Root surface treatment for delayed replantation of avulsed teeth in animal models: a systematic review

Short title: Root surface treatment for delayed replantation

Authors:

Stephanie Díaz Huaman, e-mail: stephdiazh@usp.br, phone 55 16 3315 4057

Marina Moscardini Vilela, e-mail marina.vilela@usp.br, phone 55 16 3315 4057

Paulo Nelson-Filho, e-mail nelson@forp.usp.br, phone 55 16 3315 4119

Andiara De Rossi, e-mail andiara@usp.br, phone 55 16 3315 4786

Alexandra Mussolino de Queiroz, e-mail amqueiroz@forp.usp.br, phone 55 16 3315 4115

Francisco Wanderley Garcia Paula-Silva*, e-mail franciscogarcia@forp.usp.br, phone 55 16 3315 4113

All from the Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Brazil

Research field: Dental traumatology

*Correspondence author:

Avenida do Café, s/n. 14040-094. Faculdade de Odontologia de Ribeirão Preto, Bloco M, Sala 28. Ribeirão Preto, SP, Brazil. Phone: 55 16 3315-4113. e-mail: franciscogarcia@forp.usp.br

ABSTRACT

The aim of this study was to perform a systematic review of the *in vivo* effectiveness of different types of root surface treatment materials used in delayed replanted teeth following tooth avulsion in animal models. A systematic review was conducted according to the PRISMA statement. Two reviewers performed a database search for studies published between January 1966 and April 2019 which were indexed in the PubMed, Scopus, and Bireme databases. Studies performed *in vivo,* in animal models with an avulsion/delayed replantation design (≥ 20 min of extra oral dry time) that evaluated the use of different materials for root surface treatment were included. The assessment for risk of bias was performed following recommendations included in Cochrane handbook for systematic reviews of interventions. We found 21 types of materials used for root surface treatment alone and 29 materials used with associations. Stannous fluoride, sodium fluoride, citric acid, doxycycline, Emdogain, alendronate, minocycline, Odanacatib, MFR buffer, recombinant human bone morphogenetic protein, gallium nitrate, acidulated phosphate fluoride, vitamin C, propolis, zoledronic acid, diode laser, indomethacin, fibrin sealant, adipose-tissue derived stem cells treatment and basic fibroblast growth gel. After Grading of Recommendations Assessment, Development, and Evaluation, four studies were scored as low quality of evidence, fifteen studies with moderate quality and six with high quality of evidence. Meta-analysis was not performed due to heterogeneity among studies and materials used for root surface treatment and therefore it was not possible to ascertain which material or protocol present better efficacy when used as root surface treatment material.

Key-words: root surface treatment, delayed replantation, avulsed teeth, systematic review.

INTRODUCTION

Dental trauma is one of the most common urgencies treated in oral health care centers worldwide. [1,2] Among them, avulsion is the most harmful, since the displacement of a dental piece out of its socket due to traumatic forces, causes more serious and irreversible damage to periodontal tissues, needing to be managed as soon as it happens. When a dental piece is avulsed, periodontal structure become compromised, causing disruption of the periodontal ligament (PDL) and neurovascular bundle, and exposing periodontal tissue to environmental contamination.[3]

The aim of replantation is to guarantee the vitality of periodontal ligament and dental pulp; however, its success relies in different associated factors that influence the treatment

outcome. When the tooth remains a long period out of socket (longer than 60 minutes), periodontal ligament cells and pulp necrosis may occur, tooth resorption and an eventual tooth loss.[4-6] Despite the impaired outcomes, delayed replantation has been contemplated as a treatment option by the IADT in complicated case scenarios, mainly because of aesthetics reason.[3,6,7] Delayed replantation has been reported to lead to mineralized tissue resorption process caused by inflammation and tooth loss later on. In light of that, several materials and protocols have been tested such as root surface treatment aiming to support a suitable response of the periodontal tissue aiming to reduce inflammatory resorption and improve the prognosis.

Root surface treatment materials may be an aid in preventing or delaying the root resorption process when delayed replantation is performed. Several materials have been proposed to be applied as root surface treatment, such as fluorides, citric acid, bisphosphonates, enamel matrix derivative (Emdogain), antibiotics, laser photomodulation therapy, propolis, vitamin C, non-steroidal anti-inflammatory drugs (NSAIDs), calcium hydroxide, gallium nitrate, stem cell therapy, among others. However, there is no consensus in which one the best material would be to prevent sequels. Therefore, the aim of this study was to perform a systematic review of the *in vivo* effectiveness of different types of root surface treatment materials used in delayed replantation in animal models.

