Efficacy of enamel matrix derivatives (Emdogain) in treatment of replanted teeth – a systematic review based on animal studies

Wiegand, A ; Attin, T

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Abstract

Aim: The objective of the current systematic review was to evaluate the efficacy of enamel matrix derivative (Emdogain®) on healing of replanted or autotransplanted permanent teeth.

Methods: A review of the published literature (search term: (Emdogain OR enamel matrix derivative OR enamel matrix protein) AND (avulsion OR replantation OR autotransplantation)) was conducted by two independent investigators according to defined selection criteria. For data extraction of the identified animal studies the following histomorphometric findings were considered: 1) healed PDL, 2) surface resorption, 3) inflammatory resorption and 4) replacement resorption. The heterogenity of data collection and the small amount of identified publications did not allow for statistical analysis.

Results: Four controlled trials (CT) conducted in animals, but no randomized controlled trials (RCT) or clinical controlled trials (CCT) could be received from the systematic search. From the selected studies, two CTs gave evidence of enamel matrix derivative treatment to be effective in inducing healing of replanted teeth, while one CT found no differences between enamel matrix derivative treated teeth and controls. Finally, one CT compared enamel matrix derivative and sodium fluoride application, but revealed no differences between the treatments.

Conclusion: The data of controlled trials available are limited and conflicting. Any firm conclusion regarding the efficacy of enamel matrix derivative application on healing of replanted or autotransplanted permanent teeth cannot be drawn, due to the lack of RCTs and CCTs.

Introduction

Tooth avulsion is a complex injury affecting pulp, periodontal ligament (PDL), cementum layer and alveolar bone and is usually followed by pulpal and periodontal complications which might compromise tooth survival. Complicating sequelae of pulp necrosis, damaged PDL and cementum layer may result in external inflammatory resorption or replacement resorption, which may, ultimately, result in tooth loss.

With regard to pulpal sequelae, a timely endodontic therapy is usually required to prevent or inhibit pulpal infection. Bacteria, bacterial by-products and tissue breakdown products from the root canal system could stimulate inflammatory resorption in the adjacent periodontal tissue in cases where trauma results in severe damage of the root surface leaving dentinal tubules exposed. Replacement resorption takes place when large areas of the PDL are damaged and the viability of PDL is lost finally resulting in replacement of the periodontal attachment by cells of the alveolar bone (1, 2). As the formation of new tissue on affected root surfaces might be considered as competetive healing from the socket wall and the adjacent PDL, therapeutic approaches that would regulate and promote PDL cell proliferation and differentiation are considered to improve the healing process of avulsed teeth. Since the development of resorption might be directly related to the vitality of the periodontal ligament, 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 are of high relevance (3, 4).

Enamel matrix derivative (EMD) has attracted interest to improve periodontal healing of avulsed and replanted teeth as it was reported to be effective in the treatment of periodontal intrabony effects (5, 6). Emdogain® (Biora, Malmö, Sweden, incorporated into Straumann Biologic Division since 2004) is a commercial EMD, which is extracted from developing embryonal enamel of porcine origin and contains several matrix proteins from the amelogenin family. Several studies have shown that EMD influences the migration, attachment,

proliferative capacity and biosynthetic activity of periodontal ligament cells (7-10). Thus, it is also considered to be effective in improving the healing process of replanted teeth and recommended as therapeutic agent for the management of avulsed permanent teeth (11, 12), but consensus in published guidelines and treatment protocols is still lacking.

The primary objective of this review was to analyse the impact of EMD treatment compared to controls not receiving any treatment on healing of replanted or transplanted teeth. Secondly, the effect of EMD in compared to other conditioning media, eg. sodium fluoride, should be investigated.

Methods

Research Question

According to the paradigm of evidence-based dentistry the research question of the present study was defined accordingly to the PICO format (13, 14) as:

P (Patients/Population): Replanted or transplanted teeth in *humans or animals*

I (Intervention): Application of EMD

C (Comparison): compared to teeth *not receiving any treatment* (C1) or treated with *other conditioning media* (C2)

O (Outcome): *healing patterns*

Search strategy

The search of literature was carried out in March 2007 using the electronic data bases PubMed, Medline and EMBASE. In the first step, data bases were searched for the terms (Emdogain OR enamel matrix derivative OR enamel matrix protein) AND (avulsion OR replantation OR autotransplantation). The literature search was closely related to the MOOSE Guidelines for meta-analyses and systematic reviews of observational studies (15).

