REVIEW ARTICLE

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Regeneration and Repair: A New Era in Endodontics

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ABSTRACT:

Vital pulp is essential for the tooth viability, which provides nutrition and acts as a biosensor to detect pathogenic stimuli. Management of the young permanent tooth with a necrotic root canal system and an incompletely developed root or root with open apex is very difficult. Recent treatment modalities offer high levels of success for many conditions. An ideal form of therapy might consist of regenerative approaches in which diseased pulp tissues are removed and replaced with healthy pulp tissue to revitalize teeth. Regenerative endodontics deals with replacement of diseased, missing and traumatized pulp. This article reviews the recent approach of pulp revascularization and an overview of its techniques with possible future potential of regenerating pulp as a routine dental procedure in Paediatric dentistry.

Keywords: Regenerating Pulp, Regenerative Endodontics, Revascularization.

INTRODUCTION

The regeneration of oral tissues affected by inherited disorders, trauma, neoplastic and infectious diseases is expected to solve many dental problems.[1] In an year of 2012 American Association of Endodontists defines regenerative endodontics as "biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex".[2] The main objectives of procedures under regenerative endodontics are to replaced and regenerate pulp-like tissue, regenerate damaged coronal dentin and regenerate resorbed root, cervical or apical dentin.

NEED FOR REGENERATIVE ENDODONTICS:

When a tooth loses its pulp also loses perception to pressure, its colour and translucency, and endodontic procedures also makes the tooth fragile. A vital pulp is also very essential to prevent apical periodontitis. Potential to regenerate an injured or necrotic pulp would be advantageous especially in young permanent teeth, since there is a risk that filling materials and sealers may discolour the tooth crown. Techniques for replacement of pulp tissue or revascularization of the pulp has the potential to revitalize teeth.

HISTORY[3]

Nygaard-Ostby[4] in 1961 reported about the regeneration of the pulp like tissue in the literature first time and further re-established in 1971.[5] Procedures of regenerative endodontics described by several authors, pulp tissue was removed from vital teeth and bleeding was induced within the canal with the help of endodontic instruments followed by partial root canal filling, which resulted in a connective tissue formation in the pulp space. Ham et al[6] in 1972 demonstrated induced apical closure of immature pulpless teeth in monkeys. Iwaya et al[7] in 2001 demonstrated the use of antimicrobial agents (metronidazole and ciprofloxacin) without mechanical instrumentation for the continued development of the root in a 13 year old patient with an immature mandibular second molar with a sinus tract associated with it. Francisco Banchs and Martin Trope[8] in 2004 described a technique of revascularization in immature permanent mandibular second premolar with the use of triple antibiotic paste for disinfection of root canal system, intentional

apical irritation with endodontic instrument and the use of good coronal seal.

CONSTITUENT OF REGENERATIVE ENDODONTIC THERAPY

There are three major significant components which play an important role in regenerative endodontics are[3]:

1. Stem cells
2. Growth factors
3. Scaffolds

Stem cells[3]

Stem cells are clonogenic or undifferentiated cells capable to produce cells of the same type or more multi-lineage differentiated cells. Stem cells are classified into pluripotent or multipotent cells depend on the ability of the cells. Enriched population of adult stem cells are found in mesenchymal tissues like bone, dental pulp, periodontal ligament.

Types of stem cells isolated from oral regions[9,10]

- Dental follicle stem cells (DFSCs)
- Stem cells from human exfoliated deciduous teeth (SHED)
- Periodontal ligament stem cells (PDLSCs)
- Dental pulp stem cells (DPSCs)
- Stem cells of apical papilla (SCAP)
- Gingival-derived mesenchymal stem cells (GMSCs)
- Inflammatory periapical progenitor cells (IPAPCs)
- Periosteal-derived stem cells (PSCs)
- Bone marrow stem cells (BMSCs)
- Tooth germ progenitor cells (TGPCs)
- Salivary gland stem cells (SGSCs)
- Oral epithelial stem cells (OESCs)

Stem cells are survived in presences of necrotic, infected and chronically inflamed tissue, which allows these cells get repopulated with differentiated cells in disinfected canals.[11]

Growth factors[3]

Growth factors are polypeptides and act as signals, which have the ability to bind to specific receptors on the target cells. These factors modulate or facilitate certain activities like migration, proliferation, differentiation, and apoptosis.[12,13] The main events and the growth factors which cause them are as follows -

1. **Regeneration and Repair**: PDGF (Platelet Derived Growth Factor)[14-17], TGF (Transforming Growth Factor) ,BMP[18] (Bone morphogenic protein), VEGF[19](Vascular endothelial growth factor), FGF[20](Fibroblast Growth Factor) and IGF (Insulin like growth factor)
2. **Angiogenesis**: FGF[20-22],PDGF, VEGF
3. **Neuronal growth**: NGF[23](Neuronal growth factor)
4. **Differentiation**: TGFβ[24], PDGF[24], FGF2, BMP 2, 4,7,11, IGF, NGF[23]
5. **Proliferation**: FGF2[25], SDF-1, TGFβ1, VEGF, PDGF[26]
6. **Chemotaxis:** SDF-1, TGFβ1, PDGF, FGF2[27]

