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Literature Review

A review of tissue engineering in regenerative endodontic treatment

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ABSTRACT

Background: *Regenerative endodontic treatments are classified based on approach in the procedures and principles. One is cell-free approach that involves a revitalization procedure to achieve continued root growth while the other is cell-based approach which involves pulp/dentin regeneration through isolation and ex vivo expansion of stem cells seeded in the scaffold and then transplanted into the canal space. Technically, the cell-free approach is simpler than cell-based approach because the former does not concern about external stem cell isolation and culture. Currently, the gold standard and the one that has been clinically performed is cell-free approach. Cell-based approach is still not a standard because currently the cell-based approach is still in the clinical trial stage.* ***Purpose:*** *To evaluate the biological basis and clinical protocols recently used in regenerative endodontic treatment and discuss potentially future treatment approaches.* ***Review:*** *The literature review was searched in PUBMED with the keywords: immature permanent teeth, pulp revascularization, stem cells and regenerative endodontics. The regenerative endodontic treatments with various procedures and techniques result in a significant increase in root length and dentinal wall thickness. Stimulation of stem cells in apical root canal system is required to induce tissue formation and continued root maturation.* ***Conclusion:*** *The success of regenerative endodontic therapy relies on the development of a technique that enables clinicians to create functional pulp tissue within cleaned and shaped root canal systems. It is hoped that further research studies are required to define advantages and limitations of cell-free and cell-based approach.*

Keywords: *tissue engineering; regenerative endodontics; stem cells; regeneration; medicine*

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INTRODUCTION

Pulp necrosis of immature teeth due to caries or trauma can lead to an incomplete root formation resulting in thin root canals and wide apical. In this condition, it is difficult to achieve a proper apical closure with an open apex by performing conventional root canal treatment.[1] Furthermore, there is no further root development so the roots remain shorter, thin and fragile with an increased risk of fracture and tooth loss. Apexification treatment using calcium hydroxide, mineral trioxide aggregate (MTA) or bioceramic material as apical plug is one of the treatments of choice for immature teeth and is proven to successfully close the apical foramen but it does not stimulate root growth and does not restore vitality of the pulp. In addition, an alternative treatment namely Regenerative Endodontic Treatment (RET) has been introduced to regenerate tissue, restore pulp vitality, and help complete the root development.[2]

Therefore, it is necessary to develop an improved treatment based on the principle of modern tissue engineering. Tissue engineering can be defined as an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function. The use of tissue engineering to regenerate the pulp-dentin complex overcomes the disadvantages of nonsurgical root canal therapy because it recovers the sensory, immune, and dentinal apposition roles lost in the tooth.[3] Recently, an alternative treatment namely Regenerative Endodontic Treatment (RET) has been introduced in order to replace the damaged pulp tissue with the viable tissue. Regenerative endodontic treatment is especially used to treat immature permanent teeth that have

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lost pulp vitality. Clinically, this biological procedure is designed to create and regenerate tissues to physiologically replace pulp-dentin complex damaged due to caries or trauma by developing biological substitute which restores and preserves optimal function of the damaged tooth structures, including dentin and root structures, as well as cells of pulp-dentin complex.[3,4]

Regenerative endodontic treatment is classified into two types based on the procedures and principles. The two types are cell-free regenerative endodontic therapy (CF-RET) and cell-based regenerative endodontic therapy (CB-RET).[1,5] CF-RET is a procedure that does not use additional stem cells. One of the stages is to create bleeding from periapical area into canal system by over-instrumenting to induce revascularization of the pulp tissue. Revascularization is based on the concept that multipotent stem cells from the apical area by stimulating them to complete the apex closure. It is widely used when the opening diameter of the root canal is large. Moreover, revascularization treatment enhanced root elongation and maturation. On the other hand, CB-RET is a procedure that involves the use of additional stem cells.[6] CB-RET is based on the concept that stem cells have self-regenerating capacity and are multipotent. Stem cells are used to induce pulp regeneration so as to treat immature permanent teeth in a conservative way. The assumption is that regenerative endodontic protocols which result in continued root development mean the teeth and roots are not as inherently weak and prone to fracture as the traditional techniques of calcium hydroxide apexification, MTA or bioceramic barrier placements. Studies which have compared REPs with the traditional approaches of calcium hydroxide apexification and apical barrier techniques have proven significant outcomes.[1]

