ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 3, June - 2023, Page No. : 91 - 97

Regenerative endodontics by cell homing: A new era for clinical dentistry

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How to citation this article: Dr. Vanshika Saggar, Dr. Saloni Shah, Dr. Muskan Patel, Dr. Akash P, Dr. Monika K. Kajalkar, "Regenerative endodontics by cell homing: A new era for clinical dentistry", IJMACR- June - 2023, Volume – 6, Issue - 3, P. No. 91 – 97.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

This article aims to outlines the clinical protocols of recently used technique of regenerative endodontic procedures, elaborates its biological basis, clinical considerations, its procedure and discuss future directions in pulp regeneration approaches. Clinical protocols for regenerative endodontics have been released by the American Association for Endodontists. After the reports of reports of Iwaya et al. there is increased research and application on this field. 'Paradigm shift' is the term used to describe the treatment of immature permanent teeth, this is because such teeth show the potential of root maturation. The outcome of this technique includes resolution of the sign and symptoms, root maturation and response to pulp vitality testing (return of neurogenesis)

Clinically regenerative technique is based on the concept of disinfecting the necrotic canal and lacerating the apical tissues by over instrumenting to induce bleeding in the canal space which then forms a clot which is then sealed with intracanal barrier. This procedure leads to increase in pulp wall thickness and lengthening leading to root maturation. Although more research and application of this technique needs to be done to know more about long term clinical and biological aspects but many clinicians consider it as an optimal approach for repairing the necrosed pulp of an immature permanent tooth.

Keywords: Regenerative endodontics, Stem cell, Immature permanent teeth, Root maturation, Root canal.

Introduction

Getting to know regenerative endodontics..?

Immature permanent teeth with infected root canal, necrotic pulp and apical periodontitis are conventionally treated using calcium hydroxide to induce hard tissue barrier formation at the apex or with apical MTA plugs prior to root canal filling known as apexification procedures (1). The apexification procedure using calcium hydroxide requires multiple visits over an extended period of time causing increase in chances of root fracture(2). Apexification procedure only helps to induce barrier formation of immature permanent teeth with necrotic pulp but has no potential to restore the vitality of damaged pulp tissue or promote root maturation. 'Revascularization' a new treatment term was introduced in endodontics and was first mentioned by Iwaya *et al*. in 2001 (3). In 2007 the term 'regenerative endodontics' was accepted by the American Association of Endodontists(4). 'Revitalization' was the term used by the European Society of Endodontology (ESE) .The concept behind regenerative endodontics includes the triad of tissue engineering i.e. stem cells, biomimetic scaffold and bioactive growth factors. These triad in the canal space leads to regeneration of the pulp tissue which may be necrosed by infection, developmental anomalies or trauma (5). Regenerative endodontics is an emerging field referred as a "paradigm shift" resulting in continued root maturation and apical closure of immature teeth with infected root canals (6,7). In the endodontic literature, revascularization, revitalization, and regenerative endodontics are the terms used synonymously. Regenerative endodontic utilizes endogenous stem cells. These cells are introduced in the canal space by lacerating periapical tissues to fill such as the blood fills the canal and should be used for the treatment of immature teeth with pulp necrosis (8). Nygarrd-Ostby & Hjortdal in 1971 have pioneered regenerative endodontics by inducing bleeding from the periapical tissues into the chemo- mechanically debrided canal space of the teeth(9). Extracted teeth after 9 days to 3 years on histological examination disclosed that there was formation of cellular cementum and fibrous connective tissue in the canal space at the apex of teeth containing vital pulp. Iwaya *et al*. 2001 were the first to apply clinically the concept of regeneration in the management of immature permanent teeth along with apical periodontitis and sinus tract.

Outcome showed complete extermination of clinical signs and symptoms of apical periodontitis along with increase in canal walls thickness and immature permanent tooth apical closure. Various studies have compared regenerative endodontic technique with the traditional approaches of apexification using calcium hydroxide and MTA barrier techniques and have shown comparable outcomes (10,11). In a study by Jeeruphan et al they compared the regenerative therapy protocols with conventional technique and have showed that revascularization was associated with significantly greater increases in root thickness and length as well as overall higher survival rates (12).

Murray et al. defined regenerative endodontics as 'biologically based procedures designed to replace damaged tooth structures, including dentine and root structures, as well as cells of the pulp–dentine complex' (4). Regenerative endodontic therapy based on its definition aims to regenerate the pulp–dentine complex

necrosed and damaged by dental infection, developmental anomaly or trauma of immature permanent teeth.

Indications/Clinical consideration

Does all immature permanent teeth with necrotic pulps requires regenerative endodontic therapy?

Based on Cvek's classification of root development (13), it is recommended that:

- immature permanent teeth with necrotic pulp at the stage 1: suitable for regenerative endodontic treatment.
- immature permanent teeth with necrotic pulp at the stage 2: suitable for regenerative endodontic treatment.
- immature permanent teeth with necrotic pulp at the stage 3: suitable for regenerative endodontic treatment.
- Immature permanent teeth at stage 4: can be managed either with regenerative endodontic treatment or an apical MTA plug and root canal filling.

for stage 1, stage 2, and stage 3- the root is short, canal walls are thin, and apex is wide open making them suitable for RET as apexification has no potential for root maturation.

For stage 4- the canal walls have enough thickness and strength.

Discussion

Clinical considerations/ protocol to be followed during regenerative endodontic treatment:

The American Association of Endodontists (AAE) defines the success of regenerative endodontic treatment based on 3 measures (14). i.e.

