Case Report

Pulp Regeneration in an Immature Maxillary Central Incisor Using Hyaluronic Acid Hydrogel

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Abstract

Pulp regenerative procedure is one of the treatment options for endodontically involved immature permanent teeth. The regenerative endodontic procedure was performed in a child of 9 years. After thorough canal disinfection using triple antibiotic paste for 21 days, bleeding was induced from the apex to provide for the stem cells. After that hyaluronic acid (HA) hydrogel was introduced into the canal space to act as injectable scaffold for pulp regeneration. This was followed by mineral trioxide aggregate placement to provide tight seal from the coronal aspect. Later, the tooth was restored with composite restoration. This approach offers the clinicians great opportunity to physiologically strengthen the immature root walls. The present report presents a regenerative endodontic procedure with HA hydrogel for a traumatized central incisor with arrested root development. The continued root development in the present case suggests that this treatment option may be able to resume the root maturation process in immature teeth with open apices.

Keywords: *Gengigel, immature permanent teeth, pulp regeneration*

Introduction

The management of endodontically involved permanent immature teeth poses many potential complications. Different treatment options include apexogenesis, apexification, and pulp regenerative procedures depending upon the pulpal status. Apexogenesis is not possible in cases where the radicular pulp is either inflamed or nonvital. For those cases, we are left with either apexification or pulp regeneration. Pulp regeneration offers the clinicians a great opportunity to avoid need for multiple visit apexification with calcium hydroxide or artificial barrier with either mineral trioxide aggregate (MTA) or biodentine. This treatment approach has the potential to physiologically strengthen the immature root walls. Furthermore, long-term calcium hydroxide treatment may leave the tooth even weaker and more susceptible to fracture, emphasizing the need for an improved treatment technique. Single-visit apexification procedures provide adequate apical stop to accomplish further root canal treatment but do not physiologically strengthen the root walls.

Pulp revascularization is very technique-sensitive procedure. It is necessary to create an environment conducive to revascularization of the root canal system. Prerequisites for tissue regeneration are bacteria-free canal, stem cells, scaffold, and growth factors.

Bacteria-free canal can be achieved by the use of either calcium hydroxide[1] or triple antibiotic paste.[2] Stem cells can be either placed from outside source like transplantation of dental pulp or other stem cells[3] (dental pulp stem cells, stem cells from human exfoliated deciduous teeth, periodontal ligament stem cells, and stem cells from the apical papilla) or from induced bleeding from the periapical area. Induction of a stable blood clot will not only serve as a scaffold but also provide factors that stimulate their cell growth and differentiation of these cells into odontoblast-like cells.[4,5] Scaffolds provide a framework through which cells and a vasculature can grow.[6] Various synthetic and natural biomaterials have been investigated as scaffolds for dental pulp regeneration such as hydrogels, extracellular matrix, and bioceramics.[7] Hyaluronic acid (HA) is a ubiquitous molecule of connective tissues and is a promising biomaterial in the field of tissue engineering and regenerative medicine.[8] Its properties include

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biocompatibility, biodegradable, its metabolites have been shown to promote angiogenesis, a key process in tissue regeneration, and have been found to primarily modulate the development of dentin and enamel matrix during tooth formation.[9,10] Most of the biomaterials that have been proposed as scaffolds for dental pulp regeneration lack approval from the Food and Drug Administration (FDA), but HA is the FDA approved drug and thus was chosen for the regenerative endodontic procedure.[11] Furthermore, *in vitro* study has proved its role in construction of dental pulp-like tissue.[8] HA is bioactive, nonimmunogenic, and nonthrombogenic.[12,13]

Cell differentiation results from a study by Chrepa *et al*. demonstrated the ability of Restylane (HA hydrogel) to stimulate stem cells from the apical papilla mineralization, and odontogenic differentiation.[11]

Growth factors are proteins that bind to receptors on the cell and act as signals to induce cellular factors found in platelets and dentin. Dentin contains a number of bioactive molecules that, when released, may play an important role in the regenerative procedures.[14] Oligosaccharide HA fragments' interaction with vascular endothelial growth factor can induce angiogenic response greater than the sum of that provoked by each agent individually.[15]

There is currently no other reported clinical case that used HA hydrogel in regenerative endodontic therapy. The present report describes the regenerative endodontic treatment of a necrotic, immature maxillary central incisor using HA hydrogel and shows the continued root maturation in the tooth with arrested root development.

