

Regenerative endodontics on necrotic mature permanent teeth – A review

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Abstract: *The goal of endodontics is the preservation of natural dentition. Conventional endodontic treatment are performed to obturate the disinfected root canal system with filling materials such as guttapercha. Although orthograde treatment has a very high success rates, these teeth are devitalized and therefore susceptible to reinfections and fractures.The American Dental Association (ADA) formed several clinical codes for regenerative endodontic procedures in necrotic immature permanent teeth in children and adolescents. It provides a new perception and perspective in many dental specialties, including endodontics. Recently REP also shows promising results in mature teeth. The aim of this review was to explore the potential of REP application in adults, who consists of the great majority of endodontic patients.*

Keywords: *Pulp necrosis, Closed Apex, Mature teeth, Regenerative Endodontic Procedures*

1. INTRODUCTION

The primary goal of endodontics is the preservation of natural dentition without any clinical signs and symptoms and healing or preventing apical periodontitis^[1]. RCT which is principally applied in mature teeth includes proper disinfection of the root canal system, by

chemo-mechanical preparation, intracanal antimicrobial medicaments and obturation with foreign, biocompatible materials. However, endodontically treated teeth are more prone to reinfection and fracture and the failure rate is approximately 25% at 3-5 years^[2]. Besides, endodontically treated teeth will remain non-vital throughout the patient's lifetime and hence they are not defensive to new caries lesions^[3,4]. Preclinical and clinical research strived to regenerate necrotic pulp tissue teeth during the past decades^[5]. The main objective of regenerative endodontics (REP) is designed to physiologically replace damaged tooth structures including dentin, root structures and cells of the pulp-dentin complex. REP uses the concept of tissue engineering to replace the root canal and surrounding tissue. The regeneration of the dental pulp and blood vessels offers the potential of activating the immune system which involves the migration of lymphocytes and macrophages that can eliminate the residual infection^[6]. REP has been studied mainly for treating immature necrotic teeth as a venture to complete the development of the fragile dentinal walls and revitalize the tooth. But, in clinical practice, most cases of pulp necrosis are found in mature teeth. Since regenerative endodontics have shown promising results in immature permanent teeth, the present review was aimed to explore the probability of applying regenerative techniques in mature permanent teeth.

RATIONALE AND ROLE OF REP IN MATURE TOOTH

The irreversible loss of the pulp tissue during RCT has many drawbacks, such as lack of sensation and immune mechanism along with high susceptibility to root fracture^[7]. Crown discoloration is another undesirable effect of RCT. Endodontic treatment is a lengthy procedure, often involving many visits and expensive for both the patient and the dental practitioner. Also, endodontically treated teeth are more prone to future complications like flare-ups and fractures. The removal of the pulp paves a way to subsequent loss of moisture which alters the light-transmitting properties of root-filled teeth leading to the change of translucency of the tooth^[8]. A meta-analysis of showed successful outcomes after endodontic treatment have not significantly improved over the years, in spite of the introduction of new techniques and materials for root canal preparation, medication and obturation. Regenerative endodontic treatment in mature teeth could overcome these disadvantages providing a "biological obturation" of the root canal with newly -formed tissues, thereby re-establishing sensory and immune mechanisms. This could probably lower the incidence of flare-ups and might be more fracture resistant than traditionally approach.

PRINCIPLE OF REVASCULARIZATION

The principles of revascularization include the use or recruitment of stem cells, scaffold and growth factors^[9]. Platelet-rich plasma (PRP) has been suggested as an ideal biomaterial to improve treatment results as it releases many growth factors and acts as a scaffold^[10,11].

STEM CELLS

Stem cells of dental pulp origin have been named as stem cells from human exfoliated deciduous teeth in deciduous teeth (SHED), stem cells from apical papilla (SCAPs) in immature permanent teeth, and DPSCs in adult permanent teeth. In mature teeth, there is no evidence of the existence of apical papilla. DPSCs are collected from dental pulp itself and thus show a natural tendency to differentiate into secondary odontoblasts and form reparative dentin^[12]. DPSCs are removed during endodontic treatment with pulp extirpation, and

SHEDs belong to the deciduous dentition. Stem cells from the periapical tissues that are available for regeneration in mature teeth are periodontal ligament stem cells (PDLSCs)^[13], bone marrow stem cells (BMSCs)^[14], stem cells from inflamed periapical tissues (iPAPCs)^[15]. BMSCs shows dentinogenic, osteogenic, angiogenic, and neurogenic differentiation potential^[16]. PDLSCs have the ability for fibroblastic, osteoblastic, cementoblastic, adipogenic, chondrogenic, neurogenic, and angiogenic differentiation which could be considered a valuable target in future treatments^[17].

SCAFFOLD

Scaffold provides support for cell organization, proliferation, differentiation and vascularization. Its degradation rate coincide rate of tissue formation. A high porosity and an adequate pore size facilitates cell seeding and diffusion throughout the whole structure of both cells and nutrients^[18]. Natural scaffolds include PRP, PRF, Collagen, blood clot etc. Cell homing by intracanal bleeding evoked by the instrumentation of periapical tissues is the most simplistic endodontic approach in clinical practice.

GROWTH FACTORS

Growth factors are proteins that bind to receptors on the cell and facilitates cellular proliferation and/or differentiation. Basic fibroblast growth factors (BFGFs) for chemotaxis and angiogenesis. Vascular endothelial growth factors (VEGFs) for chemotaxis, mitogenesis, and angiogenesis. Platelet-derived growth factors PDGF for angiogenesis. Nerve growth factors (NGF) for survival and growth of nerve fibers. Bone morphogenetic protein-7 (BMP-7) for mineralized tissue formation^[19].

