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Rohit Pannu
M.D.S. (Conservative Dentistry and Endodontics). Consultant, Bhiwani, Haryana, India.

Correspondence
Rohit Pannu
M.D.S. (Conservative Dentistry and Endodontics). Consultant, Bhiwani, Haryana, India.

Pulp revascularisation - An evolving concept: A review

Rohit Pannu

Abstract
As the importance attributed to conservative endodontic treatment increases manifold, pulp revascularization represents a recent and promising therapy for immature teeth, highly recommended as an alternative to apexification in cases of endodontic treatment of irreversible pulpitis and pulp necrosis, whether or not associated with periapical lesion. This review is an attempt towards the recommendation of revascularization as an alternative to apexification.

Keywords: Revascularization, apexification, scaffolds, bioactive ceramics, synthetic polymers, PRF

1. Introduction
Revascularization may be defined as the invagination of undifferentiated periodontal cells from the apical region in immature teeth [1]. Tissue in-growth is directed towards the root canal space after passive decontamination that removes, partially or totally, pulp tissue and/or its necrotic remnants. Pulp tissue regeneration may present an ideal alternative treatment to traditional root canal therapy. The present concept of pulp tissue regeneration includes two possible approaches. The first is revascularization, where a new pulp tissue is expected to grow into the root canals from the remaining tissues that exist apically in the root canal [2]. The second includes the replacement of the diseased pulp with a healthy tissue that is able to revitalize the tooth and restore dentin formation process [3]. The stem cell therapy, gene therapy, three-dimensional (3D) cell printing, scaffold implantation, and pulp implantation are suggested for this approach.Root canal revascularization procedure aims to restore the blood supply of necrotic pulp tissues of permanent immature teeth [2]. Some researchers indicate revascularization as a regenerative approach [3]. Others consider that pulp regeneration is incomplete if restricted only to revascularization and should include other significant events such as alignment of odontoblasts on the dentin surface, and generation of the different types of dental pulp nerve fibers (i.e., nociceptive, sympathetic, and parasympathetic) [4].

History
Revascularization, per se, is not new. It was introduced by Ostby[5] in 1961, and in 1966, Rule and Winter[6] documented root development and apical barrier formation in cases of pulpal necrosis in children. In 1972, Ham *et al.* [7] demonstrated apical closure of immature pulpless teeth in monkeys. In 2001, Iwaya *et al.* [8] and in 2004, Banchs and Trope [2] demonstrated the advantages of this treatment modality, which resulted in a radiographically apparent normal maturation of the entire root.

Rationale of Revascularization
According to Windley *et al.* [9] (2005), the successful revascularization of immature teeth with apical periodontitis is mainly dependent upon:

1. Canal disinfection:
   This is regarded as a key factor for successful treatment.
2. Scaffold placement in the canal for the growing tissues:
   Once canal disinfection has been completed, the apex is mechanically irritated to induce clot formation, which will serve as a scaffold for tissue generation.
3. Bacteria-tight sealing of the access aperture:

The access cavity is restored using a material that seals it against bacteria. The revascularization technique depends on the induction of bleeding through the open apical foramen into the chemically cleaned canal. The canal dentin and the blood clot[2] provide scaffolds in the root canal revascularization. More recently, platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) are suggested as further possible scaffolds [10].

Mechanism of Revascularization:

1. It is possible that a few vital pulp cells remain at the apical end of the root canal and these cells might proliferate into the newly formed matrix and differentiate into odontoblasts under the organizing influence of cells of Hertwig's epithelial root sheath, which are quite resistant to destruction, even in the presence of inflammation. The newly formed odontoblasts can lay down atubular dentin at the apical end, causing apexogenesis (elongation of root), as well as on lateral aspects of dentinal walls of the root canal, reinforcing and strengthening the root [11].
2. Another possible mechanism of continued root development could be due to multipotent dental pulp stem cells. These cells from the apical end might be seeded onto the existing dentinal walls and might differentiate into odontoblasts and deposit tertiary or atubular dentin [12].
3. The third possible mechanism could be attributed to the presence of stem cells in the periodontal ligament which can proliferate, grow into the apical end and within the root canal, and deposit hard tissue both at the apical end and on the lateral root walls [12].
4. The fourth possible mechanism of root development could be attributed to stem cells from the apical papilla or the bone marrow. Instrumentation beyond the confines of the root canal to induce bleeding can also transplant mesenchymal stem cells from the bone into the canal lumen. These cells have extensive proliferating capacity [13].
5. Another possible mechanism could be that the blood clot itself, being a rich source of growth factors, could play an important role in regeneration. These include platelet-derived growth factor, vascular endothelial growth factor (VEGF), platelet-derived epithelial growth factor, and tissue growth factor and could stimulate differentiation, growth, and maturation of fibroblasts, odontoblasts, cementoblasts, etc from the immature, undifferentiated mesenchymal cells in the newly formed tissue matrix [14].
6. The root anatomy of immature teeth (e.g. presenting open apex, wide root canal and thin radicular dentin walls) may favor the communication of canal space & periodontal tissue to achieve apical healing with periodontal tissue. With regard to the apical opening, revascularization seems to be more predictable when the apical diameter is greater than 1 mm and is unlikely to occur in apical openings narrower than 0.3 mm [15].

