WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Regenerative Endodontics: A Review

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A B S T R A C T

Regenerative endodontics is a cutting-edge method of treating teeth that have been traumatized or infected with the goal of restoring and regenerating the damaged dental pulp and surrounding tissues. The molecular underpinnings and current clinical procedures for regenerative endodontic treatments (REPs) are described in this review along with potential future developments in pulp regeneration techniques. Because REP therapy offers the possibility of more root development, it has been called a "paradigm shift" for treating immature teeth.

In a clinical setting, root canal therapy (REPs) involves cleaning the system without harming the apical papilla's and other tissues' endogenous stem cell potential. By first causing a blood clot and then applying an intracanal barrier to stop microleakage, these stem cells are inserted into the root canal space. The trio of elements comprise the biological concept of REPs: scaffolds, stem cells, and signaling molecules. The "pulp dentine complex" is now being mended instead of fully regenerating, and the pace at which new roots grow in the future fluctuates. Doctors may think that using REPs to treat teeth is the best option for young teeth with pulp necrosis.

Keywords: Regenerative endodontic protocols, immature teeth, pulp necrosis, root maturation, triple antibiotic paste, calcium hydroxide

Introduction

In dental clinics, pulpal and peri radicular pathosis which can be brought on by trauma, caries, or irregularities in the teeth is a common condition that requires treatment. For fully grown permanent teeth with excellent clinical outcomes, root canal treatment (RCT) is the usual approach for managing endodontic problems; for immature permanent teeth with pulp necrosis, the typical treatment strategy is apexification surgery. The goal of endodontic therapy is to protect teeth by removing pulp and periapical inflammation/infection [1]

DEFINATIONS

Tissue engineering is an interdisciplinary field that uses life sciences and engineering ideas to build biological substitutes that maintain, enhance, or restore organ function. (Vacanti and Langar) "Understanding the principles of tissue growth and applying this to produce functional replacement tissue for clinical use" is the definition of tissue engineering. (Oreffo and McArthur) Regenerative endodontic procedures (REPs) are biologically based treatments intended to restore dentin, root structure, and pulp dentin complex cells that have been injured. (Murray) [2]

REGENRATION VS REPAIR

After receiving the proper care, tissue damage brought on by trauma or infection will either regenerate or repair itself. Regeneration is the process of replacing damaged tissue with identical tissue and restoring biological functioning. Replacement of injured tissue with new tissue that differs from the original tissue and loss of biological functions is called repair. The ability of the tooth pulp to regenerate is restricted. [3]

TISSUE ENGINEERING

Combines dental stem cells, scaffold, and signalling molecules to mimic a suitable microenvironment for regenerating pulp-dentin complex. Numerous studies have been established to examine the effects of dental stem cells, scaffold, signalling molecules, and their combinations in pulp regeneration, providing a new insight in the field of regenerative dentistry and opening a great opportunity for further clinical applications.[4]

History

Nygaard-Östby (1961) was the first to examine the promise and potential of regenerative endodontic therapies in necrotic teeth. He investigated the possibility of repair when bleeding was caused by over-instrumentation past the apex before partial root filling of the canal, but his findings were not very successful. Forty years later, in 2001, Iwaya et al. reported a case on an infected necrotic immature premolar tooth that demonstrated thickening of the root canal walls with mineralized tissue and continued root development, utilizing a process called "revascularization." The effectiveness of this approach was also shown in later case reports, mainly in premolar teeth when calcium hydroxide or a triple-antibiotic paste was used. Additional research showed that injured central incisor teeth might be successfully restored. Regenerative endodontic procedures have been referred to as a "paradigm shift" in the treatment of juvenile teeth with necrotic pulps by several writers.[3]

TRIAD OF TISSUE ENGINEERING

3.1 Stem cells:

A stem cell is commonly defined as a cell that can continuously divide and produce progeny cells that differentiate into various other types of cells or tissues. Duailibi et al in 2006 defined stem cells as “Quiescent cell populations present in low numbers in normal tissue, which exhibit the distinct characteristic of asymmetric cell division, resulting in the formation of two distinct daughter cells a new progenitor cell and other daughter cell capable of forming a differentiated tissue.[5]

Characteristics of stem cells:

1. Exist as undifferentiated cells and maintain this phenotype by the environment and/or the adjacent cell populations and they are exposed to and respond to appropriate signals.

2. Ability to self-replicate for prolonged period.

3. Maintain their multiple differentiation potential throughout the life of the organism.[2]

The Source of Stem Cells:

Stem cells can come from a variety of sources, and numerous studies are being conducted to support the use of stem cells for therapeutic purposes.

Embryonic stem cells are derived from embryos and are thought to have the most potential because they can develop into any type of specialized human cell.