In the second step, two investigators independently screened each English publication for eligibility by examining title, abstract and keywords. References from the identified publications were manually searched to identify additional relevant articles.

Selection criteria

In the third step, two reviewers (A.W. and T.A.) applied the following inclusion criteria: randomized controlled trial (RCT), clinical controlled trial (CCT) or controlled trial conducted in animals (CT), where EMD application was compared with controls not receiving any type of treatment. For the second objective of the review, RCTs, CCTs and CTs, in which EMD application was compared with other surface conditioning treatment, were selected. Clinical trials without an adequate control as well as reviews and case reports were excluded. Authors of the identified studies were contacted for clarification of missing information.

Data extraction

In the forth step, the following histomorphometric findings were considered as outcome measures of CT: 1) healed PDL, 2) surface resorption, 3) inflammatory resorption and 4) replacement resorption. Outcome measures for RCT and CCT were defined as follows: 1) tooth loss, 2) radiological evidence for surface resorption, inflammatory resorption or replacement resorption and 3) clinical evidence for ankylosis. However, the selection criteria revealed no RCT and CCTs to be included in the forth step.

Data extraction was done in duplicate by both examinators.

Data synthesis

The results presented in this study are in form of an organized, qualitative, and systematic review of the evidence gathered on the efficacy of EMD compared to controls not receiving of any kind of treatment in healing of replanted or autotransplanted teeth. Given the paucity of

relevant studies addressing this question as well as the variability in research designs, meta-analysis including an overall statistical analysis of the evidence seemed not appropriate.

Results

Study identification

In the first and second step, 22 relevant publications could be identified. Only 5 publications met the inclusion criteria applied in the third step. Thereby, the selection criteria revealed no RCT and CCTs and only 5 CTs to be included (16-20). Seventeen publications were excluded for the following reasons (Table 1): Case report or review (21-29), CT not in English and information could be not obtained from the author (30) and inadequate or missing control (31-37).Sound, non-explanted teeth (31-33) as well as historical controls (36, 37) were considered as inadequate. During the data extraction (fourth step), one study (20) was excluded due to missing statistical analysis.

As a result, 4 studies were available for final analysis. Three studies could be obtained, in which EMD treatment was compared with controls not receiving any kind of relevant treatment (16-18). For better illustration, a short description of these studies including the most relevant results is provided in Table 2. One study compared the effects of enamel matrix derivative application with sodium fluoride (19).

EMD versus no kind of treatment

Two controlled trials found EMD treatment to be superior compared to controls without any kind of treatment. Iqbal et al. (16) assessed the effect of Emdogain in re-implanted teeth of nine beagle dogs. One-hundred and two teeth were extracted and air dried for 15, 30 or 60 min. The necrotic PDL was not removed, and the teeth were assigned to Emdogain coating or no treatment (homologous teeth). Histomorphometric analysis was performed in three groups:

1) teeth splinted for 1 week and animals sacrified after 8 weeks, 2) teeth splinted for 1 week and animals sacrified after 12 weeks or 3) teeth were not slinted and animals sacrified after 12 weeks. Eighty teeth could be followed-up and statistical univariable analysis found a significant higher percentage of normal PDL in the Emdogain group (60.2% ± 5.2) compared to the control (43.4 % ± 5.2). Also, the replacement resorption was significantly less in the Emdogain treated teeth (4.5% ± 3.1) compared to the control (14.9 ± 3.1), while surface and inflammatory root resorption differed not significantly. The multivariate analysis was carried out for EMD, follow-up and extraalveolar period and found significantly less replacement and inflammatory resorption for the EMD group. The incidence of root resorptions between splinted and non-splinted teeth was not significantly different.

In the study by Lam et al. (17), incisors and mandibular posterior teeth of seven monkeys were endodontically treated, extracted, dried for one hour and replanted after receiving one of the following treatments: 1) none, 2) PDL removal, 3) Emdogain application, 4) PDL removal and Emdogain application, 5) PDL removal and EDTA treatment before Emdogain application. Teeth that were immediately replanted and considered as negative control showed the best outcome. Roots that were replanted with remaining PDL after dried for 1 hour exhibited significant less replacement resorption compared to the other groups. However, treatment with EDTA and Emdogain (group 5) led to significant less replacement resorption compared to teeth with PDL removed (group 2). Healing patterns after application of Emdogain only (group 4) were not superior to group 2.

