

Maturogenesis: A novel concept based on regeneration for paediatric patients

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Abstract

The problems encountered while treating immature, necrotic teeth has led to a shift in the treatment protocol. The biologically-based principles and regenerative endodontic protocols replacing the traditional methods. Preliminary research suggests that Revascularization has emerged as such an alternative. The stem and progenitor cells from the pulp and/or periodontium lead to root development. The aim of this paper is to accomplish a literature review concerning this novel concept.

Keywords: Maturogenesis, Regeneration, Immature Teeth, Revascularization, Revitalization.

Introduction

The last two decades have seen surplus increase in the clinical “tools” (i.e., materials, instruments, and medications). The knowledge, concepts from the trauma and tissue engineering fields has also revolutionized the treatment involving the dentin-pulp complex.¹

Conventionally, for immature teeth (incompletely developed apices) vital pulp therapy is the ultimate treatment of choice. Scientific evidence report that it is one of the most challenging situations for the practitioner is through debridement of pulp canal space accompanied with increased possibility of root perforation and fractures around the cervical area. The open immature root apex does not let the apical seal of a root canal treatment resulting in subsequent failure.

Among children several other obstacle are seen: history of trauma, anatomical variations of the tooth such as dens invaginatus, and untreated dental caries, patient at prepubertal age is uncooperative.² The walls of the root canal system are very fragile and thin in young patients, intensive biomechanical preparation cannot be achieved and the tooth remains weakened even after successful endodontic treatment. Difficulties are encountered while condensating the filling materials in the root canal system. Henceforth apical seal is also not achieved because of the widely open apical foramen.³ The success rate was quite low.

Kaiser, in the early 60 year proposed the clinical protocol utilizing calcium hydroxide Ca (OH)₂ for the closure of apical seal. It was suggested to repeatedly change of Ca (OH)₂ every 3 to 6 months as it will induce the formation of calcified tissue. This served as the gold standard treatment in such patients for a long time.^{3,4} The flexural strength was compromised making these teeth more prone to fractures.

Recently, a innovative bioactive material, Mineral Trioxide Aggregate (MTA) was introduced, by torabinejad and his colleagues with an aim to overcome

the problems stated above. This new treatment shortened the treatment period and visits and to avoid increased fragility of the teeth.⁵ The major limitation of apexification which uses MTA is discontinuation of root development, making teeth susceptible to cervical root fractures.

In 2001, Iwaya published the very first case report which incorporated tissue engineering technique in the field of modern regenerative endodontic. These Regenerative endodontic procedures are biologically based primarily designed to repair or replace damaged tooth tissue structures, including dentin and root structure, including the cells of the pulp-dentin complex. The internal environment of the root system was modified so to produce a blood clot from which pulp regeneration will occur. Continued root development including apical closure and root thickening was made possible in the absence of true pulp regeneration by inducing environment that permits root maturation. Histological reports define it as a repair process rather than regeneration.⁶ Consequents reports have been published by Huang GT, Ghorbanzadeh A et al and Mustafa MM.⁷⁻⁹

This process explained above is known as Maturogenesis. It has been defined as physiologic root development, not restricted to the apical segment. The continued deposition of dentin occurs throughout the length of the root, providing greater strength and resistance to fracture.

However, there are still uncertainties regarding the correct terminology, and several different terms are used for these procedures. There is paucity of literature related to this concept especially in the field of pediatrics. Hence this review was attempted to throw light in this direction which would help the clinician to successfully manage the cases encountered in routine practice.¹

Regenerative endodontic: Terminologies

Revascularization: Iwaya coined this term for the first time.¹⁰ This term was subsequently defended by claiming that the nature of the tissue inside the root system was not predictable. However, the term “revascularization” indicates the restoration of blood supply to the already damaged tissue.¹¹

Revitalization: This term refers to the presence of nonspecific restoration of the vital tissue within the root system, without its relation to the formation of hard tissues and further development of the root.¹²