Adult stem cells are present in adult tissues such the brain, blood, and bone marrow; however, their potential is restricted in comparison to embryonic stem cells.

Cord blood stem cells: this type of stem cells comes from cord blood and has a lot of promise for treating illnesses.[6]

Classification considering the source:

Allogenic: derived from a donor of the same species; autologous: derived from the same individual

Xenogenic: derived from an individual of a different species

Syngenic: derived from creatures with identical genetic makeup

Classification considering potency:

Totipotent: able to differentiate into every form of extra-embryonic and embryonic cell.

Pluripotent: capable of differentiating into any kind of cell, except for embryonic membrane cells.

Multipotent: capable of differentiating into many mature cells

Unipotent: capable of differentiating into a single cell type.[5]

Stem cell isolation:

1. By employing a flow cytometer and labelling the cells with antibody markers. The term "fluorescent antibody cell sorting (FACS)" refers to this procedure.

The parameters used in physiologically and histology to isolate stem cells include phenotypic, chemotaxis, proliferation, differentiation, and mineralization.

3. The choosing of immunomagnetic beads.

4. Staining using immunohistochemistry.[2]

Isolated and described human dental stem cells are as follows:

BM-MSCs: bone marrow mesenchymal stem cells

DPSCs: human dental pulp stem cells

SHED: human exfoliated deciduous teeth

PDLSCs: periodontal ligament stem cells

SCAP: stem cells from apical papilla

GMDSCs: gingival-mesenchymal derived stem cells. [7]

BM-MSCs: bone marrow mesenchymal stem cells

It has been demonstrated in recent years that BM-MSCs have been extensively employed in regenerative medicine for clinical application goals. These cells may produce various somatic cells and germ cells both in vitro and in vivo, and they are readily available. [9]

SHED: human exfoliated deciduous teeth

Human deciduous incisor pulp has been used to isolate mesenchymal progenitors. These cells were called SHED, and their ability to differentiate into neurons, adipocytes, osteoblasts, and odontoblasts demonstrated their great plasticity. While in vivo SHED cells can stimulate the creation of bone or dentin, DPSCS was unable to generate a dentine pulp complex, in contrast to dental pulp.[5]

SCAP: stem cells from apical papilla

SCAP refers to MSCs that live in the apical papilla of permanent teeth that have immature roots. They were found by Sonoyama and associates. SCAP are likely the cell source of primary odontoblasts to produce root dentin, and they are also capable of generating odontoblast-like cells and creating dentin in vivo. Apexogenesis can happen in infected juvenile permanent teeth with peri radicular periodontitis or an abscess; SCAP facilitates this process.[8]

PDLSCs: periodontal ligament stem cells

Scientists have effectively obtained human periodontal ligament stem cells from the removed teeth. Seo et al. initially identified and described this in 2004. The ability of cultured PDLSC to differentiate into cementoblast like cells, adipocytes, and collagen framing cells in vitro, as well as the capacity to generate a cementum/PDL like structure in vivo, have demonstrated the potential of PDLSCs to develop into other cell lineages and acquire periodontal ligament like characteristics.[5]

DPSCs: human dental pulp stem cells

Dental pulp contains mesenchymal stem cells, or DPSCs. In vitro, DPSCs have osteogenic and chondrogenic potential. Additionally, they can differentiate into dentin and dentin-pulp-like complex in vivo. A pluripotent subpopulation of dental pulp stem cells (DPSC) produced during dental pulp organ culture was recently discovered as immature dental pulp stem cells. [8]

GMDSCs: gingival-mesenchymal derived stem cells

Scientists are searching for a population of stem cells that are responsible for the distinct wound healing that occurs in gingival wounds, without the need for scarring. Gingival mesenchymal stem cells (GMSCs) are a novel class of multipotent MSCs with significant immunoregulatory potential that are found in the gingival tissue and are easily obtained from patients' gingival tissue through gingivectomy techniques or from biological waste tissue at dental clinics.[10]

GROWTH FACTORS

Growth factors are signals that cause cells to proliferate and/or differentiate. Examples of important growth factors in regenerative dentistry are 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 researched for their potential applications. The main disadvantage of growth factors is that a distinct set of growth factors is needed to induce stem cells from different sources to achieve specific differentiation. In addition to this safety concern, the amount and timing of growth factor delivery present a significant challenge that can be addressed by using bio-mimetic ECM embedded scaffold, which can be produced in large quantities and customized for each patient without immune response complications.[11]

The following are some growth factors and how they work:

1. TGF-β. It is kept in an active state within the dentin matrix and is secreted by odontoblasts. It also promotes an increase in the secretion of the tertiary dentin matrix and the proliferation and differentiation of pulp cells.

2. BMP. It controls how pulp cells differentiate into preodontoblasts. Additionally, it functions as a modulator of its activity regarding the onset of odontoblasts' cytological and functional differentiation.