MATERIAL AND METHODS

Protocol

This systematic review was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.

Focused question

What is the best root surface treatment material or technique to be used in delayed replantation following tooth avulsion?

Literature search and eligibility criteria

The articles included in this study were obtained in the databases MEDLINE (1966 – December 2019). The search strategy was based on the following Medical Subject Heading

terms (MeSH), Text words [tw] and combination strategies: “replantation” [MeSH term] OR “reimplantation” [tw] AND “teeth” [MeSH term] OR “tooth” [MeSH term] AND “avulsion”.

For assessing the studies after MeSH terms search, articles were chosen initially by title, then by abstract and finally, full text article was read to evaluate its relevance in this review (Figure 1). The search was performed by two examiners (SDH and MMV) and in case of disagreement about articles’ importance, a third examiner made the final decision (FWGPS). The articles were chosen based on inclusion criteria such as papers fully written in English, studies performed *in vivo* in animal model with an avulsion/delayed replantation design (≥ 20 min of extra oral dry time) that evaluated the use of different materials for root surface treatment in not endodontically or periodontally-compromised teeth, presence of a control group that represented teeth with late replantation without root surface treatment.

Data extraction

The assessment of heterogeneity was performed by two examiners (SDH and MMV) including study design features such as following: animal species, root formation stage, control group, type of teeth, extra oral dry time, removal of necrotic periodontal ligament, material used for root surface treatment, material used for root canal treatment, splinting regimen, follow-up period and outcome measurement. Both authors extracted all the relevant data from the selected studies and organized them into tables. In order to appraise the effectiveness of the material employed for root surface treatment of delayed replanted teeth, data referring periodontal ligament status, presence of inflammation and presence of resorption was extracted.

Quality assessment and level of evidence

The assessment for risk of bias was performed by two examiners (SDH and FWGPS) following recommendations included in Cochrane handbook for systematic reviews of interventions (Table 1). Included studies were assessed considering the following criteria: randomization, completeness follow-up, balanced experimental group and outcome reporting. The studies were rated as having high, moderate, low, and very low quality of evidence according to the sum of scores based on the GRADE (Table 2) (Grading of Recommendations Assessment, Development, and Evaluation) system.[8]

A meta-analysis was not conducted because the included studies did not have data similar enough to be pooled.

RESULTS

The databases search resulted in 954 articles and forty-two remained for final full text evaluation (Figure 1). Articles with a title not related to the topic and unclear abstracts were not included. Although, all manuscripts dealt with avulsion and replantation, seventeen articles were discarded due to a different extra oral time, different experimental procedures, evaluation of storage medium instead of root surface treatment and administration of systemic medication that could affect the outcome. Finally, 25 articles were included into this review.

After GRADE evaluation, we scored four studies as low quality of evidence, fifteen studies with moderate quality and six with high quality of evidence (Table 3). Between the studies graded as low quality, we found that treatment protocol used to perform root surface treatment had difference to the IADT Guidelines recommendation, mainly among earlier studies where much information and biological processes were unknown at the time.

The relevant study design features were organized in Table 4. The features included were animal species studied, root formation stage, control group, intervention characteristics such as: type of teeth – multi-rooted or single rooted, extra oral dry time, method for removal of necrotic periodontal ligament, material used for root surface treatment, material used for endodontic treatment, splinting regimen, follow-up time and outcome measurements.

The selected studies were published from 1971 to 2019, in which 11 studies used rats as experimental animals (Sprague Dawley, Wistar or breed not described), 11 used dogs of different breeds (Beagle, Mongrel or undefined breed) and 3 studies used monkeys (Macaca and Vervet monkeys).

The interventions were performed using different types of teeth, predominantly incisors with incomplete root formation. Five studies did not report the root formation stage of the experimental teeth. When molars or premolars were included, tooth section was performed before extraction; nevertheless, it was not always detailed in the article. Before the intervention, teeth were left to dry on a bench, from 15 min to 6 hours. Only in 10 studies were specified the method used for periodontal ligament detachment.