Regenerative endodontic procedure (REP): This term officially coined by the American Association of Endodontists (AAE), which includes therapies employing the principles of tissue engineering leading to the restoration of tissue resembling dental pulp. Unfortunately, even under sterile conditions in animal models, it was not possible to use the current protocol of maturogenesis to stimulate the regeneration of the dental pulp or similar tissue.¹³⁻¹⁶

Maturogenesis: This was firstly used with direct capping of the pulp of immature permanent teeth. It describes the physiological continued development of the entire root, and not only the apical segment.^{9,17}

Regenerative endodontic: Tissue engineering

A multidisciplinary field combining engineering, medicine and biology with an aim to restore the function of damaged or completely destroyed tissues or organs. It is the knowledge of growth factors effecting broad range of cellular activities including migration, proliferation, differentiation and apoptosis of dental pulp as well as stem/progenitor cells. Its main components are: stem cells, tissue factors, and internal matrix.¹⁸

1. Stem cells: The multipotent mesenchymal stem cells (MSC) play an important role in maturogenesis. Niches, small defined areas are present in them through which regulation occurs. These niches are seen mostly perivascularly⁽¹⁹⁾ and have three basic features.^{20, 21} An anatomical area, is formed where these stem cells are regulated. It also affect the stem cells mobility. These stem cells are maintained in a quiet mode, when necessary, their differentiation is induced and their regenerative capacity is set in. Stem cells do

survive under certain environmental conditions in the root canal system. They may also be actively transported to the root system by blood, or they may be attracted by tissue factors on the “cell homing” principle.

- a. **Stem cells of apical papilla (SCAP):** The most important role in maturogenesis is played by these cells. These are basically the precursors of radicular pulp, which are less differentiated^{22,23} and primary odontoblasts involved in the formation of radicular dentin. It is probably due to the proximity of the apical papilla to the apex that much higher concentrations of mesenchymal stem cells occur in blood from periapical region than in the bloodstream.²⁴
 - b. **Dental pulp stem cells (DPSC):** Their role in maturogenesis is assumed when necrosis extends coronapically. There have been cases reporting that apical residual pulp was probably present in an immature tooth with an extensive periapical finding.^{25,26} It was also shown that the DPSC were present unchanged in teeth with irreversible pulpitis.^{27,28}
 - c. **Periodontal ligament stem cells (PDLSC):** The ability of these cells to form calcified tissues is significantly lower compared to the above mentioned cells.^{29,30}
 - d. **Inflammatory periapical stem cells (iPAPSC):** These are stem cells around the periapical granulomas or periapical cysts.^{31,32} It is unlikely that these stem cell lines could play a big role in maturogenesis.
 - e. **Bone marrow stem cells (BMSC):** These are very heterogeneous, well-researched mesenchymal stem cells, with limited role in maturogenesis.
- 2. Growth Factors:** Tissue factors encased in the collagen matrix of dentin during dentinogenesis play a major role in maturogenesis. They modulating cell behaviour by acting as signalling molecules. They mediate intracellular communication. They are polypeptides or proteins that bind to specific receptors on the surface of target cells and act locally on target cells. Recent work enlist the following growth factors (Table 1):

Table 1: Growth factors in regenerative endodontics

S No.	Growth factors
1.	Cytokines- initiate a cascade of intracellular signalling and acting in either autocrine or paracrine manner. ^{32,33}
2.	Platelet-Derived Growth Factor (PDGF): It is released by platelets, and has potency in promoting angiogenesis and cell proliferation.
3.	Transforming growth factor- β (TGF β): They monitor cellular activities, such as cell proliferation, cell differentiation, cell migration and extracellular matrix synthesis, cell proliferation and production of the extracellular matrix in dental pulp tissue culture are regulated by this, and