REGENERATION IN NECROTIC MATURE TOOTH

REP, which is being recently used for immature permanent necrotic teeth replacing apexification procedures includes disinfection mainly with copious irrigation and intracanal medicaments, minimum mechanical preparation, dentin conditioning, bleeding-induction, blood clot formation, covering the scaffold with a biocompatible material, and adequate coronal restoration^[20].

The major difference in regenerative endodontic procedures for teeth with mature necrotic pulps is that complete mechanical debridement is essential to help eliminate root canal infection and remove necrotic tissue. In immature teeth, because of the very thin and fragile dentin root walls, mechanical preparation is restricted and disinfection is accomplished with copious irrigation and intracanal medicaments^[20]. In most cases of necrotic mature teeth, the teeth were mechanically prepared and the apical foramen was enlarged from 2 to 6 sizes larger than the master apical file (MAF) due to the fact that mature teeth have less stem/progenitor cells and narrower apical, together with greater difficulty in disinfecting root canals in mature teeth. In another study it has been concluded that the average diameter of human MSCs ranges from 17.9 μm to 30.4 μm ^[21], which is considerable small than the apical diameter which can facilitate their passage inside the root canal. Apical foramen as small as 0.32 mm did not prevent the growth of new tissue^[22]. Even though the apex diameter may play some role in revascularization, the critical apex size has not yet been determined. Apical enlargement should be carefully considered to avoid undermining the physical durability and resistance of the root to fracture. Disinfection of the root canal system plays a crucial role in the success of REP and is much more difficult to achieve in mature than in immature teeth, because mature teeth have more complex root canal system anatomy, with narrow canals, lateral canals, isthmuses, fins, and ramifications, or multiple foramina. Sodium hypochlorite

solution in concentrations ranging from 1% to 5.25% was used as an irrigant in most cases. NaOCl 5.25% was reported to have cytotoxic effects on stem cells from periapical tissues which in turn affected odontoblastic differentiation^[23]. Hence 1.5% NaOCl is suggested for REP in immature teeth which is again reported to be insufficient for root canal disinfection^[24]. As intracanal medicament, calcium hydroxide paste alone or and antibiotic paste alone were used^[25]. DAP (ciprofloxacin and metronidazole) is less acidic than TAP, exhibits lower demineralizing activity on intertubular dentin than TAP, and does not discolor dentin, due to the absence of tetracyclines. Comparison of Ca(OH)₂, 5 mg/ml double antibiotic paste (DAP), and 1 mg/ml DAP did not show significant differences in direct antimicrobial efficacy. Hence lower concentrations of DAP is preferred. Intracanal medication is suggested for at least 1 week after REP for at least one week^[26]. During the second visit, lignocaine without epinephrine is injected and the medicament is removed ultrasonically using passively activated distilled water followed by 5 mL 1% NaOCl for 1 minute. The root canal was then irrigated with 2 mL 5% EDTA for 1 minute. NaOCl detrimentally influences stem cell attachment to dentin, and growth factor release^[27]. The use of EDTA 17%, as a final irrigation solution, can moderate or improve the above-mentioned side-effects of NaOCl. Bleeding alone was induced in the canal by passing sterile K-file beyond the apex^[28] or bleeding-induction along with PRF (platelet-rich fibrin) in one^[29], and only PRP (platelet-rich plasma) in one^[30]. According to Chrepa et al., bleeding-induction inside the root canals of mature teeth with periradicular lesions expressed Multipotent Stem Cell (MSC) markers and demonstrated intense mineralizing differentiation potential with humoral and cellular components of immunity^[31]. Bleeding-induction in mature teeth can play the same role to ensure an influx of stem cells as in immature teeth. After bleeding-induction, MTA was placed over the blood clot. MTA is considered to be the medicament of choice for scaffold coverage in REP, due to its biocompatibility and excellent mechanical and sealing properties.

PROGNOSIS

In all reported cases, REP led to the remission of clinical and radiographic signs and symptoms. These findings indicate that tissue regeneration is possible in mature necrotic teeth with or without apical periodontitis after REP. Also in a study by Paryani et al., there was a positive response to electric pulp test (EPT) when the patient was recalled after 1 year. This “biological obturation” offers vitality to previously necrotic teeth, and the capacity for innate and adaptive immune mechanisms and re-sensation, which can protect teeth from future microbial attacks and act as an alarm for harmful stimuli. REP was also applied in a mature tooth with a mid-root horizontal fracture^[32] which showed progressive healing of the fracture line with deposition of hard tissue at the 19-month follow-up.

FACTORS AFFECTING REP IN NECROTIC MATURE TEETH

The age of the patient, and subsequently, the age of the stem cells, is another parameter that plays a significant role in tissue regeneration. Aging leads firstly to a decrease in the amount of stem/progenitor cells^[33] and secondly to the decrease in their stemness and the loss of their capability to proliferate, differentiate, and support tissue regeneration. Cellular senescence should be considered in case selection of the treatment protocol, RCT or REP, in older patients. According to Chrepa found no correlation between age and MSC marker expression in cells isolated after bleeding-induction inside the root canals of mature teeth.

2. CONCLUSION

The very promising findings indicate that REP can to some extent replace RCT, since elimination of clinical signs and symptoms, as well as apical lesion resolution, can be accomplished by using REP. In future, large-scale clinical studies should be performed with patients of different ages, more complex tooth types and with longer follow-up periods.

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