- Primary goal: To eliminate the symptoms and the affirmation of bony healing.
- Secondary goal: Increase in the thickness of root wall along with/ or increase in the root length.
- Tertiary goal: Response to vitality testing should be positive (15).

Root canal disinfection is critical to the success of regenerative endodontic procedures as infection blocks repair, regeneration, and stem cell activity (16,17). Selection of disinfectant should be accurate as some irrigants or disinfectant with bactericidal/ bacteriostatic effect may damage the proliferative capacity of the patient's stem cells (18). Lower concentrations i.e., 1.5% of sodium hypochlorite irrigation is advised followed by saline or EDTA such that the irrigating needle is positioned 1 mm above the root end to minimize the stem cell cytotoxicity in the apical tissues. Other benefits of EDTA includes it demineralises the dentine causing exposure of the dentine matrix, which in turns releases the growth factors from the dentine matrix (19,20). EDTA also promotes the migration, adhesion, and differentiation of dental pulp stem cells on dentin (21). Therefore, lower concentration of sodium hypochlorite followed by final rinse with EDTA should be followed to achieve appropriate result.

Triple antibiotic pastes have shown to disinfect dentine in infected root canals. It acts by diffusing the drugs throughout the entire root canal dentine (22,23). According to AAE protocol triple antibiotic paste should be used at concentrations of 0.1 mg/mL or less. Triple antibiotic paste at this concentration is helpful to stem cell for survival and proliferation (24) and it also eliminates microorganisms from the root canal (25).

After disinfecting the canal and when the symptoms get resolved, the next step in regenerative endodontic involves lacerating the periapical tissues. This is done to initiate bleeding or the use of platelet-rich fibrin (PRF). Effective coronal seal is an equal consideration for clinical use. Once a blood gets clot in its place within the canal, a coronal barrier placement becomes necessary to prevent leakage of microorganisms from coronal region.

Regenerative endodontic clinical procedure

First Appointment	Local anaesthesia and rubber dam isolation. Access to the canal Root canal disinfection with 1.5% of sodium hypochlorite irrigation with needle positioned 1 mm above the root end. Drying the canal with paper points. Placement of Triple antibiotic paste. Temporary restoration till next visit.
Second Appointment (1-4 Weeks After First Visit)	Check for the sign and symptoms. Local anaesthesia and rubber dam isolation. Access to the canal Irrigation with EDTA Drying the canal with paper points. Lacerating the apical tissue by over instrumenting to induce bleeding.
	Place a resorbable matrix over the blood clot. Restore the tooth.
Follow-up	Clinical inspection and radiographic examination. Resolution of symptoms. No sinus tract seen. Pulp vitality test. Resolution of apical radiolucency seen within 1 year after treatment. Increase in root wall thickness and root length.

Clinical outcome of regenerative endodontic treatment

Clinical outcome is based on achieving the goals declared by the Association of Endodontists (14) for regenerative endodontic procedures. As mentioned earlier the goals define success of the procedure by three measures: primary goal, secondary goal, and tertiary goal. The primary goal which is to resolve the associated signs/symptoms of the infection and promote bone healing are generally achievable (26). The failed cases can be attributed to improper disinfection protocols. A systematic review done recently reported about 96% teeth treated with regenerative endodontic procedure between 2001 and 2014 showed some degree of apexogenesis along with increase in root thickness, increase in root length and apical closure. (26).

With all the above advantage, regenerative endodontic treated teeth tend to show some level of discoloration later (27) which may be the cause of concern when anterior teeth are taken in consideration.

Failed cases after regenerative endodontic treatment: failure in achieving success of the treatment may be due to multiple associated factors such as improper disinfection of canal (28,29), minimal instrumentation leading to inadequate removal of biofilm (30) or may be due to re-infection due to coronal leakage (10). some cases, has shown root fracture (24). In study by song et al. about 62.1% cases show the prevalence of revascularization-associated intracanal calcification (31) which becomes more difficult to treat further. These immature permanent teeth after failed regenerative endodontic treatment can be further managed by root canal treatment, regenerative endodontic retreatment again or apexification.

Future Perspective: What Does The Future Hold?

Future perspective in regeneration of the necrotic pulp may be achieved by cell based and cell homing/ cell free approaches. Clinical regenerative endodontic procedures can be considered a cell-free approach. The cell-free approach described in this article is simpler than cell-based approach. The cell-based approach employs ex vivo isolation of stem cell and seeding in the canal these include dental pulp stem cells known as DPSCs or stem cells from apical papilla and stem cells from exfoliated deciduous teeth (32-35). The cell-based approach can form cells like odontoblast with may lead to deposition of dentin like tissue. For future more research on cell based regenerative endodontic treatment should be taken into consideration keeping in mind the factors making the procedure difficult to be used clinically.

Although both the methods of regeneration are still under trials but there is huge scope of this treatment modality from future prospect pulp tissue regeneration. This procedure appears to be an attainable goal with more clinical success.

Conclusion

Based on the concept of tissue engineering technology regenerative endodontics presents a new era to clinically regenerate the dentine–pulp complex in the root canal space of the damaged immature permanent teeth. This technique seems to be promising for the continuation of arrested root growth. With regenerative endodontic treatment it is possible to achieve the primary goal of endodontic therapy which includes elimination of patient's clinical signs and symptoms along with resolution apical periodontitis. Immature permanent teeth with a necrotic pulp can be successfully managed with regenerative endodontic treatment where the symptoms get eliminated and functional as well as aesthetic goals can be achieved. Further research in this area of stem cell-based regeneration is required for more easier techniques and improved treatment outcomes.

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