Clinical Management of Avulsed Permanent Incisors Using Emdogain: Initial Report of an Investigation

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Abstract

The enamel matrix derivative Emdogain was recently approved for clinical use in a number of countries, including Canada. It has been shown to stimulate regeneration of periodontal ligament following periodontal surgery in adults. This paper reviews pertinent clinical and laboratory studies of Emdogain and describes the protocol and methods used for a longitudinal outcome study of replantation of avulsed permanent incisors in children and adolescents. Application of these methods is described in an illustrative case report of Emdogain use. This paper is meant to inform clinicians and guide those who are instituting similar investigations.

MeSH Key Words: *dental enamel proteins/therapeutic use; incisor/injuries; tooth avulsion; tooth replantation*

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Guidelines and treatment protocols for the management of avulsed permanent teeth have been published and recently reviewed.[1-3] Consensus opinion is that predictable post-replantation healing with the re-establishment of a normal periodontal ligament (PL) is not yet possible. Replanted incisors commonly undergo pulpal necrosis and are extracted because of external root resorption or become ankylosed and infraoccluded.[4] Barrett and Kenny[5] reported that the expected five-year survival rate of replanted permanent maxillary incisors in children is 57%. Furthermore, all surviving incisors are affected by external root resorption. Andreasen and others[6] reported that 30% of all replanted permanent maxillary incisors were extracted over the course of a large clinical study that involved both children and adults. These results support a guarded long-term prognosis for replanted incisors in children and adolescents.

Andreasen and others[6] also showed that minimal extra-alveolar time was linked to prediction of the prognosis of avulsed teeth. Extra-alveolar duration in excess of five minutes was associated with a decreased likelihood of PL regeneration (assessed radiographically). These results support the findings of Andersson and Bodin,[7] who found that external root resorption was not likely to be found in avulsed teeth replanted within 10 minutes but was found in 50% of teeth replanted between 10 and 15 minutes. Clearly, immediate replantation has an overwhelming influence on the outcome of replantation.

Despite the importance of minimizing extra-alveolar duration, immediate replantation is usually not performed. In a recent clinical study, Barrett and Kenny[5] reported that the mean extra-alveolar duration of 58 replanted incisors was 114 minutes. Based on these findings, it can be concluded that most replanted teeth have guarded prognoses.

Laboratory Studies

Clinical studies are supported by investigations of the influence of extra-alveolar duration on PL cells, which play a predominant role in the regeneration of wounded periodontium. Cells with some characteristics of early PL progenitors are found in the middle portion of the PL or are derived from the surrounding alveolar socket.[8] Wounding the PL causes these cells to proliferate, migrate and produce cells that can synthesize alveolar bone, cementum and PL.[9]

Studies of the proliferative (clonogenic) capacity of human PL cells from the root surface have demonstrated that they are very sensitive to extra-oral storage time and conditions.[10] The proliferative capacity of cells obtained from the PL of avulsed teeth is crucial for repopulation of the PL. A reduced percentage of progenitor cells significantly affects healing and adversely affects the survival of replanted teeth. However, factors capable of augmenting cell repopulation (e.g., growth factors or extracellular

matrix) could promote PL cell repopulation and regeneration even if a reduced number of viable PL cells were present.[10]

Recently, a therapeutic agent that promotes PL regeneration after periodontal surgery was approved for use in North America. Enamel matrix derivative (Emdogain, Biora AB, Malmo, Sweden), extracted from developing embryonal enamel of porcine origin, contains proteins of the amelogenin family.[11] It is dispensed as a sterilized aqueous solution of propylene glycol alginate.

The precise mechanism of action of Emdogain is unknown, but in vitro studies have demonstrated that it influences the migration, attachment, proliferative capacity and biosynthetic activity of PL cells.[11] Emdogain has been shown to enhance PL cell proliferation and protein production in addition to promoting mineral nodule formation by PL cells. Emdogain may act as a matrix for cells responsible for regenerating PL at a wound site.

Since the innovative mechanism is designed to produce new PL from socket-side PL cell populations, there are marked changes in methodology from conventional guidelines.[1-3] Some differences are biologically based; others come from periodontal applications of Emdogain. Most innovative is the concept that root-side PL cells and fibres have been significantly altered by ischemia and desiccation and become biologically foreign protein. The removal of root-side PL changes the entire concept of rapid replantation. Once the incisor has been avulsed more than 15 minutes, replantation can be delayed up to 12 hours. Periodontal applications of Emdogain use conventional pumice prophylaxis to remove PL fibres and cells. This method produces minimal root surface damage and does not leave organic residue. It is designed to produce a receptive surface for PL cell attachment.