Scaffold for Pulp Tissue Regeneration

Blood clot

The utilization of a blood clot to regenerate dental pulp tissues was first practiced by Ostby and resulted in a growth of granulation tissues, fibrous tissues or cementum-like tissues into the root canals [5]. In 1974, Myers and Fountain[16] succeeded to generate 0.1-1.0 mm of soft connective tissues into the root canal using blood clots. The blood clot consists of fibrin matrix that traps cells necessary for tissue regeneration [17]. It also provides a suitable pathway for cells from the periapical area including macrophages and fibroblasts to migrate into the root canal and enhance the new tissue growth [18]. The rich content of growth factors allows the blood clot to play an important role in cell differentiation and thus, promotion of tissue regeneration [19].

Dentin

The root canal space is wholly enclosed by acellular dentin matrix rich with growth factors [20]. Some of them are Growth hormone, IGF-1 and -2, [21] bone morphogenetic protein-2 (BMP-2), -4 and -6, [50] and TGF-β-1, -2 and -3. [20] When released from dentin matrix, these growth factors play a key role in regulation the inflammatory response, tissue healing and regeneration and odontoblast differentiation [21]. EDTA-treated dentin was able to induce the regeneration of complete dentin tissues *in vivo* [20].

PRP and PRF

The PRP was introduced to dentistry world in 1997 by Whitman [22]. It was suggested that PRP is able to attract stem cells from surrounding periapical tissues [10]. When PRP is combined with dental pulp cells, increased vital tissue regeneration was observed in root canals of dog's immature teeth [23]. Clinically, the ability of PRP to create vital tissue in the root canal is relatively faster [10]. PRP is referred as a first-generation platelet concentrate, and the PRF as a second-generation platelet concentrate. PRF was developed first by Choukroun *et al*. (2001). It has the benefit of slow release of growth factors for a prolonged period of 7-14 days. Hence, it is superior to PRP which shows fast release growth factors in 7-14 h [24].

Synthetic polymers

Synthetic biodegradable polymers such as polyglycolic acid (PGA), polylactic acid (PLA) and poly-lactic-coglycolide, application of these polymers as matrices for cell transplantation was the first suggested by Vacanti *et al*. [25] The first attempt for pulp tissue engineering *in vitro* was achieved using PGA with human pulpal fibroblasts. A new tissue-like construct with similar cellularity as in normal pulp tissue could be observed [26]. The poly-L-lactic acid (PLLA) scaffold was able to produce tissue similar in architecture and cellularity to dental pulp tissue when transplanted with human dermal microvascular endothelial cells [27]. or stem cells in human exfoliated deciduous teeth (SHED) into immunodeficient mice [28]. A PGA/PLLA scaffold was also successful for the regeneration of a tooth crown contained enamel, dentin and a well-defined pulp chamber using cells isolated from tooth buds and transplanted into rat omentum [29]. The synthetic open-cell PLA (OPLA) is another promising polymer for dental pulp regeneration. SHED seeded on OPLA and transplanted into cleaned, and shaped canals of human extracted teeth were able to attach to the root canal dentin [30].

Bioactive ceramics

Cells cultured on the porous form of ceramics could attach, proliferate and expressed dentin sialophosphoprotein, which is a dentin marker [31] HA [$(Ca_{10}$ $(PO_4)_6(OH)_2$] has been suggested as an effective scaffold for regeneration of dentin and dentin-pulp complex. HA is a non-biodegradable ceramic while β-TCP [β-TCP $Ca_3(PO_4)_2$] is considered as biodegradable [32]. When pulp-derived cells were mixed with

HA or HA/TCP and transplanted subcutaneously in nude mice, bone and dentin-like mineralized tissues were generated [33].