3. PDGF. This growth factor is an angiogenic agent.

4. VEGF causes the pulp that has been cut to undergo an angiogenic reaction. It facilitates the process of revascularization as well. [12]

5. SCAFFOLDS/MATRIX

A three-dimensional microstructural network of biologically active substances is what is referred to as a scaffold. These compounds cooperate to guarantee the safe delivery of bioactive cells, which are crucial for promoting tissue regeneration and repair.

1. To provide a spatially accurate location for the cell, scaffolding is required.

2. Control metabolism, differentiation, or proliferation while encouraging gaseous and nutrition exchange.[2]

Classification of scaffolds

- ***Based on degradability of matrices****:*

Biodegradable scaffolds

Permanent or biostable scaffolds

- ***Based on form:***

Solid blocks

Sheets

Porous sponges

Hydrogels (injectable scaffolds)

- ***Based on presence or absence of cells:***

Cell free scaffolds

Scaffolds seeded with stem cells

- ***Based on origin***

➢ Biological or natural scaffolds:

Platelet rich plasma

Platelet rich fibrin

Collagen

Chitosan

Glycosaminoglycans/hyaluronic acid

Demineralized or native dentin matrix

Blood clot

Silk

➢ Artificial or Synthetic scaffolds

Polymers

PLA

PGA

PLGA

PCL

Bio ceramics

Calcium/phosphate materials

Bioactive glasses

Glass ceramics **[13]**

BLOD CLOT

In regenerative endodontics, the current strategy involves inducing bleeding and creating an intracanal blood clot to offer a scaffold for pulp-dentin regeneration. To bring mesenchymal stem cells and platelet-derived growth factors into the canal area for potential pulp tissue regeneration, a blood clot is used as a scaffold. In an immature tooth with open apices, inducing bleeding facilitates the transfer of SCAP from the tooth's peri radicular tissues into the root canal space via the apical foramen.

COLLAGEN

Extracellular matrices mostly consist of collagen, which gives tissues their high tensile strength. Collagen functions as a scaffold that facilitates the insertion of cells and growth factors and permits the replacement of degraded tissues with natural tissues.

Glycosaminoglycans

One of the glycosaminoglycans found in the extracellular matrix (ECM), hyaluronic acid (HA), has shown to provide enormous promise for tissue engineering. In addition to encouraging osteogenesis, HA can foster the conditions necessary for chondrogenesis.

Demineralized or native dentin matrix

The organic matrix of dentin is known to contain 233 total and 68 common proteins, including a variety of collagenous and non-collagenous proteins. Dentin is dominated by a rich ECM and not cells. [14]

Polymers

Scaffolds for pulp regeneration have been made from a variety of synthetic polymers, including polylactic acid (PLA), polyglycolic acid (PGA), polylactic acid (PLLA), polyepsiloncaprolactone (PCL), and PLGA.

Bioceramics

Materials made of calcium and phosphate, glass ceramics, and bioactive glasses fall within this group of scaffolds. Ceramics based on calcium phosphate (CaP) are the most widely used biomaterials. CaP scaffolds, like -TCP or HA, have been thoroughly studied for bone regeneration because of their similarities to mineralized tissues, resorption, biocompatibility, minimal immunogenicity, osteoconductive, and other attributes. [13]

6. TREATMENT PROCEDURE

The main steps in performing a root end preparation (REP) are as follows:

(a) minimal canal wall instrumentation

(b) disinfection with irrigants

(c) dressing with an intracanal medication

(d) introducing bleeding into the canal space and forming a blood clot; (e) capping with bioceramic materials

(f) an efficient coronal seal.

Clinical protocols may vary.

6.1 IRRIGATION PROTOCOL

The AAE18 and ESE19 guidelines suggest using 1.5%–3% NaOCl after 17% EDTA in the first visit and 17% EDTA in the second appointment for REPs, based on evidence. Notably, chlorhexidine has been demonstrated to be cytotoxic to stem cells and lacks the ability to dissolve tissue, hence it is not advised for use with REPs.

Irrigation techniques like negative pressure irrigation, passive ultrasonic irrigation (PUI), photon-induced photoacoustic streaming (PIPS), or laser can be utilized to increase the effectiveness of disinfection in root canals.

6.2 INTRACANAL MEDICAMENT

It has been shown that the TAP combined with 1:1:1 ciprofloxacin, metronidazole, and minocycline is effective at disinfecting necrotic root canal syste ms.

It should be mentioned that TAP contains a component called minocycline, which can discolor teeth.

Options include using DAP without minocycline or substituting antibiotics such cefaclor and clindamycin for minocycline.