	promotes odontoblastic differentiation of dental pulp cells. ^{35,36}
4.	Vascular Endothelial Growth Factor (VEGF): It is a heparin-binding protein and functions are proliferation of endothelial cells and their enhanced survival, stimulating neovascularization in the area of injury. ³⁹
5.	Bone Morphogenetic Protein (BMP): It is subgroup of the TGF β . This super family is involved in biological activities such as cell proliferation, differentiation, and apoptosis. They have very strong osteoinductive and chondrogenic effects, inducing mineralization. ^{37,38}
6.	Fibroblast Growth Factor (FGF): During embryonic development and wound healing, They plays key roles in cell migration, proliferation and differentiation. It also regulates tooth morphogenesis by controlling cell proliferation and differentiation. It is a potent angiogenic factor stimulating new blood vessel formation in the dental pulp, along with PDGF, and VEGF. ⁴⁰
7.	Insulin-like Growth Factor (IGF): They are single chain polypeptides. Their sequence is similar to proinsulin. They contribute in odontogenesis and dental tissue repair through cell proliferation and differentiation. ⁴¹
8.	Nerve Growth Factor (NGF)/ Neutrophins: They promote the survival and maintenance of sympathetic and sensory neurons. They also induce the differentiation of immortalized dental papilla cells into odontoblasts. It acts as a stimulant for mineralization. ⁴²
9.	Dental Pulp/Dentin Regeneration by Cell Homing: A recent study reported , cell homing approach. The regenerate of the pulp-dentin complex occurs by the delivery of growth factors rather than cells in entire human teeth following root canal treatment. Various growth factors, including NGF, PDGF, bFGF, VEGF and BMP7 were delivered singularly or in combination into root canal spaces of endodontically treated human teeth (without gutta percha filling). ⁴³

3. Internal matrix: Scaffold

In tissue engineering, seeding of cells on scaffolds is known as 'creating a tissue construct'. This is essential to promote the formation of higher order tissue structures on which bioactive molecules called growth factors are embedded.

A 3D, physico-chemical-biological microenvironment is established at a local site where the framework for cell growth, differentiation and organization takes place. It should be porous so as to allow for placement of cells, biocompatible with host tissue and biodegradable so that it can be easily replaced by regenerative tissue.¹⁸ It should also allow for transportation of nutrients and waste and removal of waste products.⁴⁴ It can be natural (collagen, dentin, fibrin, silk, alginate), and degraded enzymatically or synthetic (various polymers like PLA, PGA, etc.) and degraded by simple hydrolysis respectively.⁴⁵

The blood clot formed after the stimulation of bleeding in the periapical area was used as scaffold on a wide scale for many years. However some studies have also reported PRGF as an alternative to the blood clot scaffold. In vivo tests on dogs were done to examine the quality of the resulting tissue using blood clot or PRGF, no difference was found between these two matrices in terms of success of the apical closure, the amount of the newly formed tissue and its quality.⁴⁶⁻⁴⁸

As the tissue-engineered pulp is not required to provide any structural support to the tooth. Therefore this tissue can be administered in a soft three-dimensional scaffold matrix framework. A polymer hydrogel, having similar physical properties to that of living tissue: high water content, soft and rubbery consistency and low interfacial tension with water or biological fluids was injected at the site (injectable scaffold delivery). This Research focused on making hydrogels photo-polymerizable or self-hardening e.g., silanized hydroxyl-propyl-methyl cellulose, so that they form rigid structures once they are implanted into the tissue sites.⁴⁹

Another injectable scaffold under research is: tricalcium phosphate. β -tricalcium phosphate. This is an alginate in gel phase and forms beads in solid phase. Treated dentin matrix also provides suitable environment for regeneration of dental tissue. Silk scaffolds are being used for mineralized osteo-dentin formation. The size and shape of silk scaffold pores guide mineralized tissue. A new material: Enamel matrix derivatives (Emdogain) with amelogenins as a major component have also been used as potential scaffolds.^{49,50}

Clinical Protocol

On the recommendations of the AAE, Regenerative endodontics committee in 2006 was established suggesting a workflow. In April 2015, the latest version was regarding the concentration of irrigating solutions and medications within the root canal. This standard protocol recommended two visits therapy, although successful case studies have been reported with one-visit therapies only.⁵¹

The general indications and contraindications for maturogenesis fall in line to the indications and contraindications for endodontic treatment.