However, another study that compared the traditional and regenerative protocols showed revascularization was associated with significantly greater increases in root length and thickness compared with calcium hydroxide apexification and barrier placement as well as higher overall survival rates[7]. In fact, pulp revascularization is reported as a promising approach for treating immature permanent teeth. The purpose of this article was to review the biological basis and clinical protocols recently used in regenerative endodontic treatment and discuss potential future treatment approaches in using regenerative endodontic procedures in clinical endodontics.

METHODS

An article search in English was conducted, using the PUBMED database to identify research of regenerative endodontic treatment published from 2013 to 2023. The following keywords were searched: immature permanent teeth, pulp revascularization, stem cells, and regenerative endodontics. The information gathered was obtained from secondary data derived from studies previously published articles.

RESULTS

Regenerative Endodontic Treatment

Regenerative endodontic treatment (RET) presents a viable alternative to traditional endodontic approaches, such as revascularization or revitalization procedures, which are biologically based. The fundamental concept behind RET is to stimulate the natural physiological development of immature permanent teeth with necrotic pulp. This treatment has also proven effective in eliminating clinical symptoms of apical periodontitis and necrotic pulp tissue. However, necrotic immature teeth with open and divergent apexes are not suitable for conventional cleaning and obturation methods due to their thin and weak dentinal root canal walls, making them prone to post-treatment fractures.[8,9]

There are various treatment options available for a necrotic or infected immature permanent tooth. Historically, apexification with calcium hydroxide or MTA has been the standard treatment for immature permanent teeth with apical periodontitis or necrotic pulp, requiring several visits over an extended period.[4] While calcium hydroxide can create a calcified apical barrier, it has significant drawbacks, including reduced root strength due to prolonged exposure and an extended treatment timeline. The long-term use of intra-canal medication can lead to root fractures and defects in the root walls due to its porous nature. Consequently, alternative apexification methods, such as MTA, have been proposed recently, which offer a one or two-step apexification procedure and shorter treatment periods, proving more effective than calcium hydroxide.[10]

However, it should be noted that apexification with MTA does not strengthen the root or promote further root development. Consequently, the roots may remain thin and fragile, necessitating the exploration of other treatment approaches. Since apexification alone cannot maintain pulp vitality or facilitate root maturation (thickening of root canal walls and/or apical closure) in immature permanent teeth, the canal walls may remain thin, and continued root development may not occur, making these teeth susceptible to fractures after root canal treatment.[11] Thus, regenerative endodontic procedures have been recommended for treating immature permanent teeth with necrotic pulp tissue and apical periodontitis. Studies have shown that these procedures result in increased canal wall thickening through hard tissue deposition and encourage continued root development in incompletely formed roots of immature permanent teeth.[12]

Biological features of regenerative endodontic treatment

Regenerative endodontic treatment (RET) is an advanced form of endodontic therapy that is centered around the biological properties of the pulp. RET adheres to the principles of tissue engineering, which involve three key components essential for its success. These components consist of stem cells capable of forming pulp tissue, signaling molecules that stimulate cellular processes like growth and differentiation, and a three-dimensional physical

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scaffold that supports cell growth and differentiation.[13] Stem cells possess the remarkable ability to differentiate, self-renew, proliferate, and transform into various types of tissues, making them crucial for tissue engineering procedures [14].

Stem cells have shown promising improvements when they are used in the systemic conditions, such as diabetes mellitus.[15,16] Bacterial involvement are often connected with failures of endodontic treatments.[17] However, stem cells have many advantages, such as the ability to withstand the presence of bacterial endotoxins.[18] Bacterial endotoxin such as lipopolysaccharides plays a determining role in the process of peri radicular destruction.[19] Stem cells can also survive in conditions where oxygen levels are low or in hypoxic condition.[20-22] Stem cells are found to be compatible with scaffolds, such as gelatin hydrogels and hydroxyapatite and tricalcium phosphate.[23,24] Preconditioning of these stem cells are also possible to increase the positive effects of their use, such as in the presence of calcium hydroxide.[25-27] The selection of ideal source of stem cells significantly influences the effectiveness of regenerative endodontic therapy.[28]

