

## Regenerative Endodontics

Mohamed Hany Ahmad Abd Elghany<sup>1\*</sup>, Ghaliyah Aedh Alshahrani<sup>1</sup>, Yazeed Abdullah Altowairqi<sup>1</sup>, Adi Hatem Turkistani<sup>1</sup>, Mohammed Ahmed asiri<sup>2</sup>, Abdullah mana saeed Almofrej<sup>2</sup>, Majed Saeed Saad Alqahtani<sup>2</sup>, Abdullah salim Alshehry<sup>2</sup>, Mohammed Abdullah alshahir<sup>3</sup>, Khalid hamoud alamri<sup>3</sup>, Ahmad Farid atteya<sup>3</sup> and Maha Abdulaziz Altaifi<sup>4</sup>

<sup>1</sup>Cairo University, Saudi Arabia

<sup>2</sup>King Khalid University, Saudi Arabia

<sup>3</sup>Ministry of Health, Saudi Arabia

<sup>4</sup>Batterjee Medical College, Saudi Arabia

\*Corresponding Author: Mohamed Hany Ahmad Abd Elghany, Cairo University, Saudi Arabia.

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### Abstract

**Introduction:** Endodontic Therapy saves millions of teeth each year. Modern treatment modalities offer high levels of success, but an ideal treatment might comprise of regenerative approaches in which diseased or necrotic pulp tissues are replaced with healthy pulp. Regenerative endodontics is based on the concept of tissue engineering and attempts to restore the root canals of teeth to their healthy state to encourage continued development of the root and surrounding tissue. Concepts from the fields of pulp biology, dental trauma, and tissue engineering are applied in this biologically based treatment modality as attempts are made to promote continued root development, apical closure and increased thickness in the dentinal walls in permanent teeth with necrotic pulps and immature apices. These developments have a promising impact on the efforts to retrain natural teeth, the primary goal of endodontic treatments.

**Aim of Work:** This review provides an overview of regenerative endodontics, the clinical considerations for regeneration therapy, and an assessment of the expected outcomes.

**Methodology:** This article is a comprehensive review of PUBMED from the year 2001 to 2017.

**Conclusion:** Revascularization/revitalization procedures performed according to the current clinical protocols have been able to achieve clinically and radiographically successful outcomes for immature necrotic permanent teeth. However, repair rather than true regeneration is achieved with the current protocols, and it is hoped that new research in the field of stem cell-based pulp engineering will pave the way for true pulp dentin regeneration and improve the treatment outcomes.

**Keywords:** Regenerative Endodontics; Revitalization; Immature Teeth

### Introduction

Dentistry is a fast-evolving field thanks to constant researches and developments. One such development that has become popular in recent years is Regenerative Endodontics. Regenerative endodontics is based on the concept of tissue engineering and attempts to restore the root canals of teeth to their healthy state to encourage continued development of the root and surrounding tissue. Concepts from the fields of pulp biology, dental trauma, and tissue engineering are applied in this biologically based treatment modality as attempts are made to promote continued root development, apical closure and increased thickness in the dentinal walls in permanent teeth with

necrotic pulps and immature apices. These developments have a promising impact on the efforts to retrain natural teeth, the primary goal of endodontic treatments [1].

By definition, Regenerative endodontic procedures are “biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex” [1]. According to this definition, the aim of Regenerative Endodontics is to regenerate the pulp-dentine complex of permanent teeth with immature apices that may have necrotic pulp due to infections, trauma, or developmental anomalies. This is done by applying the concepts of stem cells, tissue engineering biomimetic scaffold, and bioactive growth factors in the canal space [1].

The American Association of Endodontists in 2007 adopted the term ‘Regenerative Endodontics’ for these procedures based on a concept of tissue engineering. The European Society of Endodontology (ESE) used the term ‘Revitalization’ for these procedures in their statement. However, in endodontic literature, the terms regenerative, revitalization, and revascularization have been used interchangeably and synonymously [2].

Compared to MTA and  $\text{Ca}(\text{OH})_2$ , teeth with regenerative endodontic procedures used for apexification have shown a higher survival rate. In teeth with anomalies and complex anatomies, like dens invaginatus, Revascularization/revitalization techniques have been advocated [5].

### Clinical considerations

The clinical protocol that should be kept in mind while doing regenerative procedures can be summed under these headings:

1. Disinfection of the root canal system.
2. Intracanal medicaments.
3. Provision of a scaffold.
4. Adequate coronal seal [3].

