

REGENERATIVE ENDODONTICS -TREATMENT OPTIONS AND CHALLENGES TO SUCCESS

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ABSTRACT

When maintenance of tooth in a vital condition is no longer possible, the traditional treatment philosophy advocates endodontic treatment to retain it in a functional state. A paradigm shift of this thinking occurred with revascularization/regenerative procedures. Dental pulp is a specialized tissue organized in an order spatial arrangement and regenerating it is somewhat exigent. With advancements in molecular science and tissue engineering, the approach is becoming being refined with higher success rates. This review article will detail some of the methods of regeneration and the challenges to achieve success in these procedures.

KEYWORDS: Pulp regeneration; revascularization; pulp stem cells; tissue engineering; scaffolds; pulp vitality

INTRODUCTION

Advances in molecular biology and stem cell technology have resulted in the emergence of regeneration as a new treatment modality in medical science. Regenerative medicine is described as a process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function.^[1] A quarter century after its inception, several treatment procedures which earlier focused on replacement with artificial structures have been substituted with regenerative procedures.

The concept of regaining the vitality of dental pulp as a potential treatment option has astounded the endodontic community.^[2] Since then, for teeth identified to have a favorable response to the new treatment, there has been a paradigm shift from routine root canal therapy to vital pulp therapy, initiating an era of pulp revascularization/regeneration. The tissues of interest in regenerative endodontics include dentin, pulp, cementum and periodontal tissues.^[3] The new tissue formed has been described variably as pulp-like, dentine-like or cementum-like and the literature is replete with various methodologies of achieving this outcome. The message from these sources often is ambiguous - does regeneration or revascularization of the pulp actually takes place? This article reviews the literature on the various approaches to achieve pulpal regeneration and the challenges to achieve success in the treatment.

PHILOSOPHY OF REGENERATION

Dental pulp is a unique and self repairing tissue composed of fibroblasts, progenitor cells, vascular cells, nerve cells and immune cells. Like any other injured tissue in the body, pulp also mounts an initial defense response in an attempt to remove the infection and favor wound healing.^[4] A layer of odontoblast cells line the pulp chamber in a spatial order which maintains the dentine formation equilibrium as long as pulp is vital. Any assault to the pulp causes disruption of this balance. In revascularization procedure, a blood clot is intentionally created to form a

scaffold on which regeneration can occur, to a great extent in the identical manner as any natural wound healing in our body.^[5] Normally, this has been adopted in teeth with immature/open apices in which cellular responses are likely to be most favorable and can lead to root growth and apical closure. The 'regenerated' pulp tissue may not closely resemble its physiological counterpart, however. The use of triple antibiotic paste and restorative materials that provide the best coronal seal in these revascularization procedures are based on the contemporary methods to suppress infectious/inflammatory events.^[6] important.

TRILOGY OF REGENERATION

The concept of tissue engineering was introduced by Charles Vacanti and Robert Langer (1993) as an inter-disciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function.^[7] These approaches to repair and regenerate depend on the basic principle of tissue engineering; i.e. the interaction of a scaffold/matrix with cells and signaling molecules, albeit in the guise of natural wound healing events.^[8]

Stem Cells

A stem cell is one that continuously divides and produces progeny cells and can differentiate into various other types of cells or tissues.^[9] They are categorized according to the lineage of development as embryonic stem cells (foetal stem cells) and post-natal (adult) stem cells.^[10] Oral stems cells come under the post natal stem cell category and includes:

- Dental pulp stem cells (DPSCs),
- Stem cells of the apical papilla (SCAP),
- Inflammatory periapical progenitor cells (iPAPCs),
- Periodontal ligament stem cells (PDLSCs),
- Stem cells from human exfoliated deciduous teeth (SHED),
- Dental follicle stem cells (DFSCs)

Scaffolds (Extra Cellular Matrix)

The cells have to be seeded into an artificial structure capable of supporting three dimensional tissue formations. In mid 1980's, Dr Joseph Vacanti and Robert Langer designed scaffolds that were fabricated synthetically in laboratory

with the ability to alter the physical and chemical properties. They are polymers that provide a physicochemical and biological three-dimensional microenvironment for the cells to grow and differentiate, promoting cell adhesion and migration.^[11,12] Scaffolds can be natural (collagen, glycosaminoglycans), synthetic (polycaprolactone, polyglycolic acid, polylactic acid) or mineral (hydroxyapatite, calcium phosphate).

