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REVIEW ARTICLE

Enamel matrix derivative (Emdogain) in treatment of replanted teeth – a systematic review

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ABSTRACT

Objective: The main purpose of the present systematic review was to evaluate the efficacy of enamel matrix derivative Emdogain in healing of replanted teeth in humans.

Materials and Methods: This review conducted in adherence to PRISMA standards and was registered in PROSPERO with registration number CRD42017062736. We graded the methodological quality of the studies by means of Cochrane's tool of risk of bias in non-randomized studies – of interventions (ROBINS-I).

Results: In total, 65 studies were identified for screening, and five studies were eligible. The uneventful healing of replanted teeth was varied from 20% to 75%. Two controlled trials found Emdogain treatment significantly reduced resorption of replanted teeth and improved the healing of periodontal ligament compared with controls. Two studies showed high recurrent resorption in Emdogain treated teeth.

Conclusions: To conclude, the number of publications that met all inclusion criteria were limited and did not allow for drawing evidence for Emdogain being effective in supporting healing of replanted teeth.

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Avulsion; enamel matrix derivative; emdogain; systematic review; transplantation

Introduction

Avulsion of tooth is a complex form of traumatic dental injury affecting alveolar bone, cementum layer, periodontal ligament (PDL), and pulp [1]. The usual sequel with regard to pulpal necrosis, a timely endodontic treatment is usually required to prevent or inhibit pulpal infection [1]. The development of inflammatory or replacement resorption is directly related to the vitality of the PDL, the length of extra-alveolar time, the type of storage (wet or dry), kind of storage media, and the pre-treatment of teeth prior to replantation [1,2]. In the mid-1980s, an important discovery revealed that enamel-related proteins mediate the formation of acellular cementum on the root of the developing tooth providing a foundation for all necessary tissues associated with functional periodontal attachment [3]. Based on this observation, an enamel product named Emdogain has been developed. It is a commercial enamel matrix derivative which is extracted from developing embryonal enamel of porcine origin and contains several matrix proteins from the amelogenin family [3]. The influence of Emdogain on periodontal ligament cells according to several studies is by its effect on migration, attachment, proliferative capacity, and biosynthetic activity [3–8]. It is recommended as therapeutic agent for managing avulsed permanent teeth due to its effectiveness in improving the healing process of implanted teeth [4,9–14]. But few studies gave conflicting results regarding the role of Emdogain in healing of replanted avulsed teeth [15,16]. When we searched for the literature we came across a systematic review of animal studies conducted to analyze the impact of Emdogain on healing of replanted or transplanted teeth [17]. No systematic reviews have been conducted regarding human studies. The present systematic review is conducted to analyze the efficacy of Emdogain in healing of replanted or transplanted teeth in humans.

Materials and methods

The planning, conduction, and reporting of the present review was in adherence to PRISMA standards of quality for reporting systematic reviews and meta-analysis [18]. The PROSPERO registration number for present review is CRD42017062736. Institutional Review Board approval was not required.

Questions

We sought to examine the quantitative effects of the Emdogain on healing pattern of replanted or transplanted teeth compared to the teeth not receiving any treatment or treated with other conditioning media. The research question of the present systematic review was defined according to the PICO format as follows:

P (Population/Patients): Subjects with replantation or transplantation of teeth, only humans (avulsed teeth both

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mature and immature, extracted ankylosed teeth, unankylosed extracted teeth).

I (Intervention): Enamel matrix derivative in treatment of replanted or transplanted teethC (comparison): Subjects not receiving any treatment or treated with other conditioning media.

O (Outcome): Healing of periodontium following replantation or transplantation of teeth, assessed by clinical and or radiographic method.

Study eligibility

The studies that investigated the effects of Emdogain on healing patterns of replanted or transplanted teeth in human published in English language were considered eligible for inclusion. Papers were excluded at this stage if they were editorial letter, case report, *in vitro*, animal studies, Emdogain used for other purposes.