Case Report

A 9-year-old child presented to the postgraduate pedodontic department with broken upper anterior tooth. The patient was asymptomatic now and gave history of sensitivity to cold 1 year back when the patient's anterior tooth was fractured due to fall. On intraoral examination, the tooth 21 was fractured [Figure 1] and had no response to Endo-Ice (Coltene/Whaledent), electric pulp test (SybronEndo), and nontender to percussion. The tooth had probing depths of 2–3 mm with normal physiological mobility. Radiographic examination revealed that tooth 21 had open apex [Figure 2]. Adjacent teeth 11 and 22 were unremarkable on clinical and radiographic examination; 21 was, therefore, diagnosed with pulp necrosis and asymptomatic apical periodontitis.

Because of the presence of open apices on tooth 21, treatment options of apexification or pulp revascularization using HA hydrogel were discussed. The patient elected to have pulp revascularization. Informed consent was reviewed and signed. The pulp revascularization therapy for tooth 21 was performed. Access was made to the pulp space where a necrotic pulp was confirmed clinically. Working length

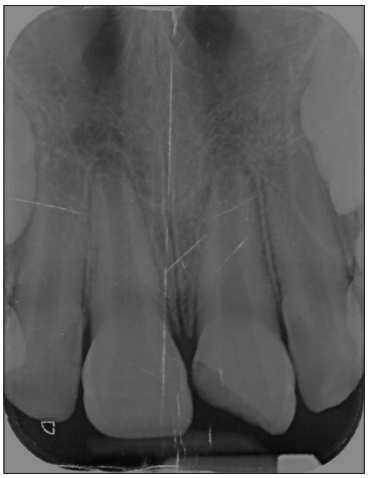

Figure 1: Preoperative radiograph illustrating fractured upper left central incisor

was taken, but the canal was not instrumented in the normal manner. Copious irrigation with 1.25% sodium hypochlorite (NaOCl) was done and dried with sterile paper points. A creamy paste of equal proportions of metronidazole (Flagyl, Abbott, India), ciprofloxacin (Ciplox, Cipla, India), and cefaclor (Keflor, Ranbaxy, India) mixed with sterile water was applied to the canal space with a lentulo spiral in a slow-speed handpiece. The paste was tamped down in the canal space using the blunt ends of sterile paper points 2 mm short of working length. The access cavity was closed with cotton pellets, followed by glass ionomer cement for coronal sealing.

The patient was recalled after 21 days. Under local anesthesia and rubber dam isolation, the canal was reentered, copious irrigating with 1.25% NaOCl was done, and antibiotic paste was washed off and to make space for a blood clot. No instrumentation of the canal space was performed. The apical tissues were stimulated with a sterile endodontic file to induce bleeding into the canal space. After that Gengigel (Ricerfarma, Milano, Italy) was inserted into the canal space [Figure 3]. White MTA (Dentsply) was then mixed with sterile water and applied over the blood clot. A cotton pellet moist with sterile water was placed over the MTA and after approximately 1 h, it was removed. The MTA exhibited a hard set [Figure 4].

To have immediate seal of the canal space, the composite build was done [Figure 5]. The patient was recalled for follow-ups at regular intervals for 12 months after the gengigel placement. Radiographs revealed normal periapical structure with continued root development, but it was nonresponsive to stimulation with CO_2 ice [Figure 6]. Even if the tissue in the canal space undergoes necrosis and subsequent infection at a later time, the prognosis for conventional endodontic therapy would be much better than had it been attempted with the open apex.