We found 21 types of materials used for root surface treatment alone and 29 materials used with associations. Stannous fluoride (SnF_2), sodium fluoride (NaF), citric acid, doxycycline, Emdogain, alendronate, minocycline, Odanacatib, MFR buffer (5mM L-

glutamic acid, 2.5% glycine, 0.5% sucrose, 0.01% polysorbate 80, pH 4.5; Wyeth Research), recombinant human bone morphogenetic protein (rhBMP), gallium nitrate, acidulated phosphate fluoride (FFA), vitamin C, propolis, zoledronic acid, diode laser, indomethacin, fibrin sealant, adipose-tissue derived stem cells treatment and basic fibroblast growth (bFGF) gel. Doxycycline, FFA 2% and NaF 2% were the materials that were used as experimental groups in most of the studies.

As for results, only 9 studies reported presence of inflammation in the experimental group, meanwhile the information was missing in 18 articles. Ankylosis was reported in 9 studies and only 7 studies reported the periodontal ligament fibers orientation after healing. Ankylosis information was missing in other articles. “Normal Healing” as a feature was used to describe periodontal ligament of the experimental group in 7 studies. “Surface resorption” and “Replacement resorption” were found to be used equally and with the same meaning between included articles. However, its presence was reported only in 8 studies, frequently accompanied by inflammatory resorption.

Statistics analysis differed among the studies, however only one study specified about needing to considerate cluster readjustment and statistics when experimental teeth are included in more than one animal. Some studies mentioned statistics processes performance. Two studies did not performed statistics analysis being graded with a low grade.

Meta-analysis was not performed due to heterogeneity between the studies and materials used for root surface treatment.

DISCUSSION

In recent years, root surface treatment protocol has been a controversial subject of discussion. Although the use of sodium fluoride 2% (NaF) for coating the root surface before delayed replantation had been previously recommended,[3] currently there is no evidence to establish NaF as a gold standard between root surface treatment materials. Novel substances that may potentially delay replacement resorption and decrease the possibility of adverse outcomes such as inflammatory resorption had been reported. In need to reach consensus in which material for root surface treatment could improve the treatment success, we performed a systematic review to identify materials that have been applied in an animal model to determine their efficacy.

After searching databases, we found that root formation stage was not specified in 5 studies, 13 included teeth with incomplete root formation and 6 teeth with complete formation. Previous studies have reported root formation stage as an important predictor of the replantation outcome.[33] Case reports of immature teeth having better outcomes after replantation have been found in current literature, unfortunately, scientific evidence is still lacking.[6,33] Information about root formation was not found in all studies included in this review.

Control groups used in these studies was diverse and the extra oral time were different in every study. The IADT guidelines had established that up until 60 minutes could be considered immediate replantation. We included studies that had a control group where root surface was exposed to an extraoral environment up to 60 minutes or that had been immediately replanted. However, in order to have a more comparable results, experimental models should have a positive control group where delayed replantation is performed without any surface treatment. Studies with immediate replantation or with a control group with an unclear treatment or no treatment at all, received lower scores.

We also found that root canal treatment was only performed in some studies. Studies that did not performed root canal treatment were held in the 1980's decade. It could be presumed that at that time, the relevance of pulp tissue contamination due to dental trauma on periodontal healing was not known. However, now is well known that the presence of bacteria in the root canal will prevent repair and sustain the inflammation in the periodontal ligament.[34]

Systemic administration of antibiotics has been also used to improve periodontal ligament healing. Systemic administration of doxycycline was investigated in one study held by Cvek.[12] Doxycycline is an antibiotic that has been widely studied to be used in the treatment of avulsed teeth, as storage medium in solution and as a surface treatment material. It has been reported that its topical use may present antimicrobial effect enhancing the replantation success rate.[12,13] However, when used systemically, doxycycline was not been found to improve the outcome after replantation of avulsed teeth.[12] On the other hand, administration of amoxicillin or tetracycline had a positive influence on the repair process in delayed tooth replantation.[11] IADT guidelines recommend antibiotics prescription as a measure of prevention when dental trauma occurred in highly contaminated areas and in

situations where cleansing of avulsed tooth was not adequate.[3] In this review, we considered the inclusion of a systemic antibiotic as a favorable feature in the experimental design since its absence may ultimately affect the outcome.[35]

Periodontal ligament removal treatment was not specified in 13 studies. In 11 studies necrotic periodontal ligament was removed with different methods: curettes, finishing burs, citric acid, NaOCl, scalpel blade and gauze. Periodontal ligament detachment treatment with gauze was found to not provide protection from ankylosis or replacement resorption in delayed replanted teeth.[33] However, IADT recommends the removal of necrotic periodontal ligament since it was found that presence of necrotic tissue induces osteoclastogenesis and larger resorption areas.[34,35] Studies that did not specified or do not performed the periodontal ligament detachment treatment received lower scores.