Dental pulp management involves changes in methodology that are based on the principle of reduction of inflammatory stimuli. Immediate removal of the dental pulp and abandonment of calcium hydroxide root medication both support this principle. Necrotic pulp tissue is a stimulus to inflammatory root resorption, and calcium hydroxide produces a basic environment thought to be hostile to PL cells expected to move from alveolar socket to root surface. Pulp removal is simpler when the tooth is avulsed, because "touching" the root surface is no longer contraindicated. Freedom from previous time and handling constraints allows the placement of a zinc oxide-eugenol apical seal in incisors that have immature root apex formation.

Emdogain has been shown to significantly improve PL regeneration after periodontal surgery in adults.[12] In a 36-month, placebo-controlled, randomized clinical trial, Emdogain treatment was associated with significantly increased radiographic bone heights and clinical attachment (probing depth) compared with the control. Increases in bone height and clinical attachment have also been demonstrated in a case report and in an animal trial that used monkeys.[11,12] It is reasonable to assume that if Emdogain significantly improves the prospects of periodontal regeneration in previously diseased tissues, a similar effect should be observed in traumatized tissues. The clinical safety of Emdogain has also been demonstrated. A study of over 100 patients who received treatment with Emdogain found no adverse clinical or immunologic effects.[13]

In July 1999, approval was obtained from the Research Ethics Board of The Hospital for Sick Children to initiate a longitudinal outcome study to investigate the influence of Emdogain on the replantation healing of permanent maxillary incisors in children. Barrett and Kenny[5] demonstrated that incisors with immature root formation were significantly more likely to be extracted. Furthermore, almost all incisors with immature root formation were extracted by 1.5 years after injury. The primary causes of extraction — ankylosis in a growing child and severe external root resorption at any age — are discernible by six months and definitive by one year. The authors expect one year to be adequate to demonstrate change or lack of differences between treatment with Emdogain and conventional treatment. Therefore, in the case of incisors with incomplete root formation, sufficient data may be available in less than two years to support or disprove its use in this population. The control for the current outcome study is the results of Barrett and Kenny,[5] the only outcome study that is restricted to the age group selected. Methods of radiographic evaluation, statistical methods and data management will be identical to those described in Barrett and Kenny.[5] The methods of this investigation are identical to those approved by the Research Ethics Board and are meant to guide investigators from other centres.

Methods

Inclusion Criteria

Any patient under 18 years who has avulsed a permanent maxillary incisor for less than 12 hours satisfies the age and extra-alveolar duration parameters. Avulsed incisors that have been stored in non-physiologic media (i.e., air or tap water) in excess of 15 minutes are eligible for treatment if root maturity is classified from stage 4 to 7 as illustrated in Fig. 1.[14]

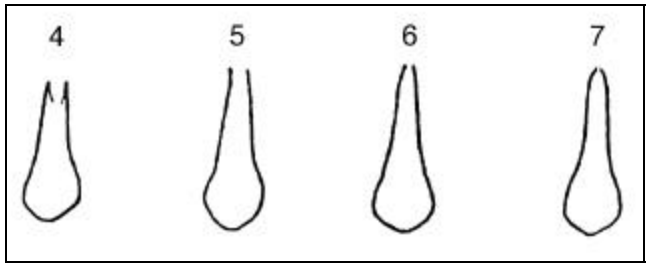

Figure 1: *Illustration of the classification system of Moorrees and others[14] for stages of root formation.*

Experimental Technique

The avulsed incisor is radiographed extraorally to classify root maturity. Next, a lingual access cavity is produced and the dental pulp immediately extirpated. If the root apex is not sufficiently constricted to allow for conventional gutta percha/sealant obturation (Moorrees and others[14] stage < 6), the apical foramen is sealed with fortified ZOE following the pulpectomy. In accordance with the manufacturer's recommendations, no calcium hydroxide products are placed in the canal. The preparation of Emdogain solution takes approximately 20 minutes; therefore, mixing of the vehicle and the

enamel matrix derivative pellet is begun before removal of the PL from the root (Fig. 2; Videoclip 1). The PL adherent to the root is removed with a rubber prophylaxis cup charged with wet flour of pumice and rinsed with water. The alveolar socket is rinsed free of blood clot without curettage, and hemostasis is fully achieved. The fully mixed solution of Emdogain has the consistency of a thick mucus and is dispensed through a blunt cannula onto the incisor root surface and socket wall. The incisor is immediately replanted (Videoclip 2). Splinting is by flexible wire secured with composite resin according to the protocol of the Royal College of Surgeons of England and the American Association of Endodontists (AAE) for 7 to 14 days.[1,3] Conventional endodontic treatment is completed within 7 to 14 days.[5]

