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INVITED REVIEW

Revascularization of Necrotic Immature Permanent Teeth: An Update

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ABSTRACT

In the recent years, there is a paradigm shift in the management of necrotic immature permanent teeth, with most of these teeth being treated by revascularization rather than conventional apexification procedure. Current regenerative endodontic protocols (REP) emphasizes the need to have a disinfection protocols that will enable good disinfection without causing damage to stem cells. The current available evidence suggest that true pulp-dentin complex is not being formed after REP, nevertheless it can result in continued root development that will enable such tooth to survive for a long time. This article highlights the recent trends in revascularization procedures.

Keywords: Growth factor, Immature teeth, Revascularization, Scaffold, Stem cell.

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INTRODUCTION

Endodontic management of necrotic immature human permanent teeth has often been very challenging to clinicians. Traditionally, these teeth have been managed by long-term apexification procedure using calcium hydroxide.[1] Other treatment alternative is by creating an apical barrier using mineral trioxide aggregate (MTA) (Flow Chart 1)[2] and, once this barrier is set, the root canal is obturated. But, both these procedures do not result in continuous root development; hence, these teeth are susceptible to fracture.

Recently, numerous case reports and case series of continued root development in immature necrotic teeth after revascularization procedure have been reported. Revascularization has been reported in immature avulsed tooth after reimplantation and, hence, it may be possible in necrotic immature teeth if the root canal space can be disinfected and the conditions are favorable.[3] Revascularization has been reported to occur not only in single rooted teeth but also in multirooted teeth as well.[4] Bose R et al in a retrospective study using radiographs compared 54 cases of revascularization with 40 control cases which consisted of 20 cases of apexification and 20 cases of nonsurgical root canal treatments.[5] The authors concluded that regenerative endodontic treatment resulted in greater increase in root length than either MTA apexification and nonsurgical root canal treatment control groups. Clinical protocols followed for revascularization by various authors differs considerably and, hence, American Association of Endodontist came out with guidelines for regenerative endodontic therapy (REP) in 2007 which was revised in 2013.[6] This article highlights the current trends in revascularization.

HYPOTHESIS BEHIND CONTINUED ROOT DEVELOPMENT EVEN AFTER PULP NECROSIS

In tissue engineering, the triad of stem cells, scaffold and adequate growth factors can result in regeneration of tissue.[7] Resident stem cells of the pulp, the stem cells of apical papilla or the stem cells of periodontal ligament (PDL)/bone are said to take part in the process of revascularization. It has been found that the stem cells of apical papilla (SCAP) and the stem cells of pulp are highly resistant to infection, and they can even survive for a very long time after pulpal necrosis.[8] The SCAP cells are able to survive even after the necrosis of pulp as they are not richly vascularized and they can derive nutrition by diffusion from the dental epithelium above it.[9] Once the root canal is disinfected, in the presence of a scaffold, these stem cells along with adequate growth factors might result in revascularization of the pulp. It has also been speculated that the presence of Hertwig's epithelial root sheath (HERS) is also necessary for continued root development occur even after pulp death.[10]

HISTORY

1961	Ostby BN[11]	Introduced concept of revascularization
1966	Rule DC and Winter GB[12]	Documented root development and apical barrier formation in cases of pulpal necrosis in children

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1966	Frank AL et al[13]	Introduced a clinical technique to induce apical closure by using repeated $Ca(OH)_2$ dressings
1972	Ham JW et al[14]	Demonstrated apical closure of immature pulpless teeth in monkeys
1996	Hoshino E et al[15]	Triple antibiotic dressing including ciprofloxacin, metronidazole and minocycline
2001	Iwaya SI et al[3]	Revascularization of an immature permanent tooth with apical periodontitis and sinus tract
2004	Banchs F and Trope M[16]	Revascularization of immature permanent teeth with apical periodontitis with triple antibiotic paste (TAP)
2007	Thibodeau B et al[17]	Reported finding of an odontoblastic layer in the root canal structure
2008	Shah N et al[18]	Reported case series—revascularization in 14 cases of immature teeth
2009	Reynolds K et al[19]	Advocated use of dentin bonding agents to seal dentinal tubules prior to placement of TAP to prevent discoloration of tooth
2010	Cohenca N et al[20]	Disinfection of immature teeth by 2.5% NaOCl irrigation using the macrocannula of EndoVac
2012	Lenzi R and Trope M[21]	Suggested the term revitalization as more appropriate because it is descriptive of the nonspecific vital tissue that forms in the root canal
2011	Galler KM et al[22]	EDTA as final rinse decalcified dentin and releases bound growth factors that can attract new cells and promote their differentiation into cells with odontoblast-like properties

