## REVIEW ARTICLE

# *Regenerative endodontics: the dawn of a new era.*

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**Abstract:**

*With the advancement in stem cell technology and molecular biology, regeneration as a new treatment method came to light. Regenerative medicine can be described as a process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function. The conceptualization that the vitality of dental pulp tissue can be regained as a potential treatment alternative has attracted enormous interest and attention in the field of endodontics in recent years. Dentin, pulp, cementum and periodontal tissues are the tissues of utmost interest in the field of regenerative endodontics. Scientific evidence demonstrates that these procedures lead to the resolving of apical periodontitis and signs and symptoms of inflammation, radiographic verification of continued root development and apical narrowing, and also helps in the restoration of vitality responses..*

***Keywords –regenerative endodontics, tissue engineering, stem cells, growth factors***

**History**

Regenerative endodontics came to light in the early 2000s with the publication of 2 exceptional case reports.[1, 2] However, Dr.Ostby in the early 1960s was the first one to evaluate the role of the apical blood clot in the healing of apical periodontitis and in the repair of pulp tissues.[3,4]

The term *revascularization* commenced from studies of various clinical cases in dental traumatology despite the different application and goals.[5] Pulpal revitalization is an additional term frequently used in the scientific literature. On account of this review, we will conjointly address these procedures as Regenerative endodontic procedures (REPs). Based on the results from various published reports it can be demonstrated that these procedures leads to the resolving of apical periodontitis and signs and symptoms of inflammation, radiographic verification of continued root development and apical narrowing, and also helps in the restoration of vitality responses.[5,6,7]

The comprehension that autogenous stem cells can be delivered clinically into root canals without the need for ex vivo stem cell expansion, motivated researchers and clinicians to consider principles of tissue engineering to improve treatment protocols and thus helped in the development of the next generation of procedures.

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**Introduction**

With the advancement in stem cell technology and molecular biology, regeneration as a new treatment method came to light. Regenerative medicine can be described as a process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function.[8] Almost 25 years later after its establishment several treatment modalities which earlier focused on replacement with

biomimeticmaterials have been replaced with regenerative procedures.

The conceptualization that the vitality of dental pulp tissue can be regained as a potential treatment alternative has attracted enormous interest and attention in the field of endodontics in recent years.[9]

Dentin, pulp, cementum and periodontal tissues are the tissues of utmost interest in the field of regenerative endodontics.[10]

The 'regenerated' pulp tissue might not bear a resemblance to its physiological counterpart. However, to suppress the infectious/inflammatory events, triple antibiotic paste and restorative materials which best prevents the coronal ingress of bacteria have been used in revascularization procedures.[11]

**What is regenerative endodontics?**

Regenerative endodontic therapy has been defined as "biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex''.[12]

**What is tissue engineering?**

Tissue engineering is an interdisciplinary field that combines the principles of biology and engineering to develop biological substitutes that replace or regenerate human cells, tissue or organs in order to restore or establish normal function .[13]The three main components of tissue engineering are stem cells, scaffolds and growth factors.

**Main components of regenerative endodontics**

**Stem Cells**

Stem cells are undifferentiated cells or partially differentiated cells that divide continuously. There are two main types: embryonic, and adult or postnatal.

Following are the different types of stem cells that have been isolated from teeth:

| DENTAL STEM CELL | |
|---|---|
| **SHEDs** | Stem cells from human –exfoliated deciduous teeth |
| **DFSCs** | Dental follicle stem cells |
| **DPSCs** | Dental pulp stem cells |
| **PDLSCs** | Periodontal ligament stem cells |
| **SCAPs** | Stem cells from apical papilla |
| **iPAPCs** | Inflamed periapical progenitor cells |
| **TGPCs** | Tooth germ progenitor cells |

**Scaffold**

Scaffold is a three dimensional structure containing the growth factors.

It has the following functions[12]:

- Helps in stem cell proliferation and differentiation.
- Supports cell organization and vascularization.
- Provides nutrient for cell survival and growth.
- Contain antibiotics to prevent bacterial in-growth in canal system.
- Leads to improved and faster tissue development.
- Mechanical and biological functions.

**Classification:**

Scaffolds can be classified as natural and synthetic.