Absolute indications

1. Tooth development status and diagnosis
2. The choice for permanent immature necrotic teeth where repeated access to the root system can be achieved.

Relative indications

1. Cvek classification:
Stage 1 to stage 3: When the Root is in early stage of development
In later stages of Stage 4 and stage: MTA apexification is more favourable.

Absolute contraindications

1. Any history of allergy to antibiotics used in the TAP / DAP
2. Tooth destruction.

First Visit

- a. Local anesthesia application is done, rubber dam placed and access cavity prepared.
- b. The working length is determined with help of an apex locator and verification done using a measuring radiograph
- c. Rinsing the canal with 20 ml of 1.5% NaOCl solution for five minutes.
- d. The tip of the irrigating cannula should be introduced approximately 1 mm from the end of the root canal to minimize the cytotoxic effect on the apical tissues.
- e. Subsequently, 20 ml of saline solution is flushed in the canal for five minutes.
- f. Paper points are used to dry the canal.
- g. Medication is introduced into the canal
- h. Firstly, Ca(OH)₂ is applied via a cannula into the coronal third of the root or secondly, The antibiotic mixture is administered via a cannula (20 G diameter) 2 mm from the end of the root canal .
- i. The other end of a paper point, can be used to achieve the condensation
- j. Temporary closure. It is necessary to apply a sterile spacer, usually in the form of a Teflon tape. Application of a 3-4 mm thick GIC is subsequently recommended, or a sandwich-type filling material using calcium sulfate material and an adhesively fixed flow composite

Second Visit

- a. The second visit is scheduled 1–4 weeks after the first visit. There should be an absence of clinical symptoms.
- b. If not, repeat the first visit.
- c. Local anesthesia without epinephrine (3% mepivacaine) is used and use a rubber dam applied.
- d. Removing the temporary fillings and repeated lavage with 30 ml of EDTA solution for 10 minutes.
- e. Drying with sterile paper points.
- f. Creating a suitable environment in the root system, using one of the two possible techniques: Induction of bleeding and clot stabilization.

The care needs to be taken so that the Hertwig's epithelial sheath is not damaged during the induction of bleeding, as it plays a pivotal role in the further development of the root. The use of sterile K-file instruments of size ISO 20-25 is recommended, which should be pre-curved by about 30° in order to induce greater irritation of the apical tissues and substantial bleeding. This instrument is to be inserted 2 mm beyond the physiological apical foramen and then rotated. As there is rich blood supply to the apical papilla, bleeding immediately occurs. The opposite end of a sterile paper point is soaked in physiological saline and attempt is made to stabilize the clot at roughly the level of CEJ. After about 15 minutes, the coagulum achieves stability.⁵²

1. Application of collagen foam to the unstable clot at roughly the level of CEJ can also subsequently act as matrix for the application of MTA.
2. Application of PRGF: PRGF is administered via a cannula into the root system. PRGF is fully stable after 5 minutes.
3. Application of MTA. MTA should be applied coronally at about the level of CEJ. In frontal region it is recommended to place the MTA rather below the CEJ because of the possibility of discoloration.
4. Another possibility is to use a nonstaining alternative to MTA, such as calcium silicate materials also known as bioceramics— the second generation (e.g. Biodentin, SEPTODONT, France) or third generation (e.g. BC RRM Fast Set Putty, Brasseler, Canada).
5. Completion of 3–4mm thick layers using GIC or adhesive filling.

Evaluation of Success of the Therapy

1. If there is no pain and the tooth is clinically asymptomatic, therapy is a success.
2. Control radiographs made 3, 6, 9, 12, 18, and 24 months after the therapy and then at yearly intervals for as long as 5 years.

Primary goal: The reduction or loss of periapical translucency radiographically.

Secondary goal: Increase in the thickness of the root wall and the root length and the degree of closure of the apical region.

Tertiary goal: Restoration the function of the pulp, particularly the sensitive and immunologic function.