### Disinfection of the root canal system

Disinfection of the root canal system is crucial to the success of Regenerative Endodontic Procedures (REPs) as infection hampers regeneration, repair, and stem cell activity. Protocols for chemical disinfection of the root canal system do not focus solely on the bactericidal or bacteriostatic properties of the agents used but also on their effect on the survival and proliferative activity of the stem cells [6].

The current clinical protocol describes a two-visit approach with the combined use of irrigants and intracanal medicaments, as very few reported cases had been performed in a single visit. The guidelines are as suggest:

- Copious irrigation with about 20 ml of low concentration (1.5%) sodium hypochlorite ( $\text{NaOCl}$ ) for 5mins per canal using an irrigation system that reduces the risk of extrusion of irrigants into the periapical region. EndoVAC, Side venting Needles, or Closed-Ended Needles can be used.
- Rinse with saline or EDTA (20 mL/canal, 5 min). The irrigating needle should be positioned about 1 mm from the root end to minimize extrusion of irrigants and damage to stem cells in the apical region [7].

Lower concentrations of  $\text{NaOCl}$  are now preferred as higher concentrations tend to significantly decrease stem cells’ survival at the apical papilla (SCAP). 1.5% concentration of  $\text{NaOCl}$  has been found to have minimal cytotoxic effects on the SCAP and is therefore recommended [7].

The use of 17% EDTA has been found to increase SCAP survival as well as partially reverse the adverse effects of  $\text{NaOCl}$ . EDTA acts by demineralizing the dentine and exposing the dentine matrix, which in turn causes the release of growth factors from the dentine matrix.

The exposing of the dentin matrix also appears to increase the adherence of newly formed mineralized tissue to the root walls. Conditioning of Dentin with EDTA has also been found to promote the adhesion, migration, and differentiation of dental pulp stem cells onto or towards the dentin. Therefore, a final rinse with EDTA is advised during REPs before creation of a blood clot is initiated [8].

Some authors have also recommended a final rinse with 0.12% chlorhexidine in addition to NaOCl for the first appointment because of its antimicrobial activity and substantivity. However, others have found it to have cytotoxic effects on the stem cell, therefore advised against its use [9].

### **Intracanal medicaments**

Along with Irrigation, the use and the concentration of the Intracanal Medicament used are also important for the ideal disinfection of the canal and survival and proliferation of the SCAP. Antibiotic Pastes have been used commonly as Intracanal Medicaments since their success in the first report of revascularization. A double antibiotic paste with metronidazole and ciprofloxacin or a Triple Antibiotic paste (TAP) with 1:1:1 ciprofloxacin, metronidazole, and minocycline have since come into widespread use in REPs [10].

Various other antibiotics, including amoxicillin, cefaclor, and rokitamycin have been used along with ciprofloxacin and metronidazole. However, the combination with Minocycline has been found to achieve better results in terms of an increase in root wall thickness as compared to the other drugs. TAPs with minocycline have also been found capable of diffusing throughout the entire dentin thickness and effectively disinfecting the deeper layers. A major drawback, however, is the discoloration observed in teeth after minocycline use [10].

According to the recent AAE protocols, triple antibiotic pastes at concentrations no greater than 0.1 mg/ml should be used for REPs. Triple Antibiotic Pastes have been found to be conducive in stem cell proliferation and also affective at disinfecting at this concentration [7].

AAE guidelines also recommended the use of calcium hydroxide [7]. Calcium hydroxide has also been found to be favorable to SCAP survival and growth. Recent studies have shown that SCAPs had the highest survival rate when cultured on dentine exposed to calcium hydroxide as when compared to dentine that had been exposed to 0.1 mg/ml concentration of Triple Antibiotic Paste. Clinically, Calcium Hydroxide, when used as an intracanal medicament has been found to promote root maturation and also has been found to be a good antimicrobial. It is suggested that if  $\text{Ca}(\text{OH})_2$  paste is used, it should be placed in the coronal half of the root to permit thickening of dentinal walls [11].

### **Scaffold creation**

At the second appointment, once disinfection of the canal is complete and symptoms start to resolve, REPs proceed to the step of scaffold creation. It takes place between 2 and 4 weeks after initiation of therapy. However, if symptoms of infection persist, additional treatment time may be required with the same antimicrobial, or with an alternative antimicrobial [13].