- Natural: Platelet-rich plasma, platelet-rich fibrin, collagen, glycosaminoglycans.
- Synthetic: Polylactic acid, polyglycolic acid (PGA) and polylactic-co-glycolic acid.

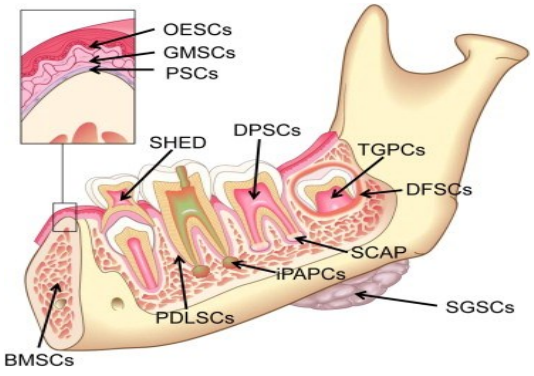



Figure 1.1 Diagrammatic representation of the sources of postnatal stem cells in the oral environment. (Adapted from Hargreaves, K.M., Teixeira, F.B., Diogenes, A., Treatment options: biological basis of regenerative endodontic procedures. *J. Endod.*, 39(3 Suppl):S30-43, 2013.)

**Growth factors**

Growth factors are proteins that bind to receptors on the cell and act as signals to induce cellular proliferation and/or differentiation.[12]

Following are the main growth factors responsible in pulp and dentin formation:

- Bone morphogenic protein.
- Transforming growth factor-beta.
- Fibroblastic growth factor.

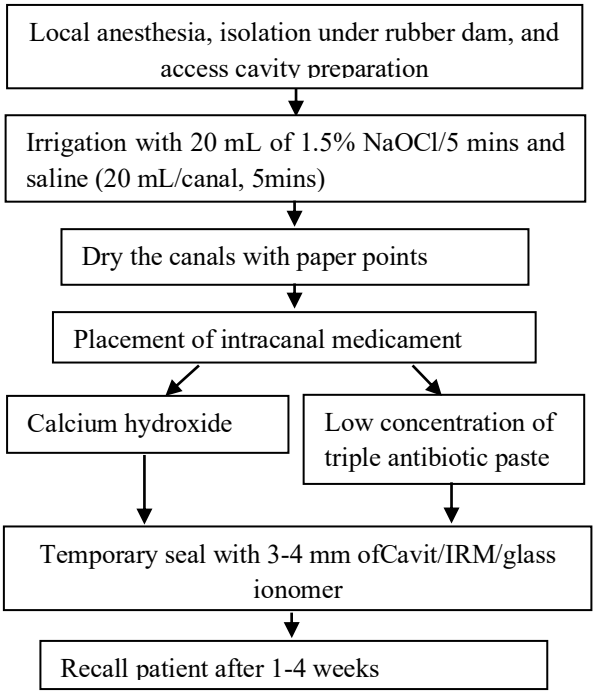
Recently growth factors found in dentin and platelet are also being used in recent regenerative endodontic procedures