Another intracanal medication used in REPs is Ca (OH)2. Although it seems to have less antibacterial power than TAP, still has a few benefits over TAP, such as no discoloration, less cytotoxicity to stem cells, increased stem cell survival and proliferation on the treated dentin, encouragement of growth factor release from the treated dentin, and simpler removal from root canals.[11]

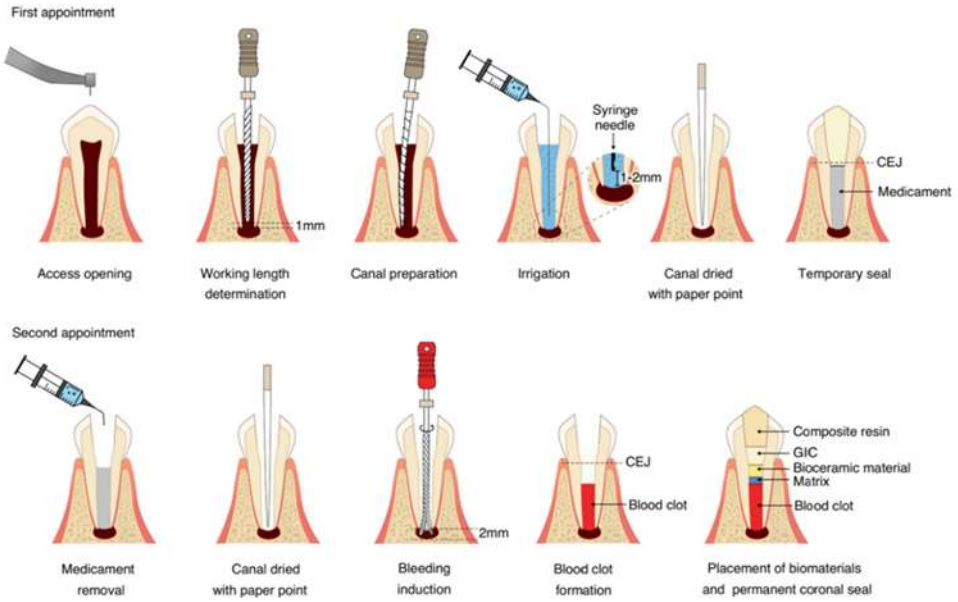

FIGURE1: TREATMENT PROCEDURE OF REP's [1]

7 RECENT ADVANCES IN REGENERATIVE ENDODONTICS

7.1Platelet Rich Plasma (PRP)

In 1988, Marx et al. presented platelet rich plasma (PRP). It is an autologous first-generation platelet concentrate with a high growth factor content that can be used as a scaffold in place of a blood clot. It contains a fibrin matrix that aids in ensnaring growth factors and is simple to produce. Five times as many platelets as the average platelet count (1 million/ml) are present.

The most significant growth factors released by platelets in platelet-derived platelets (PRP) are vascular endothelial growth factor (VEGF), transforming growth factor-b (TGF-b), platelet derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factors 1 and 2.

7.2 Platelet Rich Fibrin (PRF)

A complex fibrin matrix is produced by platelet rich fibrin (PRF), a second-generation platelet concentrate derived from autologous platelets and leukocytes. The first people to develop PRF were Choukroun et al. in France in 2001. PRF can be utilized as scaffolds in tissue engineering and facilitates the healing of both soft and hard tissues

7.3 Growth Factors Concentrated (CGF)

In 2006, Sacco created CGF, an improved second-generation platelet concentrates. It is rich in cytokines and has some utility as a pulp capping agent, but its application in the study of bone regeneration is limited. CGF encourages PDL stem cell proliferation, osteoinduction, and in vivo bone tissue creation. [14]

8.CONCLUSION

The use of regenerative endodontic procedures (REPs) has shown positive results in addressing symptoms and promoting root development in immature permanent teeth with pulp necrosis. However, the unpredictable nature of root maturation following REPs remains a significant concern in current literature, with evidence indicating that true regeneration of the pulp-dentin complex does not occur. Recently, strategies involving stem cell transplantation and cell homing have gained considerable attention for their potential to facilitate organized dental pulp regeneration.

Stem cell transplantation is a technique that involves introducing exogenous stem cells, often delivered via scaffolds, into the root canal system to promote regeneration. Animal studies have demonstrated successful pulp and dentin regeneration using these transplanted dental stem cells. Notably, in 2017,

Nakashima achieved clinical pulp regeneration in permanent teeth affected by irreversible pulpitis through the transplantation of mobilized dental pulp stem cells (MDPSCs). Additionally, a randomized controlled clinical trial reported the successful implantation of stem cells from exfoliated deciduous teeth into immature permanent teeth with pulp necrosis, resulting in the reconstruction of three-dimensional pulp tissue complete with blood vessels and sensory nerves. These findings suggest that stem cell transplantation could be a viable approach for complete pulp regeneration.

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