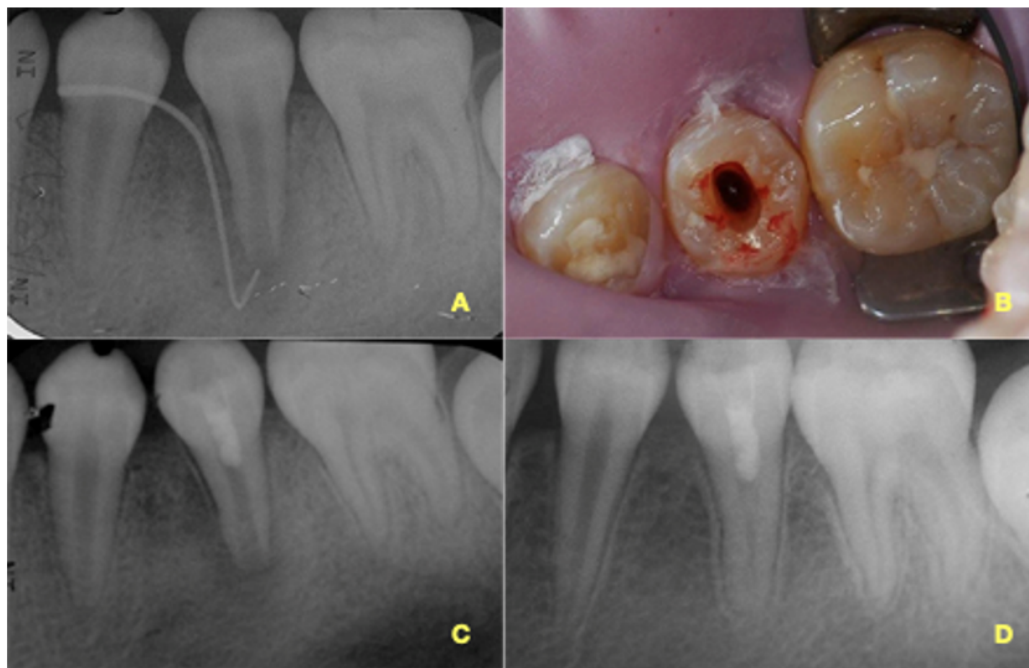
The scaffold provided a framework for the growth and development of cells and blood vessels. It can also be infused with a variety of substances to promote cell growth and differentiation. It involves laceration of the periapical tissues to initiate bleeding or the use of platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) [12].

The correct protocol for scaffold creation suggests the introduction of a sterile #20 pre-curved K file 2 mm past the apical foramen to initiate bleeding and allowing the entire canal to fill with blood to the level of the CEJ [13]. The technique has its limitations in the unpredictability of the concentration and the composition of cells trapped in the clot, thus produced and to restore function; REPs require effective concentrations and composition of cells [1]. However, there have been a number cases in which authors were unable to produce bleeding in the canal. In such cases, conventional apexification may be required. REPs with both PRP and PRF have been demonstrated

to be successful clinically as well as radiographically. This success was credited to the growth factors in these substances, which assist in stem cell proliferation and tissue regeneration. However, histological findings in some studies showed no evidence of the formation of pulp-like tissue or odontoblasts like cells with the use of PRP and PRF. In addition, expenses and difficulty are involved in the preparation and use of these substances. Therefore the use of PRP and PRF is not recommended routinely except in cases where a blood clot cannot be formed without them [14].

### Effective coronal seal

Once the scaffold or the blood clot is in place within the canal, a coronal barrier is placed to seal the canal and prevent microleakage, thus preventing reinfection of the canal space and failure of treatment. The material of choice for accomplishing coronal seal in regenerative procedures currently is MTA. MTA is a bioceramic material capable of setting even in the presence of blood. Once it sets, MTA is highly resistant to bacterial penetration. According to current protocols, after the blood clot is formed, a 3 mm thick layer of white MTA should be placed, followed by 3 - 4 mm layer of a GIC cement. A bonded composite resin restoration is then placed over the GIC. Collaplug can also be used to serve as an internal matrix for MTA placement over the blood clot [7].



**Figure 1:** Regenerative Procedure on a Mandibular Premolar with Immature root and pulpal necrosis [19].

[A] A GP marker tracks to the periapical tissues of an immature root of a mandibular premolar tooth where the evaginatus has fractured causing pulp necrosis and chronic abscess.