Growth Factors

Growth factors are extracellularly secreted proteins/signals that bind to receptors on the cell and signals morphogenesis /organogenesis during epithelial-mesenchymal interactions. They regulate the specialization of stem cells to the desirable cell type and mediates key cellular events in tissue regeneration including cell proliferation, differentiation, chemotaxis and matrix synthesis.^[13,14] Common growth factors are bone morphogenic protein (BMP), fibroblast growth factor I or II (FGF), insulin like growth factor I or II (IGF), colony stimulating growth factor (CSF), epidermal growth factor (EGF), interleukin IL1-13, transforming growth factor-alpha, beta (TGF α & β), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and nerve growth factor (NGF).

REGENERATIVE APPROACHES IN ENDODONTICS

The various regenerative approaches tried over these years have met with limited success. It appears to be a promising option nevertheless, as the techniques to achieve regeneration continue to improve. While revascularization is well documented and is easy to perform and less expensive, other methods are still in various experimental stages.

Root Canal Revascularization

Revascularization of pulp can be defined as growth of undifferentiated stems cells of periapical region into the empty sterile/disinfected root canal space.^[15] Research on revascularization commenced in the 1950's and 60's. Initially, researchers focused on methods to renovate the ischemic pulp to vital pulp. The concept of guided tissue regeneration (GTR) was introduced by Dr. Nygaard-Ostby (1961). Ostby and Hjortdal were the forerunners in the field of pulp revascularization whose first attempts in necrotic tooth were unsuccessful.^[16] Ostby demonstrated

that periapical healing could be stimulated with the help of a blood clot inside the root canal.^[17] Johnson *et al.*, in the 70's and 80's conducted studies on dogs regarding the ability of pulp tissue to regain blood supply by replanting avulsed teeth and achieved revascularization in some teeth and resorption in others.^[18,19] By early 2000, this procedure is considered as an alternative to apexification. The concept of GTR was later customized by Dr. Trope with a modified clinical protocol (2004), which is still in current practice to accomplish revascularization. The procedure starts with access preparation and disinfection of the root canal system. Irrigants are the primary agents that reduce the microbial load in infected root canal and include sodium hypochlorite (NaOCl) and chlorhexidine. NaOCl in concentrations ranging from 0.5%-6% has been used. Martin *et al* indicated that NaOCl in higher concentration had a detrimental effect on dentin as well as on stem cells in the apical papilla.^[20] Concentration of 1-1.5% had the least effect on stem cells.^[20] Chlorhexidine is recommended considering its wide antimicrobial activity and substantivity. The interaction between the CHX and root dentinal surface provide effective and prolonged disinfection. The concomitant use of sodium hypochlorite and chlorhexidine should be avoided as it leads to formation of parachloroaniline, a known carcinogen. Copious irrigation with saline is hence advised between applications of these irrigants. A final rinse with 0.12% CHX in the first appointment gave better disinfection (Happasalo).^[22] Geisler however recommended not using CHX or using it with caution, considering the cytotoxic effect of CHX on stem cells.^[22] Intracanal medicaments also have a role in the disinfection protocol. Calcium hydroxide was used in the earlier attempts followed by use of antibiotic pastes. Triple /double antibiotic paste is now being used at 0.1mg/ml concentration. The combination consists of ciprofloxacin, metronidazole, and minocycline in 1:1:1 ratio, applied for 21 days. Since minocycline was observed to cause discoloration to the crown, alternatives like cefaclor, amoxicillin, cefroxadin, fosfomycin, and rokitamycin have been mentioned by various authors.^[8] Discoloration can be prevented by sealing the dentinal tubules with dentin bonding agent^[23] before antibiotic placement. In the final