Between the root surface treatment materials that were found. Fluoride solutions such as FFA, SnF_2 and NaF were constantly used as a control group treatment, probably because of IADT guidelines recommendation. Doxicycline and Minocycline are locally applied antibiotics under the premise that systemic antibiotics do not have any beneficial effect on pulpal or periodontal healing.[36,37] In this review, we found six studies that used antibiotics, two of them associated to a fluoride. Materials such as FGF, BMP-12 and adipose tissue stem cells in association with fibrin sealant were also used as a root surface treatment. These materials were found to stimulate osteogenic differentiation and promote cell proliferation when applied to human periodontal cells *in vitro* and *in vivo*.[38]

Biphosphonates such as alendronate and zoledronic acid were also used in root canal treatment. Drugs that are applied to prevent bone resorption were used considering a similarity between enzymes, markers and cells involved in bone resorption and those involved in root resorption.[20,24] Photodynamic therapy (PDT) was also presented as a treatment option between the root surface treatment materials. PDT has a well-known set of advantages: an antimicrobial potency, induce cell proliferation, osteogenesis and endothelial cells proliferation.[39-41]

A flexible splint may provide a more favorable outcome where the periodontal ligament fibers reattach following tooth avulsion.[33] In rodent teeth, splinting after replantation is not strictly recommended since the anatomy of the socket provides a stable position.[34] We found that 12 studies included in this review did not performed splinting, from these, 11

studies where performed in rats. As IADT recommends in treatment for human teeth, we considered flexible splinting as a mandatory step to achieve healing after replantation, however, 8 studies did not detail if splinting was performed, 1 study in dogs performed rigid splinting and only 4 studies performed flexible splinting. Thus, studies without splinting included were considered of lower quality.

This systematic review has reunited classic and state of art literature about root surface treatment materials having encountered a wide variety of substances that have been tested to prevent mineralized tissue resorption and possibly heal periodontal ligament in delayed replanted teeth. However, even though, six articles were scored as high-quality evidence, due to diverse materials used during experimentation, it was not possible to perform meta-analysis.

In conclusion, we found a high heterogeneity among the studies, not being possible to ascertain which material or protocol present better efficacy when used as root surface treatment material. Nonetheless, this review shed light on methodological issues that should be considered on future research that is deemed necessary in this field.

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DISCLOSURES

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FIGURE CAPTION

Figure 1. Flow diagram illustrating the selection process of studies regarding root surface treatment and delayed tooth replantation.

Table 1. Protocol for qualitative scoring of selected studies.

Subgroups	**Item**	**Component**	**Classification**	**Score**	**Definition**
Clinical aspects	1. Treatment guidelines for permanent teeth	Root canal treatment	Yes No	1 0	Studies that performed root canal treatment
		Administer systemic antibiotics	Yes No	1 0	Studies that administered systemic antibiotics
		Apply a flexible splint	Yes, or none for rats/mice No	1 0	Studies that performed splinting
Methodological aspects	2. Sample	Animal model	Monkeys Dogs Rats	2 1 0	Studies that used rodent were scored lower due to the evolutionary distance to humans
	3. Interventions	Extra-alveolar time	≥ 60 minutes < 60 minutes Unclear	2 1 0	Studies that described extra-alveolar time and immersion period in media prior to replantation
		Root formation stage	Clear Unclear	1 0	Studies that described the root formation stage (open and closed apex)
		Removal of PDL	Removed Not removed/ unclear	1 0	Studies that performed removal of PDL
	4. Outcomes	Completely defined	Clear Unclear	1 0	Studies that clearly described the outcome(s)
	5. Control groups	Definition of control group	Delayed replantation without treatment Immediate replantation without treatment Unclear/not reported/ inappropriate control group	2 1 0	Studies that did not include a control group, did not clearly describe the control group, or did not have an appropriate control group were scored lower
	6. Statistical methods	Statistical methods used	Adequate Partial Inadequate/ Inexistent	2 1 0	The statistical analysis was satisfactory to evaluate the data
	7. Results	Data presentation	Adequate Partial Inadequate	2 1 0	The description of the results was clear and data on different root surface treatment material was fully presented

Table 2. Criteria used for grading quality of evidence of the included studies.