Study identification

Various research database were searched which include, Cochrane library (Cochrane review, Trails), Medline (PubMed, OVID Medline and Ebsco), Embase (European studies, pharmacological literature, conference abstract), Web of Knowledge (Social science, conference abstract), SCOPUS (Conference abstracts, scientific web pages), CINAHL (Nursing and allied health), PsycInfo (Psychology and psychiatry), and ERIC (Education) using key terms focused on the specific search strategy (Emdogain, enamel matrix derivative, replanted, transplanted, teeth). For grey literature following databases were searched: Google scholar, Open Grey, National Library of Medicine, Social science research, For thesis (EthOS, DART-Europe), Institutional repositories (OpenDOAR, Bielefeld Base, Lenus, RIAN, e-publications@RCSI). To supplement the searches, the tables of content of two key dental journals (Dental Traumatology and Pediatric dentistry) were searched for relevant articles. The last date of the search was 20 September 2017. We searched for additional studies in the reference lists of all articles included.

Study selection

All the titles and abstracts were screened independently and in duplicate for inclusion. In the event of insufficient information in abstract leading to disagreement, the full texts of the potential article was reviewed independently and in duplicate. The inter-rater agreement for study inclusion, as assessed using an intra-class correlation coefficient, was 0.86. Any conflicts between two reviewers was resolved through consensus.

Risk of bias assessment

Risk of bias was assessed using Cochrane's tool of risk of bias in non-randomized studies – of interventions (ROBINS-I) [19]. The following domains were assessed for risk of bias: bias due to confounding, bias in selection of participants into the study, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of the outcomes, bias in selection of the reported result. Each domain is graded as Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain), Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable with a well-performed randomized trial), Serious risk of bias (the study has some important problems), Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention), or No information (on which to base a judgment about risk of bias for this domain).

Data extraction and data synthesis

Two reviewers did data extraction independently for the included studies using data extraction sheet, and any discrepancies were resolved by discussion and consensus. The following data were extracted from each included study: first author, publication year, study type, study quality, sample size, number of teeth replanted or transplanted, follow-up period, extra alveolar time, root surface treatment, types of resorption, healing pattern, and the authors' conclusion.

Results

Trail flow

Using our search strategy, we identified fifty eight articles with an additional seven identified from our review of references and journal indices. From these, we identified five articles for inclusion in the present systematic review (Figure 1).

Study characteristics and study quality

The studies were recent, with the oldest study published in 2002.The studies included for review were all published in English language. Two studies used avulsed teeth for replantation, and one study used ankylosed extracted teeth, and one study used both ankylosed extracted teeth and avulsed teeth. The number of study participants ranged from ten to thirty four (total $n = 99$), with a mean of 19.8 (Table 1). The quality assessment rated two (40%) of the studies as being of low risk of bias and three (60%) of these studies as being of moderate risk of bias (Table 2). The follow-up period varied from 3 months to 72 months. Non-rigid splinting was applied in three studies to stabilize the replanted teeth, and number of splinting days varies from 7 d to 14 d (Table 3).

Table 4 shows the results of the included studies. The uneventful healing of replanted teeth was varied from 20% to 75%. The study by Filippi et al. showed 11 out of 15 teeth treated with Emdogain showed normal periodontal healing. Replacement resorption (RR) varied from 18.7% to 100%. Minimal (18.7%) RR was noticed in Filippi et al. study and maximum (100%) in Schjott et al. [15].