Initial Disinfection of the Root Canal

The disinfection of root canal is carried out by gentle irrigation with copious amounts of sodium hypochlorite (NaOCl). Mechanical instrumentation of root canal is generally avoided or kept to a very minimal level for the fear of weakening the thin root canal walls or creating smear layer.[23] Three percent NaOCl is the most commonly used irrigant in most of these case reports. In few of the case reports, 6% NaOCl has also been used. But more recently it has been established that 6% NaOCl exerts untoward effects on the survival and differentiation of SCAP cells, whereas 17% ethylenediaminetetraacetic acid (EDTA) when used had a positive effect on the survival and differentiation of SCAP cells.[22,24] Irrigants used should be able to disinfect the root canals without causing any toxic effects to the stem cells. A recent study reported that 1.5% NaOCl had minimal effects on the stem cells and the subsequent use of 17% EDTA partially reversed the effects of NaOCl.[25] Ethylenediaminetetraacetic acid results in the release of growth factors trapped in dentin matrix.[26] These growth factors are necessary for stem cell proliferation and differentiation. Ethylenediaminetetraacetic acid also enables better attachment and growth of stem cells due to demineralization. A slow gentle irrigation with 20 ml of 1.5% NaOCl initially followed by use of 17% EDTA has been recommended recently.[27]

Chlorhexidine (CHX) has also been used as an irriganting solution for revascularization cases. But, Ruparel NB et al in their study found out that CHX is toxic to the stem cells and, hence, it cannot be used for revascularization procedures.[28] The chances of irrigant extrusion will be very high in these cases with open apex. A recent study has proved that by using the macrocannula of the Endovac, it will be possible to deliver the irrigants without extrusion even in open apex cases.[29]

