apical periodontitis.

ETIOLOGY

Etiologies for a necrotic pulp range from caries to trauma to congenital anomalies. Trauma has been recognized as the primary etiology of pulpal necrosis permanent teeth[11]. Approximately one-half of teeth are likely to be diagnosed with pulpal necrosis[12]. Moderate to severe trauma to the developing dentition can potentially damage the Hertwig epithelial root sheath(HERS), known to be crucial for formation and maturation of roots by directing the concerted proliferation and differentiation of MSCs[13].Perhaps this may be due to trauma being an etiology with varied severity (eg, intrusions vs luxations) and potential of damaging the HERS. Studies with larger cohorts are needed to evaluate prognostic factors related to continuation of root development following REPs.

The second most common etiology of pulp necrosis in immature teeth is the presence of either dens evaginatus or dens invaginatus (approximately 36% of casestreated with REPs)[14].Dens evaginatus is more common between these two dental anomalies, accounting for the etiology of approximately 33% of cases treated with REP’s. It is seen on clinical and radiographic examination as an additional cusp, typically projecting into the occlusal table of a mandibular premolar (more common) or the facial or lingual surfaces of maxillary anterior teeth (less common). The incidence of dens evaginatus has been reported to affect up to 6% of the population, with greater incidence in certain ethnic groups[15]. Its presence often leads to rapid

pulp necrosis once teeth affected are in functional occlusion, ensuring the enamel-dentinal tubercle and direct exposure of the pulp to the oral environment. Perhaps, early intervention and the absence of trauma to apical structures results in typically observed good clinical outcomes in these cases. Nonetheless, studies comparing outcomes following REPs in teeth with different etiologies are needed to substantiate this observation.

Present Scenario Of Regenerative Endodontics

Various regenerative approaches used in endodontics are root canal revascularization, postnatal stem cell therapy, scaffold implantation, injectable scaffold delivery, pulp implantation, 3D cell printing, and gene therapy[7]. The current ADA protocol codes for regeneration are given as follows:

ADA codes for pulpal regeneration procedures

1. First Phase of Treatment (D3351): Consists of debridement and antibacterial medication.
2. Interim Phase (D3352): Consists of replacement of interim medication.
3. Final Phase (D3354): Completion of regenerative treatment in an immature permanent tooth with a necrotic pulp. It does not include final restoration.

INDICATIONS FOR REGENERATIVE ENDODONTIC THERAPY (RET)

NECROTIC PULPS:

According to the 'Clinical Considerations for a Regenerative Procedure' suggested by AAE, RET is recommended for teeth with a necrotic pulp and an immature apex[16]. Based on Cvek's classification of root development (Cvek's 1992), it is recommend that immature permanent teeth with necrotic pulp at the stage 1 (less than 1/2 of root formation with open apex), stage 2 (1/2 root formation with open apex) and stage 3 (2/3 of root development with open apex) are suitable for RET because of the short root, thin canal walls and wide-open apex as apexification has no potential for root maturation(thickening of the canal walls and/or continued root development). Immature permanent teeth at stage 4(nearly completed root formation with open apex) can be managed with either RET or an apical MTA plug and root canal filling because the canal walls have enough thickness and strength. Immature permanent teeth with a necrotic pulp requiring post for adequate coronal restoration are not suitable for RET and better treated with apical MTA plug and root canal filling.

SIZE OF APICAL DIAMETER:

Apical diameter of immature permanent teeth has been a major concern in RET. In transplantation studies, it was concluded that apical foramen of the tooth was smaller than 1 mm, revascularization was unpredictable[17].In a clinical study, it was demonstrated that regenerative procedures were successful with apical diameter as small as 0.5 mm. However, immature permanent teeth with preoperative apical diameter wider than 1 mm demonstrated greater root maturation[18].In the same study, it was also found that regenerative endodontic procedures were suitable for the patients ranging from age 9 to18 years. Nevertheless, apical diameters of 0.5–1.0 mm attained the highest clinical success rate[19].Bone, cementum, periodontal ligament and even blood vessels cannot grow into the canal space because they are the products of osteoblasts, cementoblasts, periodontal ligament cells and endothelial cells. It is because osteoblasts, cementoblasts, periodontal ligament cells and endothelial cells are able to migrate through the apical foramen from the apical area and produce bone, cementum, periodontal ligament and blood vessels in the canal space. The typical size of human cells ranges from 10 to 100 lm.

Accordingly, osteoblasts, cementoblasts, periodontal ligament cells and endothelial cells can easily enter the canal space through the apical foramen even smaller than0.5 mm in diameter.