GRADE range	**GRADE quality of evidence**	**Interpretation**
13 – 16	High	Confident that the true effect lies close to the estimated effect.
9 – 12	Moderate	The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different.
5 – 8	Low	The true effect may be substantially different form the estimated effect.
1 – 4	Very low	The true effect is likely to be substantially different from the estimated effect.

Note: Based on GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guidelines.[8]

Table 3. Quality assessment of selected studies.

	1. Treatment guidelines for permanent teeth			2. Sample	3. Interventions			4. Outcomes	5. Control groups	6. Statistical methods	7. Results	8. Quality of evidence	9. Score
	Root canal treatment	Administer systemic antibiotics	Apply flexible splint	Animal model	Extra-alveolar time	Root formation stage	Removal of PDL	Completely defined	Definition of control group	Statistical methods	Data presentation		
Bjorvatn & Massler 1971 [9]	0	0	1	1	2	1	0	0	2	0	0	7	Low
-Klinge et al. 1984 [10]	0	0	0	2	1	1	1	1	2	1	1	10	Moderate
Bjorvatn et al. 1989 [11]	0	0	0	2	1	0	0	1	0	1	2	8	Low
Cvek et al. 1990 [12]	0	1	1	3	2	0	0	1	2	1	2	13	High
Selvig et al. 1992 [13]	0	1	0	2	1	0	0	0	2	1	2	10	Moderate
Iqbal et al. 2001 [14]	1	1	0	2	2	1	0	1	2	1	2	13	High
Bryson et al. 2003 [15]	1	0	0	2	2	1	0	1	2	1	1	11	Moderate
Khin Ma et al. 2003 [16]	1	1	0	3	2	1	0	1	2	1	2	14	High

Lam e Sae-Lim, 2004 [17]	1	1	0	3	2	1	1	1	2	1	2	15	High
Sorensen et al. 2004 [18]	0	1	1	2	1	0	1	1	0	0	1	8	Low
Lustosa-Pereira et al. 2006 [19]	1	1	1	1	2	1	1	1	1	0	1	11	Moderate
Mori et al. 2007 [20]	1	1	1	1	1	1	0	0	0	0	1	7	Low
Poi et al. 2007 [21]	1	1	1	1	2	1	1	1	0	0	1	10	Moderate
Panzarini et al. 2008 [22]	1	1	1	1	2	1	1	0	0	1	1	10	Moderate
Gulinelli et al. 2008 [23]	1	1	1	1	2	1	1	0	2	1	1	12	Moderate
Mori et al. 2010 [24]	1	1	1	1	1	1	1	1	0	1	2	11	Moderate
Carvalho et al. 2012 [25]	1	1	1	1	2	1	1	1	2	1	2	14	High
Zanetta-Barbosa et al. 2014 [26]	1	1	0	2	1	0	0	1	2	1	2	11	Moderate

Panzarini et al. 2014 [27]	1	1	1	1	2	1	0	1	2	1	2	13	High
Jabarifar et al. 2015 [28]	0	1	1	2	2	1	0	1	0	1	1	10	Moderate
Barbizam et a. 2015 [29]	1	0	1	1	2	1	0	1	2	2	2	13	High
Demirel et al. 2016 [30]	1	1	1	1	2	1	0	1	2	1	2	13	High
Carvalho et al. 2017 [31]	1	1	1	1	2	1	1	1	2	1	2	14	High
Kwon et al. 2018 [32]	1	1	1	1	2	1	0	1	2	2	2	14	High

Table 4. Description of selected studies.