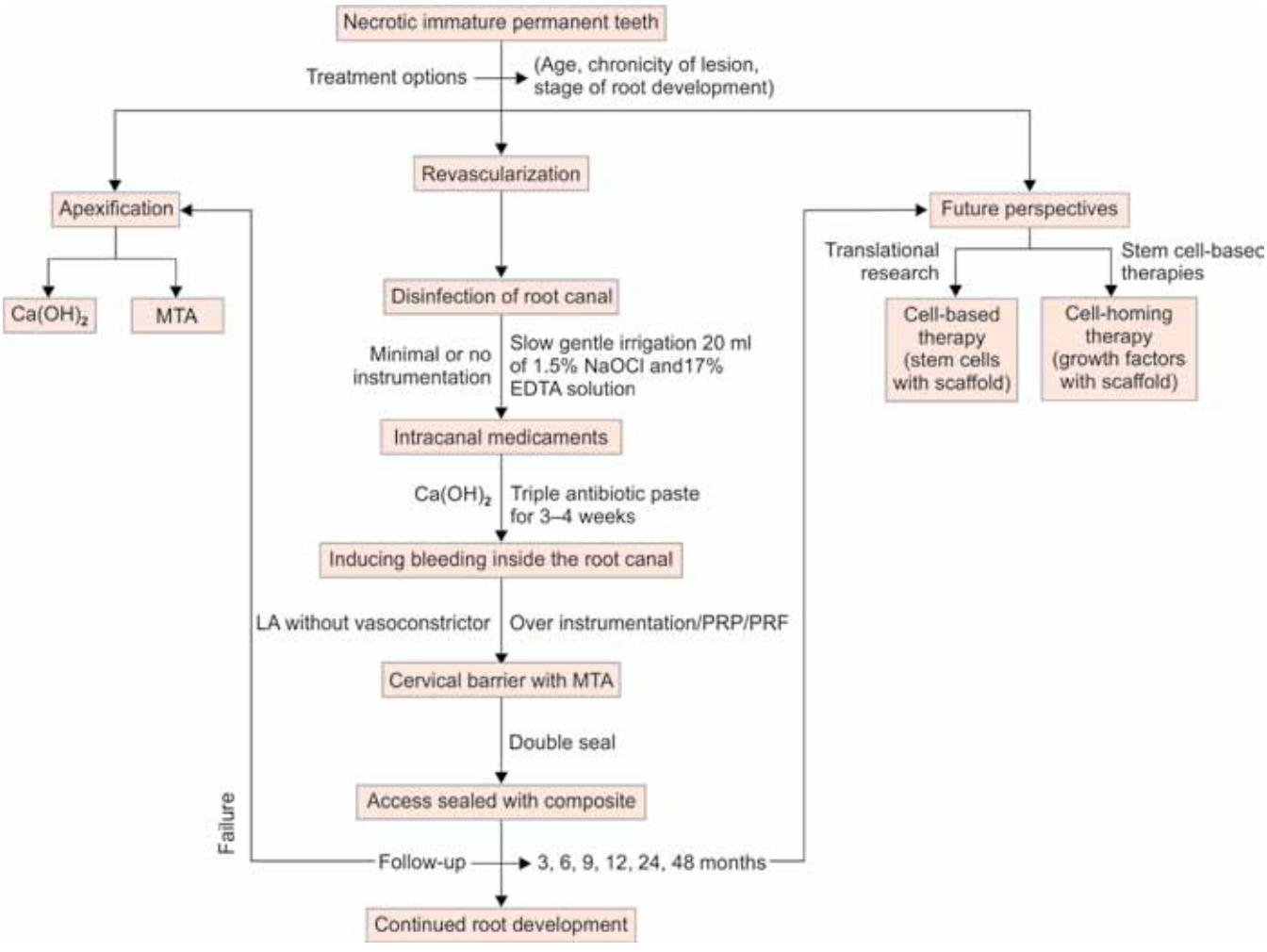
Intracanal Medicaments

Additional disinfection of root canal is achieved using intracanal medicaments. Triple antibiotic paste (TAP) consisting of a mixture of ciprofloxacin, metronidazole and tetracycline has been used in majority of the case reports as a medicament inside the root canal for 3 to 4 weeks.[16] The use of TAP for disinfection is based on an earlier finding by Hoshino et al study, wherein TAP when used as a medicament resulted in deeper penetration and better disinfection of dentin.[15]

Tetracycline causes discoloration, and hence double antibiotic paste consisting of ciprofloxacin and metronidazole has also been used without tetracycline.[3,17] In yet another case report erythromycin was used as a medicament following the use of TAP as the patient had persistent symptoms. A modified TAP consisting of ciprofloxacin, metronidazole, cefaclor or augmentin have also been suggested by Ruparel NB et al.[28]

Few authors have reported successful revascularization after using calcium hydroxide as a intracanal medicament.[30] Since revascularization depends on the survival of stem cells the medicaments used should result in good disinfection without having any untoward effects on stem cells. A recent study reported the effect of various

Flow Chart 1: Treatment option for immature permanent necrotic teeth



medicaments in different concentrations on the SCAP cells. All the antibiotic preparations were toxic to SCAP cells in a concentration dependent manner. TAP in 0.1 mg/ml was nontoxic to SCAP cells. In the same study, they found calcium hydroxide did not have any toxic effect on SCAP cells irrespective of the concentration in which it was used. It also resulted in proliferation of stem cells. Based on these findings, $Ca(OH)_2$ has been suggested as the first choice of intracanal medicament.[28]

DaSilva L et al based on a study in immature dog teeth reported that disinfection of the root canal can be achieved without using TAP. They suggested using macrocannula of the EndoVac to deliver the NaOCl into these root canals to achieve good disinfection.[31] A single visit procedure, wherein there is no need for using any intracanal medicament has been suggested by Shin et al.[32] They demonstrated successful revascularization in a teeth with chronic apical abscess using a single visit procedure.