In contrast, in the study of Molina et al. (18), healing of EMD treated incisors of wistar rats was not significantly different from teeth which did not receive any treatment (18). Each 21 incisors were extracted and kept in saline for 20 min. Thereafter, the teeth were endodontically treated and either replanted (group1), replanted after PDL removal (group 2) or replanted after PDL removal and EDTA followed by Emdogain treatment (group 3).

Histometric analysis was performed after 7, 20 and 60 days and found significantly better healing for group 1 compared to groups 2 and 3, which were not significantly different.

EMD versus sodium fluoride treatment

Only one study compared the effects of Emdogain and sodium fluoride on the healing process of replanted teeth (19). Central incisors of 24 Wistar rats were extracted and kept dry for 6 h. Root surfaces were treated with sodium hypochlorite for 10 min and assigned to 2% acidulated-phosphate sodium fluoride or Emdogain treatment for 10 min. The teeth were filled with calcium hydroxide, replanted and outcome parameter evaluated after 10 and 60 days. Statistical analysis was applied to the 60 days data, but found no differences in healing parameters (19).

Discussion

The objective of the current study was to analyse systematically whether the application of EMD facilitates healing of replanted or autotransplanted teeth. However, three quarter of the published literature had to be excluded from the current systematic review due to lack of original data or adequate controls. Consequently, the small number of included trials does not contribute toward making a final verdict on the impact of EMD on healing of replanted teeth, not at least because no RCTs or CCTs could be identified and the included CTs gave conflicting results. Moreover, the CTs that were included were too heterogeneous for inference of the data. The heterogeneity was caused by variation of the in vivo animal models, such as duration of extraoral storage, kind of replanted teeth, EDTA conditioning prior to EMD treatment or observation period. In this context it should be mentioned that the use of a rat model (18, 19) might diminish the impact of these studies, as the continuous eruption pattern and apical development of rat teeth is different from human teeth (38).

However, regarding to the included CTs, the study of Iqbal et al. (16) is considered to be most powerful as it is performed in split-mouth design rather than in parallel group design. The significance of the rat model used in the studies by Molina et al. (18) and Poi et al. (19) might be limited

It has been considered that the biological process induced by EMD is different from what can be expected by the root surface conditioning commonly applied before replantation; namely using storage media such as tetracycline, fluoride or citric acid. Tetracycline treatment was shown to increase the pulp revascularization, presumably due to a decrease of bacterial decontamination of the root surface during the extraalveolar period (39, 40). Fluoride is applied to decrease resorption and ankylosis, while acid pretreatment is suggested to demineralise the surface and expose the collagenous matrix in order to achieve new connective tissue (41, 42).

The standard treatment mainly intends to reduce the risk of root resorption and ankylosis of teeth with damaged periodontium (11, 12). The intention to use EMD is to promote regeneration and reestablishment of PDL cells on the damaged root surface. This might explain the favourable outcome of EMD treatment in the studies of Iqbal et al. (16) and Lam et al. (17) compared to the study of Molina et al. (18). In the first mentioned studies, EMD was applied on damaged PDL cells (16, 17), while PDL cells were mechanically removed in the study of Molina et al. (18).

Favorable PDL healing is a critical factor for success of replanted or autotransplanted teeth, not at least as PDL cells might induce bone production and the repair of the mechanically damaged root surface with new cementum. PDL cells of avulsed or autotransplanted teeth can be damaged mechanically during the injury or during extraction, respectively, but also bio-chemically due to various extra-oral conditions (e.g. storage media). From the present systematic review, no conclusion can be drawn regarding the evidence for EMD being effective in supporting healing of replanted teeth. The results point to the need of high-quality

studies in further research. To improve the evidence, the study design ought to be RCCts with a sample size that is large enough to detect possible effects of EMD treatment. Further research should also consider the effect of different storage conditions and media on efficacy of EMD conditioning. Moreover, it is unclear whether replanted teeth treated with EMD may benefit from smear layer removal by EDTA root conditioning, which is a suggested step when using EMD for regeneration of periodontal tissue. However, clinical studies on the healing of intrabony defects treated with EMD failed to show a significant effect of EDTA conditioning prior to EMD application (43, 44).