Growth factors, acting as mediators, play a vital role in determining stem cell differentiation. These proteins bind to cell surface receptors, inducing cell proliferation and differentiation. Depending on the specific type of tissue, growth factors are essential for tissue growth, development, repair, and overall tissue regeneration.[13] A proper scaffold material is a framework designed to facilitate stem cell adhesion, support cell proliferation and differentiation, and ultimately promote tissue regeneration. The scaffold provides the necessary environment for cell attachment and growth during the regenerative process. It is created in a three-dimensional polymer form with various shapes.

Ideally, the scaffold should possess porosity, biocompatibility with the host tissues, the appropriate shape and structure to replace lost tissues, and should be biodegradable. The scaffold plays a critical role in supporting proliferation, cell organization, differentiation, vascularization, thereby accelerating tissue development. It also contains nutrients to enhance cell survival and growth. Moreover, the scaffold serves as a catalyst for triggering direct biological responses by mimicking natural structures.[28]

DISCUSSION

Cell-free regenerative endodontic treatment

The American Association of Endodontics (AAE) proposed cell free regenerative endodontic treatment as the preferred and advanced standard procedure for immature permanent teeth with specific characteristics. These include a necrotic pulp, an immature apex, no need for post and core, and final restoration, along with having compliant patients or parents and individuals not allergic to the required medicaments and antibiotics for the procedure.[11] During the first appointment, the tooth is anesthetized and isolated with a rubber dam to create an access opening. Gentle irrigation with 20 mL of sodium hypochlorite (NaOCl) is performed using an irrigation system that minimizes the possibility of extrusion of irrigants into the periapical space. Lower concentrations of NaOCl are advised to minimize any cytotoxicity to stem cells in the apical tissues. Subsequently, the root canal is dried with sterile paper points, and an antimicrobial medicament is applied then placed into the canal space.[7]

A triple antibiotic pastes or calcium hydroxide is used to effectively disinfect the canal space against intracanal microorganisms. After the application of the antimicrobial medicament, the tooth is sealed with a temporary filling, and the patient is asked to return for a check-up after 3 to 4 weeks.[9] At the second appointment, the patient's condition is assessed for any resolution of signs or symptoms of acute infection. If there are no signs or symptoms of infection, the next step of the regenerative endodontic treatment can proceed.[7,29] A local anesthetic without vasoconstrictors is recommended during this appointment to prevent any disruption of intracanal bleeding. The tooth is then irrigated with 20 mL of ethylenediamine tetra acetic acid, followed by normal saline, to carefully remove the antimicrobial medicament. After drying the canal with a paper point, a file is placed a few millimeters beyond the apical foramen to create bleeding into canal system by over-instrumentation using endodontic file or explorer. The bleeding should be induced to reach a level of 3 mm below the cementoenamel junction, and the tooth is left for 15 minutes so that a blood clot formed. The root repair material, which serves as a resorbable matrix, is placed over the blood clot into the canal to a depth of about 3 mm, followed by the placement of the final restoration. By filling the canal with blood from the periapical area, various growth factors such as fibroblast growth factor (FGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF), and platelet-derived growth factor (PDGF) can stimulate endothelial cell precursors to initiate a series of stages of angiogenesis, leading to the formation of new blood vessels in the pulp.[8]

Recent suggestions indicate that cell free regenerative endodontic treatment can serve as a promising alternative to apexification. This treatment offers advantages such as further root development and reinforcement of dentinal walls through the deposition of hard tissue under ideal conditions, ultimately strengthening the root against fractures.[30] As a result, cell free regenerative endodontic treatment leads to an increase in root length, width, and thickness. When compared to apexification, the revascularization procedure proves to be more effective and conservative in managing necrotic immature permanent teeth.[11]