Figure 2: *Emdogain is supplied as an aqueous vehicle and dried enamel matrix derivative that is reconstituted using the supplied canulae and a 3.0-mL syringe.*

Case Report

A 14-year-old boy presented with an avulsed maxillary right lateral incisor that was stored dry for one hour and then in

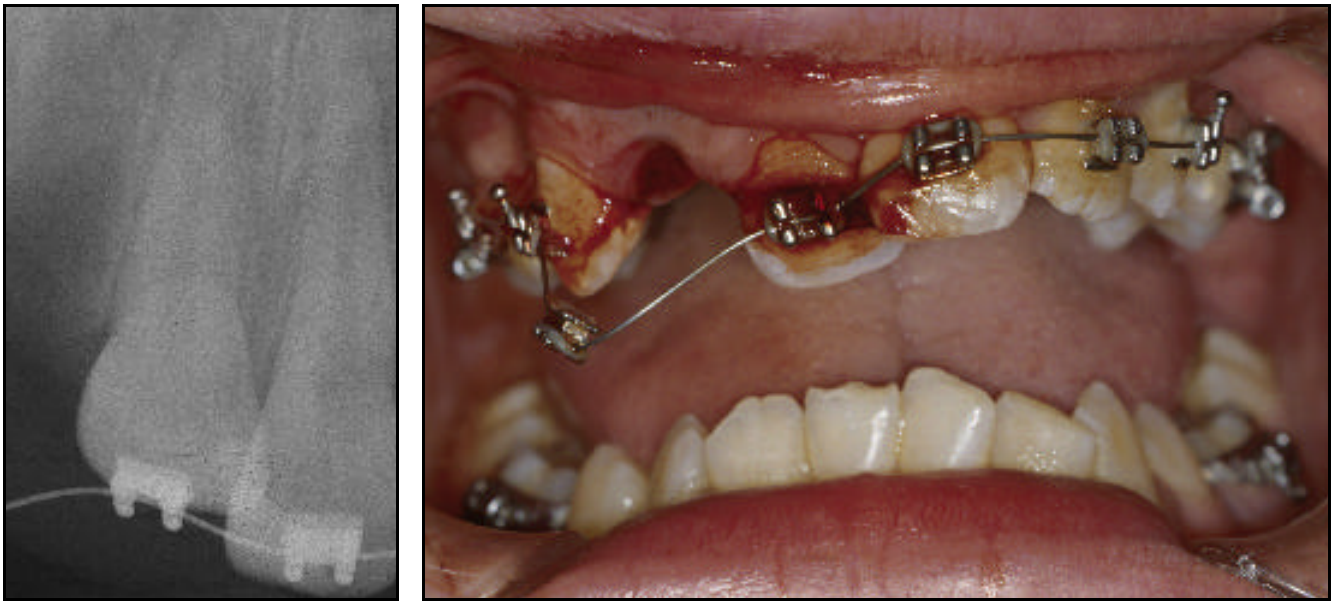

Figure 3: *Radiograph and photograph that confirm avulsion of the maxillary right lateral incisor 1.2.*

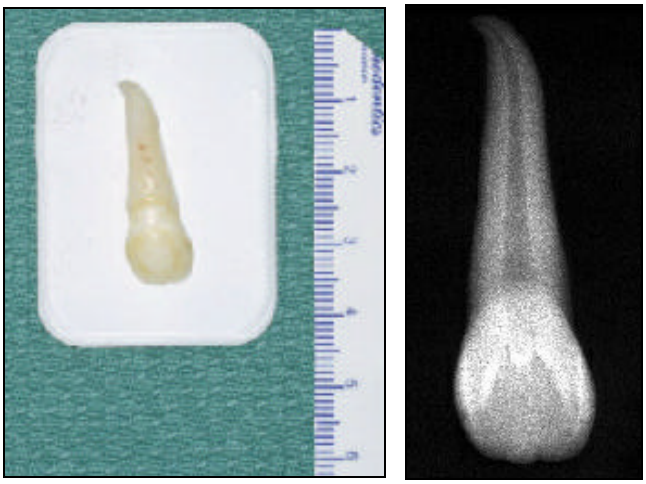

Figure 4: *Extraoral pre-replantation radiograph of avulsed incisor 1.2 for assessment of stage of root formation (Moorrees and others[14] stage 6).*