[B] A blood clot was induced into the canal to the level of the cemento-enamel junction after disinfection.

[C] A radiograph showing an intracanal barrier of MTA placed on the blood clot. The tooth was restored with glass ionomer cement and composite resin.

[D] A radiograph taken at an 18-month review showing resolution of the apical periodontitis as well as further root maturation indicated by increased width of the root dentine walls and apical closure.

### Outcome of regenerative procedures

The ideal clinical outcome for any Regenerative Endodontic procedure is an asymptomatic tooth that never needs retreatment, but vitality assessment is essential to validate that the true effectiveness of the regenerative endodontic technique.

The American Association of Endodontists in their publication, define the success of REPs by three measures [7]:

- Primary goal (essential): Elimination of symptoms and evidence of bony healing.
- Secondary goal (desirable): Increased root wall thickness and/or increased root length.
- Tertiary goal: A positive response to vitality testing.

### Outcomes of Regenerative Endodontic procedures can be evaluated at four levels:

#### Clinical evidence of periapical healing

Clinical evidence includes the absence of sensitivity to percussion or palpation and the absence of any sinus tracts or swelling. All cases of documented REPs have shown these features [15].

#### Radiographic evidence of periapical healing and root development

This ideally includes complete osseous healing of the periapical lesion, an increase in root thickness and length, and the formation of a radiographic apex. Although these outcomes are desirable, they aren't essential to deem the treatment a success and may not always be achievable [7]. There have been cases where there are mixed outcomes like no root development or apical closure without an increase in root length or root wall thickness. Longer periods of review in regeneration cases have been suggested as continued root maturogenesis has been observed in a few cases over 36 months follow up [9].

Chen., *et al.* described 5 types of possible responses of teeth treated with REPs:

- Type 1 where there is increased thickening of the canal walls and continued root maturation.
- Type 2 where there is no significant continuation of root development with the root apex becoming blunt and closed.
- Type 3 where there is continued root development with the apical foramen remaining open.
- Type 4 where there is severe calcification (obliteration) of the canal space.
- Type 5 where there is a hard tissue barrier formed in the canal between the coronal MTA plug and the root apex [16].

A possible relationship between duration of pulp necrosis and treatment outcome has been mentioned by a few authors who suggest that long-standing infections may destroy the cells capable of pulp regeneration. A few studies have found vital pulp tissue in the apical third of the root until 60 days of infection, and vital apical papilla until 90 days of infection in a rat model. Keeping these results in mind, it can be concluded that duration of pulpal necrosis is, in fact, a very important factor when it comes to achieving root maturogenesis [9].

#### Response to pulp vitality testing

Positive Response to Vitality testing is the tertiary goal of treatment and indicates a high level of success, i.e. reinnervation of the root canal, regardless of the type of tissue formed inside the canal [9].

So far, there have been mixed reports by authors with regard to vitality testing following REPs. Some authors have suggested that negative responses to vitality testing may be due to the presence of a thick layer of MTA (3 - 4 mm) as well as layers of cement and the restorative materials such as composite resin placed over the plug [17].

#### Histological evidence of dentin-pulp regeneration

Histological examination of the tissues formed inside root canal spaces in human teeth and animals after REPs have shown bone healing and root development, but none of the studies has shown regeneration of the actual dentin-pulp complex within root canal space.

Ingrowth of periodontal ligament, cementum, and bone into the root canal space has been found; in some cases, soft and hard connective tissue too was found, but no evidence of regeneration of pulp dentin complex was found.

Even in virgin immature teeth of animals and humans, that had no history of pulpal and periapical disease, bone and cementum like tissues and no pulp/dentine like tissue are formed in the disinfected canal space [18].

### Crown discoloration

The crown discoloration is a significant aesthetic problem following REPs. Two recent reviews have reported discoloration after REP in 40% of cases [17]. This is of particular concern for anterior teeth as discolored teeth may be unacceptable to the patient. The discoloration is more commonly associated with the use of Triple Antibiotic Paste that includes minocycline. However, discoloration has also been reported with calcium MTA, too, can cause tooth discoloration.

The use of Biodentine instead of MTA has been suggested to reduce the chances of discoloration. Bleaching of the discolored teeth is usually sufficient to improve the aesthetic outcome. As discoloration is a known common adverse result in teeth treated with REPs, this issue must be addressed with the patient prior to treatment [7].