Study & Year	Species (n)	Root formation stage	Control group	Intervention						Follow-up (days or weeks)	Outcome measurement
				Type of teeth / teeth	Extra-oral dry time	Method for PDL detatchment	Material for root surface treatment (time)	Material for endodontic	Splinting regimen		
Bjorvatn & Massler 1971 [9]	Rat (18 Sprague Dawley rats)	Incomplete	Dry storage for 30 and 60 min and soaked in	Molars (n = 72 teeth)	30 and 60 min	Not specified	1% SnF_2 (5 10% SnF_2 2% NaF (5 min)	Not specified	Not specified	1,3,6 weeks	Histopathological and Histomorphometric analysis
Klinge et al. 1984 [10]	Dog (6 Beagle dogs)	Complete	Dry storage for 45 min	Incisors (n = 43	45 min	Curettes, diamond and finishing	Citric acid pH 1.0 (3 min)	Endodontic treatment not	No splinting	21 days	Histopathological and Histomorphometric
Bjorvatn et al. 1989 [11]	Dog (5 Beagle dogs)	Not specified	Dry storage for 45 min	Incisors (n = 20 teeth)	45 min	Not specified	1% Doxycycline 1% SnF_2 (5 min) 1% SnF_2 (5 min) + 1%	Endodontic treatment not performed	No splinting	4 weeks	Histopathological and Histomorphometric analysis
Cvek et al. 1990 [12]	Monkey (47 Vervet monkeys *Cercopithecus aethiops pygery*)	Not specified	Treated or not systemically with doxycycline and dry storage for 30	Incisors (n = 54 teeth)	30 and 60 min	Not specified	0.05 mg/mL of Doxycycline (5 min)	Not specified	Rigid splinting	6 to 8 weeks	Histopathological and Histomorphometric analysis
Selvig et al. 1992 [13]	Dog (3 Beagle dogs)	Not specified	Dry storage for 45 min	Incisors (n = 23	45 min	Not specified	1% Doxycicline in HCl (5 min) +	Not specified	No splinting	4 weeks	Histopathological and Histomorphometric
Iqbal et al. 2001 [14]	Dog (9 Beagle dogs)	Complete	Dry storage for 15, 30 and 60 min	Incisors (n = 24	15,30 and 60 min	Not specified	Emdogain (time not reported)	Calcium hydroxide	Teeth were splinted or	8 and 12 weeks	Histopathological and Histomorphometric
Bryson et al. 2003 [15]	Dog (6 Mongrel Dogs)	Complete	Dry storage for 60 min Dry storage for 60 min and	Premolar (n = 27 roots)	60 min	Not specified	Minocycline (time not reported) Cementum defect and Minocycline (time not reported)	Gutta percha	No splinting	16 weeks	Histopathological and Histomorphometric analysis
Khin et al. 2003 [16]	Monkey (7 *Macaca fascicularis*)	Complete	Dry storage for 60 min	Incisors, premolarand molars	60 min	Not specified	0.02 mg/mL of Minocycline solution (5min)	Gutta percha and zinc oxide	No splinting	12 weeks	Histopathological and Histomorphometric analysis

Lam & Sae-Lim, 2004 [17]	Monkey (7 *Macaca fascicularis*)	Complete	Dry storage for 60 min	Incisors and posterior teeth	60 min	Pumice and root conditioning with PrefGel	Emdogain gel (time not reported)	Gutta-percha and zinc oxide and eugenol	No splinting	16 weeks	Histopathological and Histomorphometric analysis
Sorensen et al. 2004 [18]	Dog (6 Mongrel dogs)	Not specified	Extraction not performed	Incisor and premolar teeth (n =	20 to 30 min	Curette and citric acid or not	MFR #00842 buffer 1.5mg/mL of rhBMP-12	Not specified	Flexible splinting	8 weeks	Histopathological and Histomorphometric analysis
Lustosa-Pereira et al. 2006 [19]	Rat (54 rats of unspecified	Incomplete	Dry storage for 15 min	Incisors (n= 54 teeth)	30 and 60 min	1% NaOCl (30min)	3.2 mg/L of Sodium Alendronate solution	Calcium hydroxide – based paste	No splinting	15, 60 and 90 days	Histopathological and Histomorphometric
Mori et al. 2007 [20]	Rat (20 Wistar rats)	Incomplete	Not specified	Incisors (n = 20 teeth)	30 min	Not specified	20mL of 10^{-4}M of Gallium 2% NaF	Calcium hydroxide – based paste	No splinting	15 and 60 days	Histopathological and Histomorphometric analysis
Poi et al. 2007 [21]	Rat (24 Wistar rats)	Incomplete	Not specified	Incisors (n = 12 teeth)	6 hours	1% NaOCl (5 min)	Emdogain gel 2% FFA (10min)	Calcium hydroxide - based paste	No splinting	10 and 60 days	Histopathological and Histomorphometric analysis
Panzarini et al. 2008 [22]	Rat (20 Wistar rats)	Incomplete	Not specified	Incisors (n= 20 teeth)	6 hours	#15 Scalpel blade	Effervescent vitamin C 2% FFA (10min)	Calcium hidroxyde-based paste	Not specified	60 days	Histopathological and Histomorphometric analysis
Gulinelli et al. 2008 [23]	Rat (30 Wistar rats)	Incomplete	Dry storage for 60 min and saline solution	Incisors (n = 20 teeth)	60 min	# 15 Scalpel blade	15% Propolis + propylenegl 2% FFA (10 min)	Calcium hydroxide-based paste	Not specified	60 days	Histopathological and Histomorphometric analysis
Mori et al. 2010 [24]	Rat (24 Wistar rats)	Incomplete	Not specified	Incisors (n = 24 teeth)	30 min	# 11 Scalpel blade	10^{-6}M Zoledronic 2% NaF (20 min)	Calcium hydroxide-based paste	Not specified	15 and 60 days	Histopathological and Histomorphometric analysis
Carvalho et al. 2012 [25]	Rat (60 Wistar rats)	Incomplete	Dry storage for 60 min	Incisors (n = 45 teeth)	60 min	1% NaOCl immersion (10 min) and gauze	GaA1A high-power diode laser with a wave length of 810nm and an output of 1.2 to 1.0 W GaA1A high-power diode laser with a wave length of 810nm and an output of 1.2 to 1.0 W 2% NaF (20 min)	Calcium hydroxide-based paste	Not specified	15, 30 and 60 days	Radiographic, Histopathological and Histomorphometric analysis