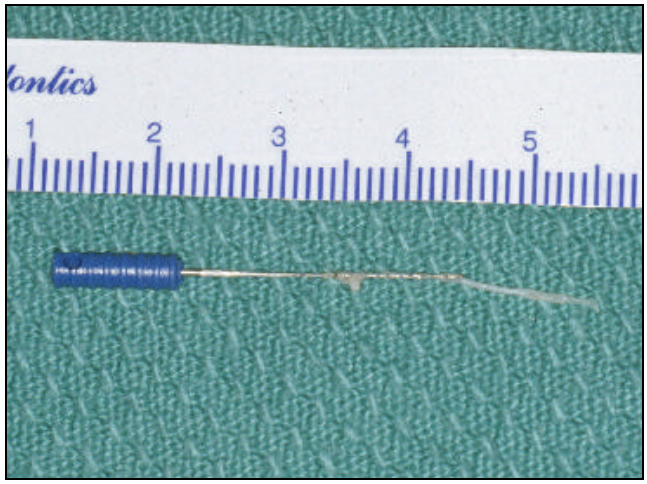

Figure 5: *Dental pulp extirpated from incisor 1.2 attached to barbed broach.*

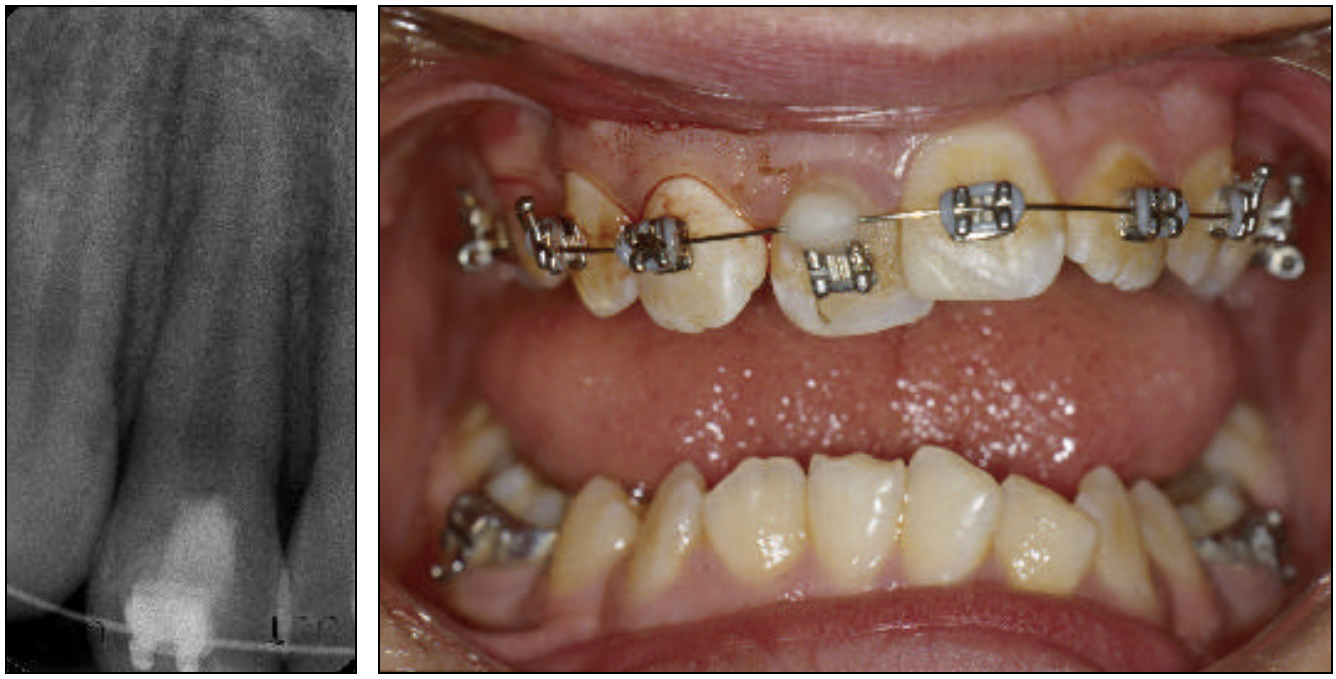

Figure 6: *Maxillary right lateral incisor 1.2 immediately after replantation and stabilization.*