### Conclusion

Revascularization/revitalization procedures performed according to the current clinical protocols have been able to achieve clinically and radiographically successful outcomes for immature necrotic permanent teeth. Although continued root development after REP is not predictable, in contrast to apexification, REP shows the potential to conduce continued root maturation of immature necrotic permanent teeth. Even though in some cases vitality may be restored in REP treated teeth, the tissue formed in the canal space RET is not like the pulp dentin complex and its biological function as a dental pulp is lost after RET.

In spite of this, based on the success seen in the many published cases in the literature, this biologically based treatment is being advocated as the first treatment of choice for immature teeth with pulp necrosis currently.

It can be concluded that repair rather than true regeneration with the current clinical protocols, and it is hoped that new research in the field of stem cell-based pulp engineering will pave the way for true pulp dentin regeneration and improve the treatment outcomes.

### Bibliography

1. Murray P E., *et al.* "Regenerative endodontics: a review of current status and a call for action". *Journal of Endodontics* 33.4 (2007): 377-390.
2. Galler K M., *et al.* "European Society of Endodontology position statement: Revitalization procedures". *International Endodontic Journal* 49.8 (2016): 717-723.
3. Bezgin T and Sönmez H. "Review of current concepts of revascularization/revitalization". *Dental Traumatology* 31.4 (2015): 267-273.
4. Jeeruphan T., *et al.* "Mahidol study 1: comparison of radiographic and survival outcomes of immature teeth treated with either regenerative endodontic or apexification methods: a retrospective study". *Journal of Endodontics* 38.10 (2012): 1330-1336.
5. Yang J., *et al.* "Pulp revascularization of immature dens invaginatus with periapical periodontitis". *Journal of Endodontics* 39.2 (2013): 288-292.
6. Diogenes A., *et al.* "An update on clinical regenerative endodontics". *Endodontic Topics* 28.1 (2013): 2-23.

7. Geisler T M. "Clinical considerations for regenerative endodontic procedures". *Dental Clinics* 56.3 (2012): 603-626.
8. Galler K M., *et al.* "EDTA conditioning of dentine promotes adhesion, migration, and differentiation of dental pulp stem cells". *International Endodontic Journal* 49.6 (2016): 581-590.
9. Geisler T M. "Clinical considerations for regenerative endodontic procedures". *Dental Clinics* 56.3 (2012): 603-626.
10. Bose R., *et al.* "A retrospective evaluation of radiographic outcomes in immature teeth with necrotic root canal systems treated with regenerative endodontic procedures". *Journal of Endodontics* 35.10 (2009): 1343-1349.
11. Althumairy R I., *et al.* "Effect of dentin conditioning with intracanal medicaments on survival of stem cells of apical papilla". *Journal of Endodontics* 40.4 (2014): 521-525.
12. Lovelace T W., *et al.* "Evaluation of the delivery of mesenchymal stem cells into the root canal space of necrotic immature teeth after clinical regenerative endodontic procedure". *Journal of Endodontics* 37.2 (2011): 133-138.
13. Geisler T M. "Clinical considerations for regenerative endodontic procedures". *Dental Clinics* 56.3 (2012): 603-626.
14. Ding R Y., *et al.* "Pulp revascularization of immature teeth with apical periodontitis: a clinical study". *Journal of Endodontics* 35.5 (2009): 745-749.
15. Iwaya S I., *et al.* "Revascularization of an immature permanent tooth with apical periodontitis and sinus tract". *Dental Traumatology* 17.4 (2001): 185-187.
16. Chen M H., *et al.* "Responses of immature permanent teeth with infected necrotic pulp tissue and apical periodontitis/abscess to revascularization procedures". *International Endodontic Journal* 45.3 (2012): 294-305.
17. Torabinejad M and Turman M. "Revitalization of tooth with necrotic pulp and open apex by using platelet-rich plasma: a case report". *Journal of Endodontics* 37.2 (2011): 265-268.
18. Torabinejad M., *et al.* "Regenerative endodontic treatment or mineral trioxide aggregate apical plug in teeth with necrotic pulps and open apices: a systematic review and meta-analysis". *Journal of Endodontics* 43.11 (2017): 1806-1820.
19. Lin L M and Kahler B. "A review of regenerative endodontics: current protocols and future directions". *Journal of Istanbul University Faculty of Dentistry* 51.3-1 (2017): S41.

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