appointment, use of ethylenediaminetetraacetic acid (EDTA) as a final irrigant removed the smear layer, thereby releasing various growth factors from dentin. In the same appointment, delivery of stem cells into the root canal is initiated by inducing bleeding,^[24] and creating a blood clot or placement of platelet rich plasma which acts as scaffold for stem cells.^[25,26] A leakage-free coronal seal is mandatory for the success of the treatment. A biocompatible material like mineral trioxide aggregate (MTA) or biodentine that provides a barrier over the blood clot or PRP is used. The permanent coronal restoration is given to prevent bacterial reinfection,^[27] thereby achieving a triple seal. The revascularization procedure is schematically represented in Fig. 1.

Postnatal stem cell therapy

This method involves placement of postnatal stem cells into the disinfected root canal for regeneration of lost dental tissue. The first postnatal stem cell therapy in medicine was done for the treatment of severe combined immune deficiency.^[28] Postnatal stem cells may be sourced from umbilical cord blood, peripheral blood, bone marrow, body fat, and other body tissues, like the pulp tissue of teeth.^[10] The drawbacks of postnatal stem cell therapy include low survival rates of injected cells, minimal chance of cells to migrate to different parts within the body,^[29] which may lead to aberrant patterns of mineralization and difficulty in isolating the cells.

Pulp Implantation

This concept seeks to renovate the two dimensional cell cultures to a three-dimensional structure by growing the cells in biodegradable membrane filters.^[14] Bohl *et al.*,^[28] reported the formation of tissue with high cell density similar to the natural pulp when pulp cells are cultured *in vitro* on polyglycolic acid (PGA). Buurma *et al.*,^[30] observed extracellular matrix to be expressed in immunocompromised mice when PGA was seeded with pulp cells and implanted into subcutaneous spaces. Angiogenesis occurred through PGA implants after three weeks of implantation. The pulp stem cells must be organized in such a way that it should support cell organization and vascularization. Growing dental pulp cells on collagen matrix was not successful and matrices like vitronectin and laminin require further investigation.^[31] The advantage of this

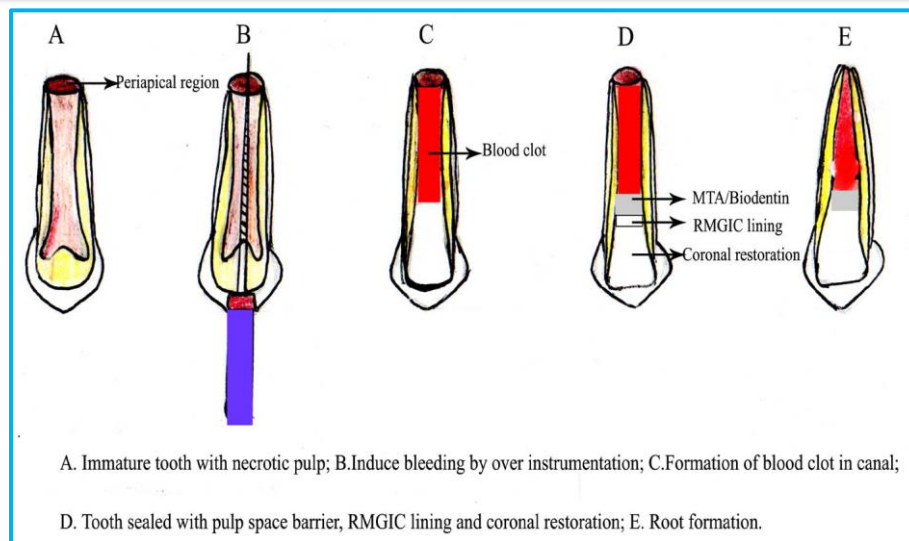


Fig. 1: Revascularisation procedure

philosophy is the ease of growing cells on filters within the laboratory and their existence as collective sheets which are a more stable than unconnected cells and can be easily injected into empty disinfected root canal systems. However, there is a need for specialized procedures to ensure proper adherence of cells to root canal walls and handling fragile filters.