Hank's Balanced Salt Solution for 30 minutes (total extra-alveolar time: 1.5 hrs). Visual and radiographic inspection of the socket confirmed complete avulsion of tooth 12 and the absence of any associated alveolar fractures (Fig. 3). A radiograph of the tooth disclosed that root maturation was stage 6 (Fig. 4). Next, access to the root canal was obtained with a high-speed handpiece, and the pulp was extirpated with a barbed broach (Fig. 5). After gentle instrumentation with a #15 Hedström file, the root canal was irrigated with normal saline and dried with paper points. The access cavity was sealed with a light-cured, resin-modified glass ionomer material (PhotacFil, Espe America, Norristown, PA).

After pulpectomy and seal of the access cavity, attention was directed to the preparation of the root surface. With the root wrapped in a gauze pad moistened with normal saline, all adherent PL tissue was removed with coarse flour of pumice and a rubber cup in a slow-speed handpiece. Next, Emdogain was mixed according to the manufacturer's directions (Videoclip 1) and applied to the root and clot-free socket according to protocol, and the incisor was replanted (Videoclip 2). Because the patient was wearing fixed orthodontic appliances at the time of the accident, the existing nickel-titanium arch wire was replaced with a passive 0.014" stainless steel arch wire (Fig. 6). To incorporate the lingually positioned 1.1 into the splint, composite resin was extended to the arch-wire, and the wire was affixed (Fig. 7). A paralleling-technique periapical radiograph confirmed ideal replantation of the avulsed tooth (Fig. 6). A 7-day post-operative course of penicillin was prescribed, and an appointment made with the patient for completion of endodontic treatment.

Endodontic treatment was completed at the first follow-up visit 13 days after replantation. Treatment was completed under rubber dam isolation with the orthodontic appliances still in place. Hand instruments were used for the root canal, which was filled with gutta percha and sealer using a combination of lateral and warm vertical condensation techniques. When the treatment was completed, the access was sealed with PhotacFil and a paralleling-technique periapical radiograph was exposed to confirm obturation of the root canal space (Fig. 8).

This incisor has been replanted for over three months and there are no early signs of rejection, root resorption or ankylosis. While these early results are encouraging, they are anecdotal and should not be interpreted as representative of the potential of Emdogain in the treatment of avulsed permanent incisors. At this early juncture, the case is included for illustrative purposes.

Discussion

Clinical outcome studies have demonstrated that the immediate replantation of avulsed permanent incisors is essential for the regeneration of the PL after replantation.[5,6] However, before this investigation, there was no treatment specifically directed toward regeneration of PL. This clinical report describes the first application of the methods adopted for a longitudinal outcome study of Emdogain. It illustrates the prolonged hostile extraoral environment to which avulsed teeth are often subjected. In the case described, there would have been no vital PL cells and the adherent fibres would contain significant quantities of denatured protein. In this case, apical development was at the interface between straight walls and minimal constriction. The age of the child and the stage of root development is a reality of the epidemiology of avulsions that is often overlooked. The preparation and application of Emdogain were uncomplicated, but care had to be taken to ensure that there was no bleeding into the socket at the time of replantation. Splint type and duration were within AAE guidelines, and conventional gutta percha/sealant obturation completed the

Figure 7: *Inclusion of the lingually positioned incisor 1.1 into the splint to stabilize incisor 1.2 (1.1 was malposed before injury).*

Figure 8: *Post-obturation radiograph of maxillary left lateral incisor 1.2.*

case rapidly. If successful, this innovative treatment will extend the time for replantation to 12 hours and drastically alter the role of transport media. The extended extraoral duration before replantation will encourage regional trauma centres.

Extrapolation of results from adult periodontal therapy appears reasonable at the cellular level. However, its use for replantation is still experimental and should be under the guidance of research ethics committees. The outcome study currently under way will apply this information to a different injury (trauma) and to a different age group (children and adolescents). ➧

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Videoclip 1

Mixing aqueous vehicle and dried enamel matrix derivative and preparing the solution for application to root and socket.

Videoclip 2

Application of Emdogain to root and socket of 1.2 and subsequent replantation.