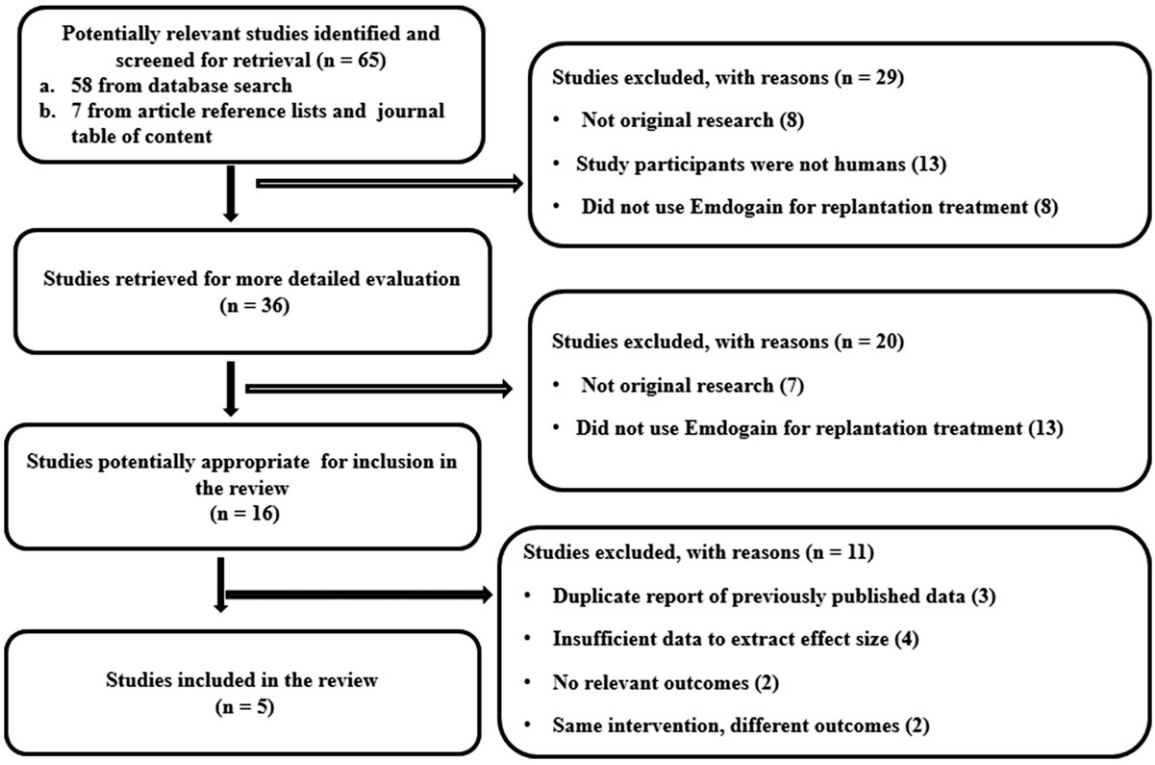

Figure 1. Study selection flow diagram of the systematic review.

Table 1. Descriptive characteristics of included studies.

Author/year	Study design	Sample size/mean age in years	Teeth included	Intervention	Author conclusion
Filippi/2002	PC	16/14.4	Extracted ankylosed teeth	E for ankylosed teeth	Emdogain delayed recurrence of ankylosis
Schjott/2005	PC	G 1: 7/12.4 G 2:7/12.7	G1: avulsed G2: extracted ankylosed teeth	G1: E for avulsed teeth within 24 h G2: E for ankylosed teeth	Emdogain was not able to prevent or cure ankylosis
Chappuis/2005	PC	34/21.1	Avulsed	G1: with E treatment G2: without E treatment	50% of RR in G1 and 22.8% of RR in G2
Barrett/2005	PC with historical controls	G1:25/12.1	Avulsed	G1: with E treatment G2 and G3: without E treatment	G1 significantly less root resorption compared to G2 and G3
Fridstrom/2008	IEC	10/ age range of 12 to 15 years	OT with extracted MPM	E and without E	Emdogain cause better healing of replanted PDL compared with control

G: group; E: Emdogain; h: hour; IEC: intra-individual experimental control study; PC: prospective clinical study; OT: orthodontic treatment; MPM: maxillary premolars; PDL: periodontal ligament; RR: replacement resorption.

Table 2. Risk of bias assessment of included studies using Cochrane's risk of bias in non-randomized studies – of interventions (ROBINS-I).

	Author				
ROBINS – I criteria	Filippi	Schjott	Chappuis	Barrett	Fridstrom
BC	L	L	L	L	L
BSP	L	L	L	L	M
BCI	S	L	M	L	L
BDI	M	M	L	M	M
BMD	M	M	L	L	L
BMO	M	L	L	L	M
BSR	L	L	L	L	L
Overall score	M	M	L	L	M

BC: bias due to confounding; BSP: bias in selection of participants into the study; BCI: bias in classification of interventions; BDI: bias due to deviations from intended interventions; BMD: bias due to missing data; BMO: bias in measurement of the outcomes; BSR: bias in selection of the reported result; L: Low risk of bias; M: Moderate risk of bias; S: Serious risk of bias; C: Critical risk of bias; NI: no information.