Scaffold Implantation

Pulp stem cells may be ordered into a three dimensional arrangement that can sustain cell organization and vascularization. This can be consummate using a porous polymer scaffold which is seeded with pulp stem cells. A scaffold should contain growth factors that aid proliferation and differentiation of stem cells, leading to enhanced and more rapid tissue development. The scaffolds that are used for this procedure are either synthetic or natural. Synthetic scaffolds include polyester materials like polycaprolactone (PCL), polyglycolic acid (PGA) and polylactic acid (PLA). Natural scaffolds may be collagen, chitosan, fibrin or glycosamino glycans. Dentin chips have been reported to stimulate reparative dentin bridge formation in teeth with exposed pulp.^[32] Dentin chips will be a reservoir of growth factors thereby acting as a matrix for pulp stem cell attachment.^[14] The scaffold may also contain nutrients, promoting cell survival and growth. To achieve the goal of pulp tissue renovation, scaffolds must meet some definite requirements – biocompatibility, biodegradability and high porosity.^[14]

Injectable Scaffold Delivery

Injectable scaffolds such as polymer hydrogels can be delivered by a syringe. These scaffolds provide an excellent substrate and can support cell proliferation and provide nutrition to the cells. The scaffolds are soft and three dimensional in nature and can be easily placed inside the root canal. These are non invasive and easy to handle. The success of these scaffolds is yet to be studied in clinical settings.^[14]

Three dimensional cell printing

A rapid prototype of computer-aided 3D technology in which cells are dispensed layer by layer using an ink-jet like gadget in a 3D hydrogel.^[14,33] This technique facilitates precise positioning of stem cells, thereby creating tissues that mimic the natural tooth pulp. Ideal positioning of cells should be in such a way that placing odontoblastoid cells around the periphery to sustain and repair dentin, with fibroblasts arranged in the core of pulp supporting vascular and nerve cells. The shortcoming of using the 3D cell printing technique is difficulty in symmetrical spatial arrangement of pulp tissue in an asymmetric apico-coronal portion of root canal.

Gene Therapy

Gene therapy is a relatively new field in regenerative endodontics where preliminary attempts focuses on delivering genes that are capable of matrix formation and mineralization into pulp space to promote tissue repair using vectors. Its practicality, potential health hazards and ethical concerns are much demanding, which accounts to the limited exploration of the

technique in endodontics. Once successful, this technique could be a landmark development in the field of regenerative endodontics.^[12]

Bioengineered tooth

The current philosophy in tissue engineering is developing/regenerating a whole new organ. This concept can be made possible by two approaches - seeding the tooth germ cells in a biodegradable tooth shaped scaffold or recreating the tooth germ from detached mesenchymal and epithelial cells.^[34] In the first method, a mixture of cells is introduced into a scaffold of desired shape. The scaffolds used are made of polyglycolate (PGA) and poly-L-lactate-co-glycolate (PLGA) and collagen sponge are preferred. In the other method, multi-cellular assembly and self-reorganization of each mesenchymal and epithelial cell is achieved first. Then, reciprocal interactions between epithelial and mesenchymal cell layers initiate organogenesis that regulates differentiation and morphogenesis.