If the tooth is clinically calm after maturation, it is recommended not to carry out subsequent endodontic treatment. This is based on the recommendations for treatment of teeth with a calcified or obliterated root system after trauma

Discussion

A new promising treatment for non-vital immature teeth with a wide, open and blunderbuss apex is Revascularization or maturogenesis. It re-establishes the repair, vitality and regeneration of tissues resulting in further growth of the underdeveloped root and leading to thickening of fragile dentin walls. The primary requisite of this therapy is to create an aseptic environment so that in-growth of new tissues can take place inside the root canal space further leading to completion of root development and periapical closure. The usage of tri-antibacterial paste consisting of ciprofloxacin, metronidazole and minocycline is very effective in disinfection of the canal. The kill the bacteria present in the deep layers of root canal dentin and also effective against all types of pathogens which cause endodontic failures.^{53,54} These triple antibiotic paste does cause crown discoloration which can be minimized by placing the paste one mm below the CEJ of the tooth as reported in literature by various authors.^{55,56} Authors have suggested that sealing of dentinal tubules within the chamber can be done to decrease the intensity of discoloration.^{57,58}

Research shows that three crucial components essential for the successful outcome of this procedure are firstly the stem cells which help in differentiation and supports the root development. An abundant number of undifferentiated mesenchymal cells into the pulp space are generated. These progenitor cells might play an essential role in regeneration of pulpal tissues. Secondly the growth factors which induce cellular proliferation and differentiation and third and last component is the physical matrix or scaffold which initiate differentiation and growth of new cells as an empty canal will not lead to in-growth of tissues from the periapical area. Thirdly, the scaffolds which can be of natural blood clot, collagen and Platelet-Rich-Plasma for the revascularization process. They provide structural and biological supports for cellular activities.^{59,60}

The traditional method to obtain fresh blood clot is extremely difficult and painful especially in pediatric patients. Also the maintenance of blood clot within the canal and placement of MTA over this blood clot technically becomes a difficult procedure. Also the

condensation of MTA results in apical displacement of the material.^{5,13,14,15,17}

These lead to introduction of a new biologically based scaffold matrix i.e. PRF. It is a PRF; an autologous healing biomaterial contains platelets, leukocytes, growth factors and key healing proteins (cytokines) in a dense fibrin matrix. It causes proliferation of human dental pulp cells and increase in protein synthesis and alkaline phosphatase activity. The human dental pulp cells present in the apical papilla remain vital and might differentiate into odontoblasts like cells under the influence of hertwig's epithelial root sheath (HERS) thereby enhancing the development of both hard and new tissue within the empty canal space. Although it is a difficult to handle due to its jelly consistency and requires specialized equipment for its processing.^{8,9,11}

To summarize, Revascularization procedures are appropriate treatment which promote maturogenesis, as well as bony healing. Several case reports on endodontic regeneration have used varying treatment protocols. The materials used for scaffold are accompanied by several advantages and disadvantages which need to be explored in consequent researches so that they can be utilised to their maximum potential. Human histological studies are the need of the hour essential to evaluate whether the revascularization procedure truly replicate the pulp-dentin complex. Clinical trials are also required to assess the overall outcomes of the procedure.^{23,24,44,52}

Conclusion

This treatment does gives favorable results when followed strictly for treatment of immature permanent teeth with necrotic dental pulp is very demanding due to weak cooperation of the patient and the. As it is very sensitive and has to be followed strictly. It does bring significant thickening of the root wall as compared to other treatment modalities. The complete recovery of the pulpodentinal tissue in the real sense is not achieved yet it is assumed that the reparative apposition of hard tissues on the inner surface of the tooth improves its mechanical properties, especially with an early stage of root development. Several limitations are encountered with this therapy are: Discoloration, the time required for disinfection of the root canal space with triple antibiotic paste or calcium hydroxide and increased number of clinical sessions, Poor Root Development, insufficient bleeding, Root Canal Calcification/Obliteration, the need for a highly skilled treating dentist which needs to be explored in further researches.

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