Discussion

The present systematic review was conducted to analyze the efficacy of Emdogain in healing of replanted or transplanted teeth in humans. Five studies were included in the present review [10,13–16].

Replanted teeth usually fail because of progressive external root resorption of either the replacement or inflammatory type [1,2]. The inflammatory root resorption may be prevented by early (<3 weeks) endodontic treatment, but the replacement root resorption is not treatable and arises from a failure of periodontal ligament regeneration [2]. In the present systematic review, the two controlled trials [13,14] found Emdogain treatment significantly reduced resorption of replanted teeth and improved the healing of

Table 3. Number of teeth, follow-up, root surface treatment of included studies.

Author	Number of teeth/ number of teeth under analysis	Method of splintting	Extra-alveolar time/ storage media	Root surface treatment	Antibiotic coverage	Follow-up time
Filippi	16/15	10–14 d with NRS (TTS)	Extracted root surface was dried, no conditioning	ERCT, E to root surface and socket, no removal of PDL before replantation	None	15 m
Schjott	G1: 16/16 G2: 11/11	7 d with SRS (Protemp)	G1and G2:25 to 270 min/dry and wet (Saline)	G1 and G2: ERCT, E to root surface and socket	Penicillin for 4 days	12 m
Chappuis	G1:10/10 G2:35/35	7–10 d with NRS (TTS)	30 min/wet storage (Dentosafe)	G1; EORCT, E to root surface and socket Control: EORCT, without E	Tetracycline topical and systemic for 10 d, and Chlorhexidine rinse	12 m
Barrett	G1: 28	G1: 6–8 weeks with flexible wire secured with composite resin	G1: 185 min/dry (64.8 min) and wet (120.2 min) G2:123 min/dry Complete removal of PDL in G1	G1; EORCT, E to root surface and socket, removal of PDL fibers before replantation Control: EORCT, without E	Penicillin or Clindamycin for 7 d	G1:20.6 m G2:30.9 m
Fridstrom	E:10/9 Control:10/9	3-7 days with Essix retainer, NRS	60 min/dry	G1; EORCT, E to root surface and socket, no removal of PDL before replantation Control: EORCT, without E	Chlorhexidine rinse for 7 days	3 m

G: group 1; NRS: non-rigid splint; SRS: semi-rigid splint; PDL: periodontal ligament; P: penicillin; E: Emdogain; TTS: Titanium Trauma Splint; ERCT: extra oral retrograde root canal treatment; EORCT: extra oral root canal treatment, lingual access; m: months.

Table 4. Outcome of included studies.

			Types of resorption			
Author	Evaluation criteria	Normal PDL, number of teeth (%)	Surface number of teeth (%)	Inflammatory number of teeth (%)	Replacement number of teeth (%)	Histologic observations
Filippi	Horizontal and vertical PT, P, PA	11 (75)	No	No	3 (18.7) at 4 m, 1 (6.2) at 12 m	NA
Schjott	P, PA	G1: 8 (50) at 2 m, 7 (41) at 4 m G2: 7 (64) at 1 m, 4 (28) at 2 m	NA	NA	G1: 8 (50) at 2 m, 10 (59) at 4 m, 16 (100) at 12 m G2: 4 (36) at 1 m, 8 (72) at 2 m, 11 (100) at 4 m	NA
Chappuis	P, PA	G1: 2 (20) G2:24 (68.6)	G1: 2 (20) G2: 1 (2.9)	G1: 1(10) G2: 2 (5.7)	G1: 5 (50) G2: 8 (28.9)	NA
Barrett	P, PA	G1: 40% G2:10% G3:5%	G1:0 G2:0 G3:5%	G1:0 G2:25% G3:35%	G1:60% G2:61% G3:55%	NA
Fridstrom	P, PA, Histological examination	E: 3 (33.3) Control:4 (44.4)	E: 2 (16.7) Control: 1 (5.6)%	NA	E: 1 (11.1) Control: 4 (33.3)	E: Attached PDL in 14–83% Control: attached PDL in 20–57%