**Clinical protocol:**

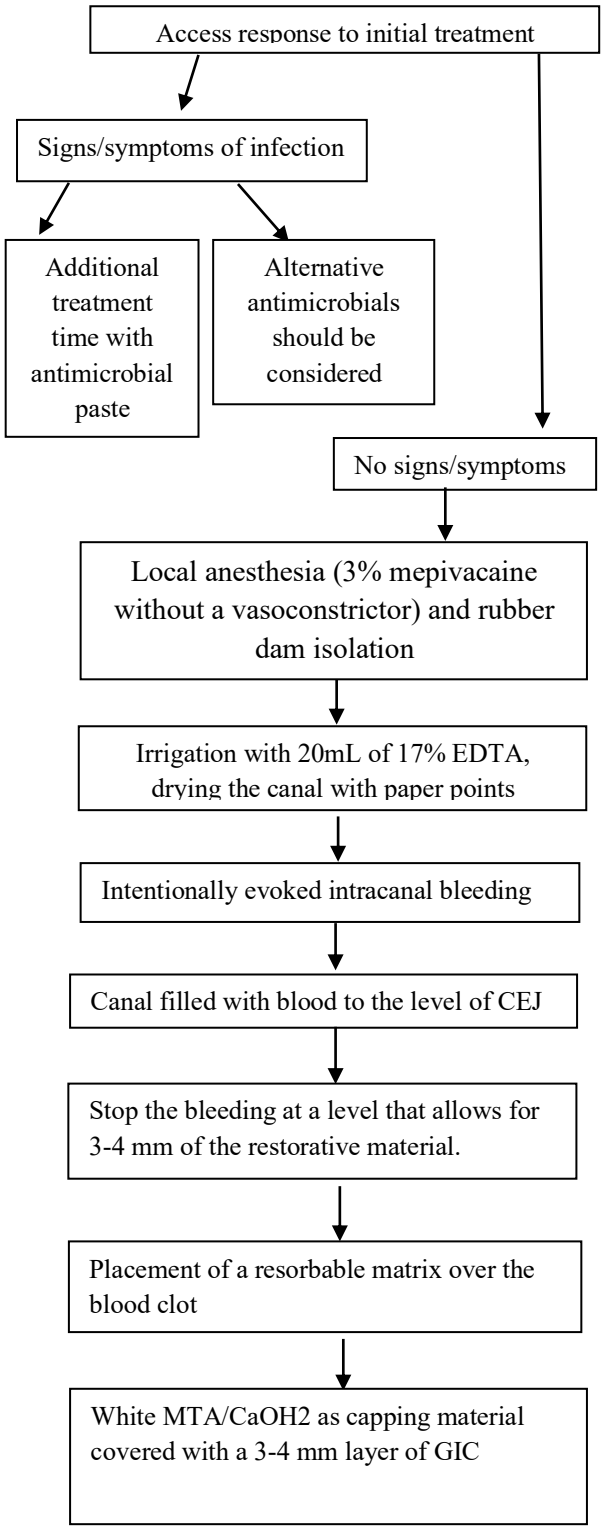
For successful clinical outcomes after regenerative endodontic procedures following features of cases are being considered[14, 15]:

- Necrotic pulp and immature apex.
- Minimal or no instrumentation of the dentinal walls.
- Young patient.
- Placement of an intracanal medicament.
- Effective coronal seal.

**Protocol for regenerativeendodontictherapy(firstappointment):**




**Regenerative endodontic therapy (second appointment)**



**What are the outcomes of regenerative endodontic procedures?**

Regenerative endodontic procedures have shown good clinical outcomes in vast majority of human case studies. Following features can be seen after a successful regenerative endodontic procedure for immature permanent teeth with pulpal necrosis[15, 16, 7]:

- Absence of clinical signs and symptoms.
- Radiographic evidence of resolution of periapical infections.
- Increased wall thickness.
- Continued root development.

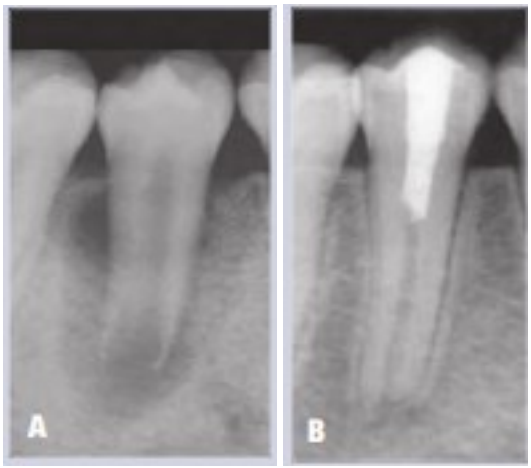



Figure 1.2 (A) Preoperative radiograph of tooth #45. (B) 24-month follow-up after regenerative endodontic treatment[1].Banchs F, Trope M. Revascularization of immature permanent teeth with apical periodontitis: new treatment protocol? J Endod2004;30:196-200.