Finally, mature or immature teeth might perform differently with regard to replantation after EMD conditioning.

The present systematic search revealed only one study which compared the effect of EMD to other surface media, more precisely to sodium fluoride conditioning. Acidulated fluoride solutions have been employed for root conditioning of replanted teeth as the application of fluoride might reduce root resorption through the formation of less soluble fluorapatite on the root surface (11, 41). Thus, the biological process induced by fluoride application is quite different from the purpose of EMD treatment, which is mainly to promote growth and differentiation of PDL cells. Taken into consideration the different objections of fluoride and EMD treatment, the identified study (19) revealed no difference between the healing patterns of roots treated with EMD or sodium fluoride. As only one single study dealt with this topic, further research is required to allow for a general statement.

In conclusion, the number of publications that met all inclusion criteria was found to be very limited and did not allow for drawing evidence for EMD being effective in supporting healing of replanted teeth.

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First step	Keyword search in the relevant data bases → next step	24 publications **24 publications**
Second step	Identified publications Search in reference list of selected 22 publications → next step	22 publications 0 publication **22 publications**
Third step	Met inclusion criteria - RCT - CCT - CT Met exclusion criteria - Neither an RCT, CCT or CT - Not English language - Inadequate (historic) control → next step	5 publications 0 publication 0 publication 5 publications 17 publications 9 publications 1 publication 7 publications **5 publications**
Fourth step	Screening for outcome measures of the remaining trials Met exclusion criteria due to inadequate report of the results/ No statistical analysis done → final analysis	5 publications 1 publication **4 publications**

Tab.1 Procedure of the literature search and applied selection criteria for inclusion or exclusion of publications

Study	No of teeth	Follow-up time	Extra-alveolar time and Root surface treatment	No of teeth under analysis	Hitomorphometric outcome			
					Normal PDL (%)	Type of resorption (%)		
						Surface R.	Inflammatory R.	Replacement R.
Iqbal et al. (10)	102	8-12 weeks	15, 30, 60 min dried, *Emdogain*	36	60.2 (5.2)	20.2 (2.6)	15.12 (5.8)	4.5 (3.1)
			15, 30, 60 min dried (*Control*)	36	43.4 (5.2)	15.8 (2.6)	26.0 (5.8)	14.9 (3.1)
Lam et al. (11)	n.a.	16 weeks	Immediately replanted	10	98.9 (2.3)	n.a.	0	1.1 (2.3)
			1 h dried	12	16.6 (19.6)	n.a.	12.3 (13.9)	71.2 (18.4)
			1 h dried, PDL removed	4	5.2 (7.3)	n.a.	1.6 (3.2)	93.2 (10.4)
			1 h dried, *Emdogain*	10	22.2 (22.8)	n.a.	5.4 (6.5)	72.4 (21.8)
			1h dried, PDL removed, *Emdogain*	6	20.3 (15.2)	n.a.	5.1 (7.4)	74.6 (14.9)
			1 h dried, PDL removed, *EDTA, Emdogain*	7	19.2 (13.9)	n.a.	8.9 (9.0)	71.9 (15.2)
Molina et al. (12)	63	7-60 days	20 min saline	21 (after 7, 20 and 60 d each n = 7)	7 d: 93.3 20 d: 30.7 60 d:19.4	7 d: 0.1 20 d: 61.1 60 d: 14.5		7 d: 0 20 d: 12.2. 60 d: 0
			20 min saline, PDL removed	21 (after 7, 20 and 60 d each n = 7)	7 d: 31.4 20 d: 4.0 60 d:14.5	7 d: 0.6 20 d: 44.0 60 d: 38.7		7 d: 0 20 d: 17.0 60 d: 6.3
			20 min saline, PDL removed, *Emdogain*	21 (after 7, 20 and 60 d each n = 7)	7 d: 18.9 20 d: 7.1 60 d: 7.8	7 d: 0 20 d: 59.5 60 d: 50.7		7 d: 0 20 d: 13.1 60 d: 4.9

Table 2: Main results of the histomorphometric parameters in studies comparing EMD versus no kind of treatment. N.a. = not available