Cell-based regenerative endodontic treatment

By definition, cell-based regenerative endodontic treatment (CB-RET) means transplanting exogenous stem cells into the root canal system of the host to allow regeneration for extensive defects. The transplanted cells have been previously removed from the host (autologous) or from other individuals (allogenic) and may have been either minimally processed (separation from tissues) or grown in cultures to expand their numbers. However, Cell-based regenerative endodontic therapy (CB-RET) is still at the stage of clinical trial.[31] As it is still in the clinical trial stage, there are no standardized guidelines regarding the CB-RET procedure. There are often differences in the stages of the CB-RET procedure from one literature to another. Most recently, the cell-based approach for pulp regeneration was initiated in clinical trial in teeth with irreversible pulpitis or necrosis pulp due to trauma. In the study by Nakashima et al. (2017), CB-RET was carried out by isolating DPSCs from extracted patient tooth samples with age of the patients ranged from 20 to 55 years and the teeth were mature single-rooted with irreversible pulpitis.[32] Autologous granulocyte colony-stimulating factor mobilized DPSCs from discarded teeth were transplanted with granulocyte colony-stimulation factor in an atelocollagen scaffold in experimental pulpectomy to regenerate the pulp–dentine complex. The pulp stem cell transplanted teeth were followed up for 24 weeks.[32]

According to the findings of a clinical trial conducted by Nakashima et al. (2017), cell-based regenerative endodontic treatment (CB-RET) successfully induced the regeneration of the dentin-pulp complex. In comparison, Cordero et al. (2020), revealed that CB-RET differs from CF-RET (cell-free regenerative endodontic treatment) in that CF-RET is limited to immature permanent teeth, while CB-RET can also be performed on adult permanent teeth.[2] One of the challenges arises from the fact that there is a greater abundance of cells, such as stem cells from the apical papilla (SCAP) or dental pulp stem cells, that can proliferate and migrate into the root canal space in immature teeth compared to mature teeth. This higher cell availability contributes to CF-RET having a higher success rate when applied to immature permanent teeth.[33] SCAP are considered a primary cell source for pulp regeneration in immature teeth, residing at the apical papilla around the root apices of immature permanent teeth. While there may be SCAP-like populations around the root apical of mature teeth, their presence has not been reported yet. These stem cells have been shown to be capable of differentiating into odontoblast-like cells and produce dentine-like mineralized tissue. Therefore, this approach has more promise to result in true regeneration.[12]

From the perspective of tissue engineering, pulp regeneration in mature teeth offers the following advantages. Reconstruction of the neurovascular system in root canals by pulp regeneration will provide pulp tissues with an immune system, which will function as the first line of defense against microbial challenge. The gain of nerve function in regenerated pulp tissues will provide an alarm system during the tissue injury and protect the pulp from further damage.[1,8] The restoration of the pulp-dentin complex may be achieved after regenerative endodontic therapy. In addition to pulp regeneration, dentin may be deposited along the root canal walls that had been lost during mechanical instrumentation after regenerative therapy by using tissue-engineering approaches. Otherwise, an endodontically treated tooth loses its blood supply and innervation and hence has no sensitivity or immune system to alert and protect itself.[11] Therefore, the root canal may become reinfected and susceptible to fracture, leading to either loss of tooth or expensive and complex alternative treatments such as root canal retreatment, surgery, and extraction. The indication and scope of regenerative endodontic procedures are limited to immature teeth but should be extended to mature teeth as an alternative to conventional endodontic treatment. Regenerative endodontic therapy in mature teeth will likely encounter more challenges than in immature teeth. Less and low variable number of stem/progenitor cells in mature teeth and narrower apical foramen for stem/progenitor cell migration will be major limitations, together with greater difficulty in disinfecting root canals in mature teeth because of the complex root canal anatomy.[30]

In conclusion, the success of regenerative endodontic therapy relies on the development of a technique that enables clinicians to create functional pulp tissue within cleaned and shaped root canal systems. The source of pulp tissue can be derived from root canal revascularization, achieved by evoking bleeding and migration of adult stem/progenitor cells into the root canal, leading to the formation of vital tissue with the potential to generate hard tissue under specific conditions. Another approach involves stem cell therapy, where autologous or allogenic stem cells are delivered into the root canals. Each of these techniques for pulp tissue regeneration has its advantages and limitations, which can be better defined through further basic science and clinical research.

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