CHALLENGES IN REGENERATIVE ENDODONTICS

- Disinfection of root canal
- Removal of smear layer
- Developing an ordered functional pulp tissue
- Appropriate coronal seal
- Appropriate method to measure the clinical outcome

Disinfection of root canal

One of the biggest challenges encountered in endodontics is inadequate disinfection of infected root canals. Reduction of microbial level is crucial for the success in both regenerative endodontics as well as routine endodontic procedures. Since instrumentation in regenerative procedure should be minimal, disinfection by chemical means is recommended in the form of irrigants and medicaments. NaOCl is the most widely recommended irrigant (concentration \leq 1.5%) . 17 % EDTA is another chemical agent that is recommended in regeneration procedure as it helps in the dissolution and release of impregnated growth factors in root dentin during dentinogenesis.^[35] These growth factors enhance the stem cell survival and its proliferation. EDTA is also useful in reversing the detrimental effect of high concentration of NaOCl. Regarding intracanal medicaments, triple antibiotic paste is

difficult to remove from the root canal and causes discoloration of the crown portion over a period of time. Calcium hydroxide has deleterious effect like weakening the root dentin,^[21] with a potential for fracture.

Removal of smear layer

Even though there is minimal instrumentation of the root canal in regenerative procedure, there is limited smear layer formation. This prevents stem cells from adhering on to root canal walls, contributing to failure of treatment. A 17% solution of EDTA as final rinse in the root canal will aid in removal of smear layer as well as enhance the attachment of the stem cells by providing a better surface on the root dentin for their survival. Other chemicals used for this purpose are doxycycline, citric acid and MTAD.

Developing an ordered functional pulp tissue

Developing a functional tissue is still a problem in regeneration. Despite best efforts to recreate lost tissue, the type of tissue is still unknown. The development of the normal harmony and spatial arrangement of dentin pulp complex is still in research. The 3D cell printing will be a possible solution in the near future, but the problem with this technology is the difficulty in exact placement and positioning inside root canal. Only by achieving such a balanced spatial oriented cell lineage in the root canal through regeneration can this method be deemed successful.

Appropriate coronal seal

A leakage-free coronal restoration is mandatory in regenerative endodontics as well as in subsequent restorative procedures. The material that provides such seal should be biocompatible, have to maintain cell viability of the regenerated pulp, should minimize microleakage and provide adequate adhesion to the overlaying restorative material.^[36] The materials under consideration are calcium silicate based cements like mineral trioxide aggregate (MTA) and biodentine.

Appropriate method to measuring the clinical outcome

Ethical issues prevent histological analysis of the implanted regenerative cells. Noninvasive tests such as laser doppler blood flowmetry, pulse oximetry and lack of clinical signs or symptoms and radiographic signs like completion of root formation and disappearance of periapical lesions have to be relied upon to verify vitality of the pulp. Pulp sensibility tests like thermal tests and

electric pulp test are not reliable in checking the vitality, since there is no conducting tissue^[14] involved in the coronal part.

FUTURE OPTIONS

Stem cell banking is a potential option in the near future. The organized establishment of stem cell banks for isolating and cryopreserving the pulpal stem cells at the time of birth or from the extracted third molars can be used in regenerative endodontics for functional restoration of teeth. Mobilized dental pulp stem cells (MDPSC) are the most reliable stem cells for this purpose. These cells have high migratory and proliferation ability that provide more stable and homogenous stem cell population with high angiogenic/neurogenic and regenerative potential⁽³⁷⁾.

CONCLUSION

Regeneration of dentin-pulp complex by harnessing stem cells of pulpal origin for endodontic treatment will become routine clinical practice in the foreseeable future. The crucial part of regenerative endodontic therapy is to understand the basic principles and its various components and optimizing and integrating each of them to produce a well oriented spatially arranged pulp-dentin complex. Regenerative endodontic procedures would require an organized and comprehensive research program which focuses on each of these components and their most appropriate application on patients. Better treatment options of high quality for the patient to maintain longevity and function of teeth will then be possible. Each of the regenerative techniques that is discussed above has its own advantages and disadvantages and some of the techniques are hypothetical or in their budding stages. The existing evidence regarding pulp revascularization was reported on young permanent teeth with open apices. However, it is undeniable that for regenerative endodontic procedures to be predictable, integrated multidisciplinary research teams which include skilled professionals in the field of endodontics, cell and molecular biology and material sciences are indispensable.

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