PT: Periotest; P: percussion sound; PA: periapical radiograph; G: group; m: months; PDL: periodontal ligament; NA: not available.

periodontal ligament compared to controls. The use of Emdogain promoted the regeneration of cementum, PDL fibers, and bone [5]. Fridstrom et al. [13] in his histological assessment of replanted teeth showed Emdogain better in PDL regeneration. Filippi et al. [10] showed application of Emdogain did not result in recurrence of ankylosis in 11 out of 15 replanted teeth. He showed if the resorbed areas are completely removed by resection and if the remaining root sections do not show any ankylosis, normal periodontal healing can be expected similar to the healing process after intentional replantation as an alternative to apicectomy. In contrast to this, the study by Schjott et al. [15] and Chappuis et al. [16] who used avulsed teeth for replantation showed high recurrent resorption in Emdogain-treated teeth compared with controls. Schjott et al. [15] and Chappuis et al. [16] applied Emdogain to avulsed and extracted ankylosed teeth where minimum of cemental periodontal cells could be expected to be alive because of drying or mechanical injury. The negative result of Emdogain in this situation seems to indicate that there must be a critical number of PDL cells alive before any protection can be established against the development of ankylosis.

The frequency of replacement resorption following replantation of avulsed permanent teeth has also been associated with extended splinting times (>10 d), type of storage media (physiologic versus artificial media), time of endodontic treatment (less than 3 weeks of replantation), antibiotic coverage both topical and systemic, and period of extra-oral storage

(less than 15 min versus more than 15 min) [2,5]. To improve the prognosis by not keeping the tooth dry during the extra oral time, but in a physiologic storage medium like milk, saline, saliva, or special cell culture media [3,11]. In addition, local and systemic administration of antibiotics is shown to have a favorable impact on periodontal healing and is recommended as a standard procedure following replantation.

The limitation of the present review were due to heterogeneity across the studies we could not do the meta-analysis of included studies. The variations in *in vivo* studies leading to heterogeneity were in terms of extraoral storage duration, the kind of tooth reimplanted, pretreatment of root prior to Emdogain, storage media used, antibiotics usage, and/or follow-up period. Therefore, no forest plots or funnel plots were constructed. Due to the disparate nature of the studies, only simple descriptive and stratified comparisons are reported. The small number of included trials does not contribute towards making a final verdict on the impact of Emdogain on healing of replanted teeth and the included clinical trials gave conflicting results. The high-quality randomized control trials are further needed to be conducted in future to accurately substantiate the evidence in this field of research.

Clinical recommendation

Emdogain is used in replantation/transplantation treatment to promote regeneration and reestablishment of periodontal cells on the damaged root surface thereby preventing ankylosis. This might explain the favorable outcome of Emdogain treatment in the studies of Filippi et al. [10] and Fridstrom et al. [13] where Emdogain was applied to damaged PDL cells. However, the studies by Schjott et al. [15] and Chappuis et al. [16] showed negative results where PDL cells were mechanically removed prior to application of Emdogain. The results point to the need for high-quality randomized controlled studies with a sample size that is large enough to detect possible effects of Emdogain treatment in replantation. Further research should also consider the effect of different storage conditions and media (EDTA root conditioning, sodium fluoride treatment, etc.) on efficacy of Emdogain treatment. Finally, mature or immature teeth might perform differently with regard to replantation after Emdogain treatment.

Conclusions

To conclude, the number of publications that met all inclusion criteria was found to be very limited and did not allow for drawing evidence for Emdogain being effective in supporting healing of replanted teeth. Emdogain treatment before replantation may be effective in enhancing normal healing and reducing inflammatory and replacement root resorption in the presence of periodontal cells.

Disclosure statement

No potential conflict of interest was reported by the authors.

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