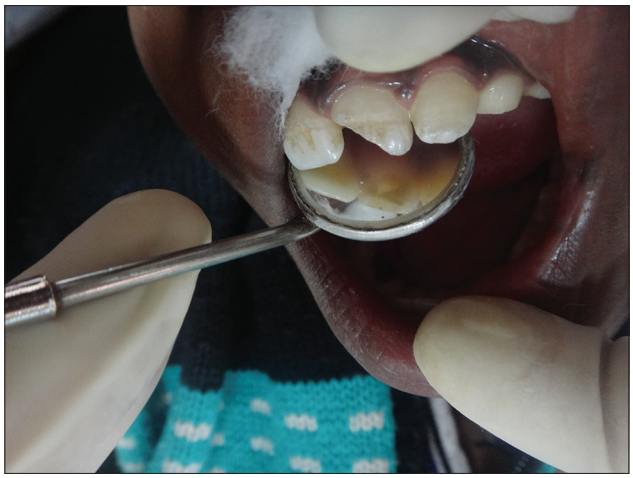

Figure 2: Intraoral photograph depicting fractured upper left central incisor

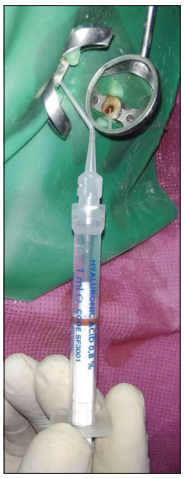

Figure 3: Intraoperative photograph depicting Gengigel being injected in the canal of the upper left central incisor

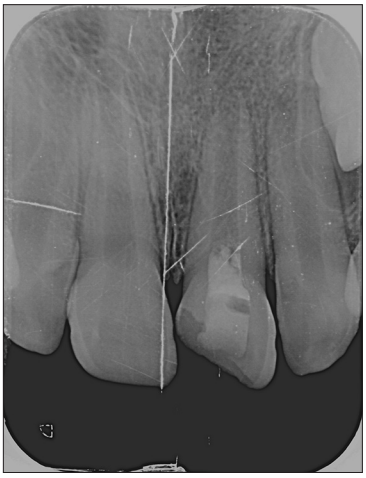

Figure 4: Immediate postoperative radiograph with mineral trioxide aggregate placed inside the canal of the upper left central incisor

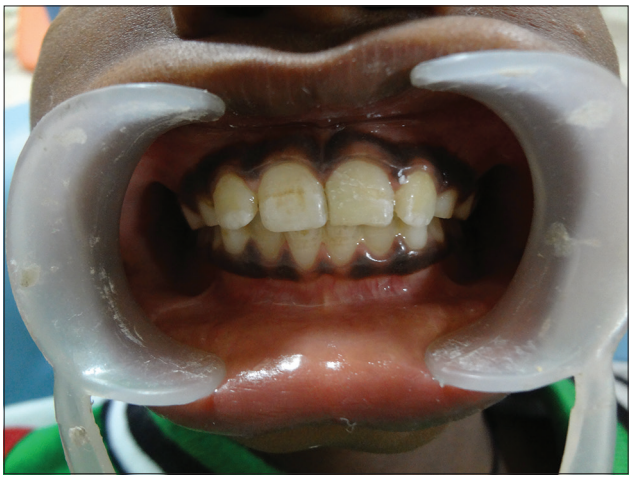

Figure 5: Postoperative photograph with restored upper left central incisor

Discussion

The revascularization technique allows the growth of root, thus reducing the risk of thin and fragile walls. This is not the case with apexification treatment. Immature teeth with a large open apex and short roots seem to be more conducive to the successful treatment of pulp revascularization. Regenerative endodontic treatment has been investigated using different treatment protocols by as documented in case reports/series.[16,17] Different scaffolds have been used for pulp regeneration in animal studies and human clinical trials.[18,19] However, HA has not yet been used in regenerative endodontic therapy in humans, although it had been tested in several clinical trials for periodontal regeneration.[20] The present report describes a regenerative endodontic treatment using HA in a necrotic, immature central incisor that achieved continued maturation in the roots.