Initiation of Blood Clot Inside the Root Canal

Intracanal medicament is usually left in place for a period of 3 to 4 weeks and is removed from the root canal following the resolution of symptoms. A reamer or file is used beyond the working length to initiate bleeding into the root canal. Initiation of bleeding inside the root canal will enable the seeding of the stem cells. Blood clot will act as a scaffold and also provide the necessary growth factors.[33] Petrino J et al suggested using a local anesthetic without adrenaline to initiate more bleeding into the root canal.[34] In a yet another case report in a multirooted teeth with insufficient bleeding in one of the canals, blood from adjacent canal was withdrawn and used.[4]

In few cases, successful revascularization has occurred without initiating the blood clot inside the root canal.[35] Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) obtained from the patient have also been used a scaffold instead of blood clot. Torabinejad M used PRP as scaffold for revascularization of a maxillary second premolar teeth.[36] Platelet-rich plasma obtained from the patient was injected into the canal space. The process for preparing PRP is simple and it is easy to use, additionally it contains growth factors, anti-inflammatory properties and promotes healing. Platelet-rich plasma clot also provides a good matrix for correct placement of MTA.[35]

But, the disadvantage of PRP/PRF will be the additional cost and the fear in patients of withdrawing blood. When compared to PRP, the PRF releases growth factors and cytokines slowly in a controlled manner. It has been found that PRF stimulates cell proliferation and differentiation of human dental pulp cells.[37]

Cervical Barrier

Mineral trioxide aggregate has been used in majority of the case reports as a cervical barrier material because of its favorable physical and biological properties.[38,39] A minimum of 4 mm of MTA is necessary to ensure a good seal. Once the MTA is set the access cavity is further restored using composite or glass ionomer cement ensuring a double seal.[40] Correct placement of MTA below the CEJ might be difficult and it has been mentioned in a few cases that it gets pushed at a deeper level. Petrino J et al suggested the placement of collagen matrix over the blood clot which will inturn enable proper placement of MTA.[34]

Nosrat A et al used calcium enriched mixture (CEM) as a barrier material instead of MTA in two of their cases. According to them, CEM is a tooth-colored water-based cement which has physical and biological properties similar to MTA and its surface characteristics is similar to human dentin and, hence, it might promote differentiation of stem cells.[4,41]

HISTOLOGICAL OBSERVATIONS IN IMMATURE TEETH AFTER REVASCULARIZATION

Even though revascularization procedures in immature teeth can lead to resolution of apical periodontitis and further root development, there is considerable controversy with regards to the nature of tissue formed inside the root canal.

Most of the histological studies in animals and histological observations in human teeth have found that the tissue formed in the canal of revascularized teeth were cementum-like, bone-like, PDL-like rather than pulp-like tissue.[17,42,43]

Only in three case reports of histological findings, in human teeth after revascularization have observed vital pulp like tissue. Torabinejad M et al reported vital pulp like tissue without bone formation in a revascularized teeth 14 months after treatment which was extracted due to fracture.[36] Similar histological findings of pulp tissue were reported by Shimizu E et al and Martin G et al in a permanent teeth after revascularization treatment.[44,45] But in two of these cases, the pulp tissue was not necrotic prior to treatment and, hence, it is possible that residual pulp tissue could have been still left in the canal.

Lenzi R et al both have reported that healing of the periapical tissues and root development can occur even in the absence of pulp tissue.[4,21]

DRAWBACKS OR LIMITATIONS OF REVASCULARIZATION

There are several drawbacks and/or unfavorable outcomes after revascularization procedure as follows:

- Discoloration of tooth after revascularization can be due to minocycline used in the TAP[46-48] and can also be due to MTA (gray/white) which is used as a cervical barrier.[34]
- Patient compliance can be a problem as the treatment can take many months to years with multiple clinical appointments.
- The nature of the tissue formed inside the root canal is uncertain, with most of the animal studies and histological findings in human teeth report that the tissue formed inside is cementum-like, bone-like or PDL-like tissue.[17,42,49]
- Poor root development has also been reported by few authors.[10,34] In event of failure of this treatment reentry and canal instrumentation will be difficult.
- Even in successful cases minimal or increased dentin wall thickness occurs in the apical one-third and middle one-third and not in the cervical one-third region—which is more prone for fracture.
- Revascularization depends on the presence of stem cells and growth factors and, hence, it is likely to be more successful only in young individuals and not in older patients.
- Recently, it has been reported that the chances for failure after revascularization is higher in teeth with long standing chronic infection.
- Calcification of the canal space after revascularization is also a commonly noticed phenomenon.[10]
- In growth of apical bone into root canals can interfere with tooth eruption if ankylosis occurs.[10]
- It is still not clear as to how the revascularized tissue will respond when there is fresh infection into the root canal space.

Translational Research in Pulp Regeneration

Stem Cell based Pulp-dentin Regeneration

Even though at present, most of the evidence points toward more of cementum/bone like tissue is being formed inside the root canal, many laboratory-based research has proven pulp regeneration is possible.[50]

Currently, two methods are being tried out in the laboratory level (no clinical trials yet) for regeneration of tissues.

1. Cell-based approach
2. Cell-free approach

Cell-based Approach

It involves the use of exogenous stem cells derived from host or allogenic in nature, being transplanted into the root canal for regeneration. Complete regeneration of pulp with newly generated dentin has been demonstrated by using stem cells in a orthotopic and ectopic animal study model. Human tooth root canals filled with human stem cell of apical papilla (HSCAP) and human pluripotent stem cells (HPSC) and scaffolds when transplanted into immune-compromised mice, there was regeneration of pulp-like tissue as well as layer of dentin-like tissue on canal dentinal walls.[51] Similar findings were also reported by Iohara K et al in a dog teeth.[52] He used cell fractions, such as CD31/CD146 and CD105 side population cells in a collagen scaffold into stromal derived factor 1 for regeneration in human canine teeth after pulpectomy. Pulp-like tissue with blood vessels and innervations were regenerated. The difficulties with cell-based therapies include problems in isolation of viable cells, huge cost and chances of immune rejection.

Cell-free or Cell-homing approach

Cell-homing is another approach which involves induced chemotaxis of endogenous cells. Cell-homing describes the migration and mobilization of cells to the site of regeneration/injury which is induced by biologically signaling molecules. Kim K et al using cell-homing approach was able to regenerate tooth like structure.[53] Anatomically based scaffold made of 80% polycaprolactone (PCL) and 20% hydroxyapatite (HA) embedded with a mixture of stromal derived factor 1, BMP 7 and type 1 collagen solution. Recruitment of endothelial cells and isolated mineralization was seen at 9 weeks. Kim JY et al showed that growth factors like vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), platelet-derived growth factor (PDGF), nerve growth factor (NGF) and bone morphogenetic protein 7 (BMP-7) were all involved as signaling molecules for pulp regeneration. Human extracted canine and incisor root canals when filled with collagen scaffold with growth factors when implanted into mice showed vascular pulp-like tissue with innervation and odontoblastic layer deposition in 3 weeks.[54]

Cell-homing techniques were simpler and economical than the cell-based techniques. According to George T et al, the present procedures for pulp revascularization can be considered as cell-homing approach.[50]

Survival of Tooth after Revascularization

The long-term survival of tooth that has undergone revascularization treatment is not discussed in most of the case reports. American Association of Endodontics (AAE) guidelines suggest following up these cases for up to 4 years.

JojoKottoor J et al reported the survival of maxillary central incisors for 5 years after revascularization.[55] Iwaya S et al followed a case of mandibular central incisors for 13 years subsequent to revascularization. Till date, this is the longest follow-up for revascularization.[56]

Another important aspect that needs to be looked into is the response of the regenerated pulp to future bacterial challenge or physiological stresses inside the oral cavity.

Even though the current evidence suggests that true pulp dentin complex is not formed after revascularization procedure, the ensuing root development that can occur after this type of treatment allows for long-term survival of teeth. Hence, revascularization should be considered as a viable treatment option in necrotic immature permanent teeth with grossly underdeveloped tooth structure (Flow Chart 1).

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