ROOT CANAL DISINFECTION

Preservation of stem cells is important in RET. However, If infection is not under control, not only regeneration but also repair will not occur [20].Although infection/inflammation can cause homing of mesenchymal stem cells by SDF-1 (stromal cell-derived factor) or other growth factors to the site of tissue injury[21]and mesenchymal stem cells also have anti-inflammatory and immuno-regulatory properties[22], pro-inflammatory cytokines, such as IL-1a, TNF-a have been shown to be capable of inhibiting stem cell to differentiate into tissue-committed somatic cells for regeneration or repair[23].Therefore, intra-radicular infection should be controlled for possibly pulp tissue regeneration to occur in RET [24].

CAN INTRACANAL ANTIBIOTICS BE SUBSTITUTED FOR ACHIEVING DISINFECTION?

The purpose behind intracanal antibiotic therapy is to eliminate microbes. EndoVac delivers irrigating agents safely to the full extent of the root-canal terminus, thereby removing of organic tissue and microbial contaminants effectively[25]. Also, it is the only method capable of cleaning the isthmus area[26]. Studies have also shown that apical positive pressure irrigation and a triple antibiotic in immature teeth irrigation resulted in similar bacterial reductions as with use of apical negative pressure with sodium hypochlorite [27]and equivalent mineralized tissue formation and the repair process resulted. Additionally, using negative apical pressure and sodium hypochlorite also avoids the risk of drug resistance, tooth discoloration and allergic reactions.

PRF AND REGENERATIVE ENDODONTICS

Regenerative Endodontics uses the concept of tissue engineering to restore the root canals to a healthy state allowing for continuous development of root and surrounding tissue. There are three key elements for tissue engineering: stem cells, growth factors[28] and scaffold. Since PRF forms a high density organised fibrin networks, it has been recognized as a scaffold material for recent regenerative endodontics[29]. PRF has been enriched with growth factors and the presence of leukocytes in the fibrin network helps with the self-regulation of inflammatory and infectious processes in the area of regeneration[30].

Surgical and non-surgical PRF applications

SURGICAL:

- Root resection procedures
- Root-end resection procedures
- Socket preservation procedures

NONSURGICAL

- Regenerative Endodontics
- Soft tissue barrier

SCAFFOLDS

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[8]as well as platelet rich fibrin[31]have been recently tried as scaffolds in regenerative endodontics. Many other materials that include natural nanotolith[32], nanofibers with the micro alga Spirulina bacterial cellulose nanocomposite nanofiber scaffold and various fibrin gels have been investigated as potential scaffolds.

GROWTH FACTORS

Growth factors act as signals to induce cellular proliferation and/or differentiation. Examples of key growth factors in regenerative dentistry include bone morphogenetic protein, transforming growth factor-beta, fibroblastic growth factor, platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF). Growth factors found in dentin are also being investigated for their potential applications. 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[33].Another drawback is application of higher loading levels of growth factors to compensate their physiologic solubility[34]can result in unwanted side effects and limited spatial control. Micro encapsulation[35]or binding of these factors to the scaffold can relieve these problems. Also microparticles containing growth factors can be used control the activity of cells.

HURDLES TO OVERCOME FOR SUCCESSFUL REGENERATIVE ENDODONTICS

In spite of the impressive growth in regenerative endodontic field, there are various hurdles that must be overcome. They are outlined below.

- Isolating, expanding and defining stem cell population for regenerative endodontic applications is a challenging task. The non-dental stem cells should also be explored for dental applications.
- Appropriate vascularized scaffolds are required that are biodegradable and have the same rate of degradation as rate of formation of engineered tissue construct.
- A better understanding and control over growth factors to get the desired quality tissue construct is required.
- Better strategies of disinfection should be employed that does not interrupt the healing and integration of engineered pulp with the root canal walls and also reduce number of clinical sessions.
- Unfavorable outcomes like poor or no root development, deposition of cementum-like hard tissue on root canal walls or formation of bony islands throughout the root canals should be dealt with[36].
- Current treatment approaches tend to stimulate more reparative than regenerative responses in respect of the new tissue generated[37].

CONCLUSION

Regenerative endodontic strategies have tremendous potential to be an effective, safe, and biological mode to save teeth which have compromised structural integrity provided the above discussed problems are dealt with. Considerable research and development efforts are required to advance the regenerative therapeutics to next level. With new discoveries, innovative ideas and high-quality research, in the future, the scope of regenerative endodontics might increase to include the replacement of periapical tissues, gingiva and even whole teeth.

Declaration by Authors

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