In previous case reports, induced blood clot, platelet-rich fibrin,[21] collagen, and poly-lactic co-glycolic acid have been used as scaffold.[19] The blood clot provides a provisional scaffolding which enables the formation of a temporary matrix in the wound bed. Besides fibrin molecules, the main component of this temporary, hyaluronan-rich matrix is also plasma fibronectin, which shows highly adhesive properties entering the interaction with numerous cells by integrin receptors and stimulates the migration and adhesion of fibroblasts, keratinocytes, and endothelial cells. Adding artificial HA (Gengigel) in conjunction with blood clot can be beneficial as HA determines tissue hydration, functions as a signaling molecule, interacts with cell surface receptors, and stimulates cell proliferation, migration, differentiation, and gene expression.[22] Linhua *et al*. utilized HA as an injectable scaffold in combination with dental mesenchymal cells to form a cell–scaffold composite that was then transplanted subcutaneously into nude mice to regenerate dentin–pulp-like tissue.[12]

Shreya *et al*. performed a study to assess the regenerative potential of young permanent immature teeth with necrotic pulp using either blood clot scaffold or combination of blood clot and an injectable scaffold impregnated with basic

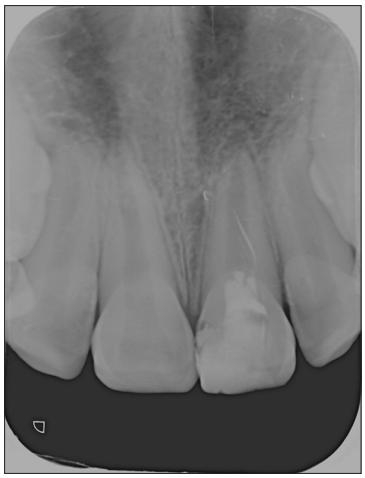

Figure 6: Postoperative radiograph after 1-year follow-up illustrating apical closure in the upper left central incisor

fibroblast growth factor. A significant increase in root width and length using a hydrogel containing basic fibroblast growth factor was demonstrated.[19] Nagy MM *et al*. showed that HA enhanced early mineralization of dental pulp cells mediated through the cell-surface glycoprotein CD44 and emphasized the promising properties of HA as a scaffold for dental pulp engineering.[23]

Chrepa *et al*. evaluated Restylane (injectable HA hydrogel) as scaffold for dental pulp regeneration in a study and their research provided evidence that Restylane promoted cell viability, mineralization, and odontoblastic-like differentiation when cultured with stem cells of the apical papilla. Thus, they reported for the first time that Restylane (FDA approved) can be a promising scaffold for chairside regenerative endodontic procedures and that it may, along with other factors, lead to dental pulp regeneration. Restylane may provide stem cells with structural, mechanical, and biological properties for a longer period of time than blood clot or platelet-rich plasma because it has a lifetime of 6 months according to the manufacturer.[11]At present, no other reported clinical case that used HA hydrogel in regenerative endodontic therapy. There was continued root maturation in the immature incisor in the present report. However, further studies need to be carried out to evaluate the actual role of HA in regenerative endodontic procedures as well its comparison to blood clot or platelet-rich plasma currently being used as scaffolds in regenerative endodontic procedures.

Conclusion

The present report represents a regenerative endodontic procedure with HA hydrogel for a traumatized central incisor with arrested root development. The continued root development in the present case suggests that this treatment option may be able to resume the root maturation process in immature teeth with open apices. Further clinical studies are required to investigate the efficacy of HA hydrogel in regenerative endodontic treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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