Scaffold[3]

Scaffold act as carriers or temporary platform for specific cells and they provides a biological three dimensional microenvironment for cell growth, adhesion, migration and differentiation. Collagen, vitronectin, fibronectin, and laminin[28] are the main extracellular matrix proteins (ECMP) which forms the natural scaffold.[29]

Blood clot is the oldest scaffold used in the procedures of regenerative endodontics.[30] The major disadvantages of using blood clot as scaffold is that it does not provide sufficient amount of cell concentration, composition and also observed degradation of erythrocytes.[31] Natural scaffold like Platelet rich plasma (PRP) which was introduced in the oral surgical practice by Whitmann and colleagues in 1997.[32] Platelet rich plasma (PRP) is composed of concentrated platelets and it is derived from the patient's own blood. Blood withdrawn directly from venous puncture and

centrifuged twice to separate plasma from red blood cells. Platelet rich plasma has a gel like consistency and can easily be placed into the pulp space. Other natural scaffolds like bone siloprotein, alginate hydrogel and synthetic scaffolds like polylactic acid (PLA), polyglycolic acid (PGA) and polycaprolactone (PCL) are also used in procedures under regenerative endodontics.

TECHNOLOGIES[2]

- Revascularization of pulp –dentin complex
- Post natal stem cell therapy
- Pulp implantation
- Scaffold implantation
- Injectable scaffold delivery
- Three dimensional cell printing
- Gene therapy

Root canal revascularization via blood clotting[2]

Revascularization of necrotic root canal system disinfection followed by establishing bleeding into the canal system via over instrumentation reported by various author in their case reports. This particular combination of antibiotics effectively disinfects root canal systems and increases revascularization of avulsed and necrotic teeth, suggesting that this is a critical step in revascularization. Although these case reports are largely from teeth with incomplete apical closures, it been noted that reimplantation of avulsed teeth with an apical opening of approximately, 1.1mm demonstrate a greater likelihood of revascularization.[33] It is not clear that the regenerated tissue's phenotype resembles dental pulp; however, case reports published to date do demonstrate continued root formation and restoration of a positive response to thermal pulp testing.

Blood clot as a natural scaffold having the capacity to regenerate a new pulp tissue are exciting, but the caution is required, because the source of regenerated tissue has not been identified. Animal studies and more clinical studies are required to investigate the potential of this technique before it can be recommended for general use in patients.

Post natal stem cell implantation[34]

In this technique, Post natal stem cells derived from various sources of stem cells like skin fat or bone and injecting these cells into the cleaned and disinfected root canal. Though this approach will not generate any immunological reaction, but the main limitation of this technique is that these cells having a low survival rate and these cells migrate to different locations if they are used without any scaffold.

Pulp implantation[35]

A new replacement pulp tissue consists of purified stem cells that is pathogen free, grown in the laboratory via cells taken from a biopsy. This three dimensional structure of replacement pulp tissue implanted into clean and shaped root canal systems. The limitation of this technique is that cell layers are extremely fragile and easily break while being implanted into the root canal systems.

Scaffold implantation[34]

Stem cells are seeded onto a porous natural or artificial scaffold which can facilitate their migration, proliferation and differentiation. These scaffolds provide the support and nutrition to the stem cells and also can be laced with growth factors. Scaffolds are highly porous and are made of polymers.

Injectable scaffolds[34]

In injectable scaffold technique, engineered cells or tissue is administered in a porous three-dimensional scaffold matrix, such as colloidal gel. This hydrogels are injectable scaffolds that can be delivered by syringe directly into the clean and shaped root canal system. This technique is very similar to scaffold implantation.

3 D Cell Printing[34]

In this technique, a three dimensional printer is used to dispense the cells in layers suspended into hydrogel, to recreate the precise shape of the pulp tissue in a particular tooth. The major advantage of this technique is the precise

placement of cells which can mimic the natural tooth pulp tissue structure

Gene therapy[34]

In regenerative endodontics procedures, gene therapy can be used to deliver a therapeutic or mineralizing genes into pulp tissue to promote tissue mineralization with the help of carrier or vector into the patient's target cells. It can be given intravenously or injected directly into a particular tissue within the body. Except for the work of Rutherford, very little research has been done on this technique of regeneration.

FUTURE TRENDS AND RESEARCH

In current scenario, Regenerative endodontic procedures are continuously being improved and updated to benefit paediatric dentistry in every possible way. To evaluate the effectiveness of two regenerative endodontics approaches (REGENDO and REVASC) compared with conventional MTA apexification, American Association of Endodontists Foundation has awarded a grant of $1.7 million in a year of 2014.[36]

The next advance in the field of regenerative dentistry is the easy availability of regenerative dental kits, which will enable the general dentists the ability to deliver regenerative therapies as part of routine dental practice.

CONCLUSION

The clinical success rates of endodontic therapy can exceed 90%. However, many teeth are not given the opportunity to be saved by endodontic treatment and instead are extracted, with subsequent placement of an artificial prosthesis, such as an implant.

Regenerative endodontic methods have the potential for regenerating both pulp and dentin tissues and therefore may offer an alternative method to save teeth that may have compromised structural integrity.

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