Revascularization protocol

The first issue is case selection; the best available evidence indicates that this treatment should be considered for incompletely developed permanent tooth that has an open apex and is negative to pulpal responsiveness testing. Teeth with an apical diameter more than 1.1 mm demonstrate a greater likelihood of revascularization [2].

First Appointment

The treatment alternatives, risks, and potential benefits should be described to the patient and guardian after collecting clinical information and establishing pulpal and peri-radicular diagnosis. Following informed consent, the tooth is anaesthetized, isolated and accessed. Minimal instrumentation is done. The root canal system is copiously and slowly irrigated with 20 ml of NaOCl followed by 20 ml of 0.12 – 2% chlorhexidine. Since canal disinfection relies considerably on chemical irrigants, it is important to place the needle into the apical third and irrigate using needles with a closed end and side port vents together with a slow rate of infusion to help to reduce any irrigants passing through the open apex.[34] The canals are dried with paper points, and a mixture of Ciprofloxacin, Metronidazole, and Minocycline paste as described by Hoshino *et al*. [35] is placed with a lentulo spiral instrument to a depth of 8 mm into the canal. If triple antibiotic paste is used, ensure that it remains below CEJ (minimize crown staining). Seal access cavity with 4 mm Cavit and dismiss patient for 3-4 weeks.

Second Appointment:

Patient is evaluated for resolution of any signs and symptoms of an acute infection (swelling, pain, sinus tracts etc).The antimicrobial treatment is repeated if resolution has not occurred. Anesthesia with 3% mepivacaine without vasoconstrictor is used which will facilitate the ability to trigger bleeding into the canal, following isolation and reestablishment of coronal access, tooth should be copiously and slowly irrigated with 20 ml NaOCl, together with gentle agitation with a small file to remove antimicrobial paste. Dry the canal with sterile paper points. Create bleeding into canal system by over-instrumenting (endo file, endo explorer) up to 3 mm from CEJ. A small piece of Colla Plug may be inserted into the root canal system to serve as absorbable matrix to restrict the positioning of the MTA. Place 3-4 mm MTA and reinforced glass ionomer [34].

Although most studies have tended to perform the therapy in two separate sessions, Shin *et al*. [36] performed pulp revascularization in a single visit through root canal decontamination with 6% sodium hypochlorite, sterile saline solution and 2% chlorhexidine, without mechanical instrumentation, followed by MTA/composite resin sealing, demonstrating root-end development and increased width of the dentin walls. The follow-up of clinical cases of revascularization is mandatory to verify clinical success. A period of approximately 6 months is required, after the treatment, to evaluate success and to identify treatment progress [37]. According to Chen *et al*. [38] immature teeth diagnosed with pulp necrosis and apical periodontitis may present four types of revascularization outcome:

Type I, increased dentin wall width and root-end development;

Type II, insignificant continued root development associated with apical closure;

Type III, root-end development without apical closure;

Type IV, calcification (obliteration) of root canal;

Type V, mineralized tissue barrier between MTA cervical plug and radicular apex.

Advantages over current treatment modalities:

There are several advantages to revascularization approach.

1. Obturation of the canal is not required unlike in calcium hydroxide–induced apexification, thus eliminates the chance for root fracture during lateral condensation [34].
2. Achieving continued root development (root lengthening) and strengthening of the root as a result of reinforcement of lateral dentinal walls with deposition of new dentin/hard tissue [39].

Limitations:

There are few limitations for this approach- [34]

1. Long-term clinical results are as yet not available, and source of regenerated tissue has not been identified.
2. Another disadvantage is revitalized tooth may susceptible to further pulp disease and may require retreatment, It is possible that the entire canal might be calcified, compromising aesthetics and potentially increasing the difficulty in future endodontic procedures if required.
3. In case, post and core are the final restorative treatment plan, revascularization is not the right treatment option because the vital tissue in apical two thirds of the canal cannot be violated for post placement.
4. The revascularization method assumes that the formation of a blood clot yields a matrix that traps the cells capable of forming new tissue. But the concentration and composition of cells trapped in the fibrin clot is unpredictable. This limitation can be overcome by use of platelet concentrates. Platelet rich plasma is an ideal scaffold for revascularization.

Conclusion

Induced generation and regeneration of vital tissues in the pulp space can thicken the root structure leading to a stronger tooth with a potentially reduced fracture risk. Apexification procedure may no longer be the preferred first option to treat immature permanent teeth with non vital pulps. Revascularization represents a recent and promising treatment modality that has been in evidence due to the preservation of biological principles and the possibility of minimizing the treatment period of immature teeth.

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