**Challenges being faced in regenerative endodontic procedures:**

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

**Future of regenerative endodontics:**

Presently the protocol for regenerative endodontic procedures is based on:

1. Proper irrigation of the root canal and release of growth factors found in dentin.

2. Induced bleeding from the periapical area to bring cells and growth factors into the root canal.

3. Blood clot and dentin walls which provide scaffolds for the generation of new tissues. [1, 17, 18]

By utilizing tissue engineering approaches under more controlled clinical conditions, the challenges faced in regeneration of tissues that mimic the original pulp and dentin-like structure can be overcome in the near future.[18, 19]

**Conclusion:**

In most of the cases of pulp and periapical lesions, endodontic therapy is not provided and instead the tooth is extracted and later on artificial prosthesis like an implant is placed.

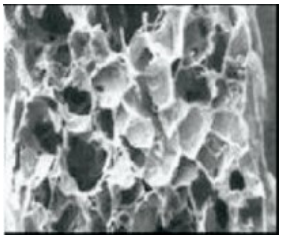
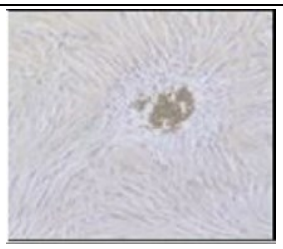
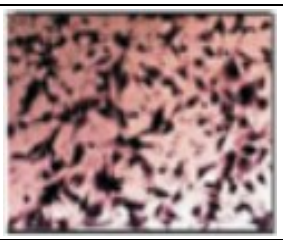
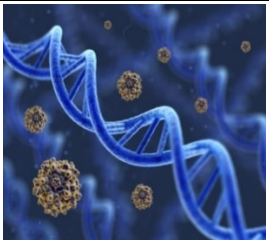
Regenerative endodontics is cutting-edge technological research which provides valuable adjuvants to the treatment and retention of immature teeth with pulp necrosis.

Several developmental approaches have been described to accomplish endodontic regeneration, each one having its own advantages and disadvantages. While some techniques are hypothetical, some are at an early stage of research.

In the foreseeable future, the ultimate goal of an endodontic treatment will be the regeneration of pulp-dentin complex which will have a promising impact on efforts to retain the natural dentition.

However, in order to achieve this ultimate goal, more research and development has to be made in this field.

**ADVANTAGES AND DISADVANTAGES OF DEVELOPMENTAL APPROACHES FOR REGENERATIVE ENDODONTIC PROCEDURES**[12] :

| Technique | Image | Advantages | Disadvantages |
|---|---|---|---|
| **Root-canal revascularization:** Open up tooth apex to 1mm to induce bleeding into the root canals. |  | Low risk of pathogen transmission.<br><br>Low risk of immunological rejection. | Very little scientific evidence until now.<br><br>Potential risk of necrosis. |
| **Stem cell therapy:** Autologous or allogenic stem cells are delivered to teeth via injectible matrix. |  | Easy insertion.<br><br>painless.<br><br>Cells are easy to harvest.<br><br>Quick. | Cells do not produce new function pulp tissue.<br><br>Low cell survival. |
| **Scaffold implant:** Pulp cells are seeded onto a 3-D scaffold made of polymers and surgically implanted. |  | Some materials might promote vascularization.<br><br>Structure supports cell organization. | Low cell survival after implantation.<br><br>Must be engineered to fit root canal precisely. |
| **Pulp implant:** Pulp tissue is grown in laboratory in layers and surgically implanted. |  | Relatively easy to develop the technique.<br><br>More stable than an injection of dissociated cells. | Low vascularization of the layers.<br><br>The layers should precisely fit the root canal. |
| **3-D cell printing:** Cell layers are injected in hydrogels and surgically implanted. |  | Multiple cell types can be perfectly placed. | It should perfectly fit the root canal.<br><br>Initial stage of research- in vivo test required. |
| **Injectable scaffolds:** Polymerizable hydrogels are delivered by injection. |  | Easy insertion.<br><br>May promote regeneration by providing replacement for extracellular matrix. | Limited control over tissue formation.<br><br>Low cell survival rate. |
| **Gene therapy:** Mineralizing genes are transfected into the vital pulp cells of necrotic and symptomatic teeth. |  | Cleaning and shaping of root canals are not required.<br><br>May avoid the necessity to implant stem cells. | Most cells in necrotic tooth are dead.<br><br>Hard control.<br><br>Risk of health hazard.<br><br>Not approved by the FDA. |

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