Zanetta-Barbosa et al. 2014 [26]	Dog (6 dogs from undefined breeds)	Not specified	Dry storage for 50 min and saline solution immersion (10 min)	Incisors (n = 18 teeth)	50 min	Not specified	50 mg/mL of $CaOH_2$ (10 min) 50 mg/mL of Indomethac 25 mg/mL Indomethacin and 50 g/mL CaOH2	Gutta-percha and zinc oxide and eugenol based - paste with intracanal medication	Not specified	120 days	Histopathological and Histomorphometric analysis
Panzarini et al. 2014 [27]	Rat (30 Wistar rats)	Incomplete	Dry storage for 60 min and saline solution	Incisors (n = 20 teeth)	60 min	Not specified	15% propolis and 2% FFA (10 min)	Calcium hydroxide-based paste	Not specified	60 days	Histopathological and Histomorphometric analysis
Jabarifar et al. 2015 [28]	Dog (4 dogs from undefined breeds)	Incomplete	Not specified	Incisors and premolar (n =	120 min	Not specifed	10% Doxycycline (10 min)	Not specified	Flexible splinting	60 days	Histopathological and Histomorphometric analysis
Barbizam et al. 2015 [29]	Dog (4 Beagle dogs)	Complete	Dry storage for 20 min and	Premolar (n = 34	20 min and 60	Not specified	Emdogain gel (time not reported)	Calcium hydroxide-based paste	Flexible	120 days	Histopathological and Histomorphometric
Demirel et al. 2016 [30]	Rat (19 Sprague – Dawley rats)	Incomplete	Dry storage for 60 min	Incisors (n = 30)	60 min	Not specified	Fibrin sealant (time not Fibrin sealant + Adipose tissue stem	Calcium hydroxide-based paste	No splinting	60 days	Histopathological and Histomorphometric analysis
Carvalho et al. 2017 [31]	Rat (50 Wistar rats)	Incomplete	Dry storage for 60 min	Incisors (n =30)	60 min	Gauze with 1% NaOCL	0.2% basic fibroblast growth gel (time not High power diode laser with a wavelength of 808 nm and an output of 1.2 and 1.0 0.2% basic fibroblast growth gel + High power diode laser with a wavelength of 808 nm and	Calcium hydroxide-based paste	No splinting	60 days	Radiographic, Histopathological and Histomorphometric analysis

Kwon et al. 2018 [32]	Dogs (4 Beagle dogs)	Complete	Dry storage for 60 min	Premolar (n = 21 roots)	60 min	Not specified	0,1 mM ODN	Calcium hydroxide-based paste	Flexible	90 days	Micro-CT analysis, Histopathological and Histomorph

$SnF_{2=}$ Stannous Fluoride; NaF= Sodium Fluoride; HCl= Chlorydric acid; HBSS= Hanks's balance salt solution; MFR #00842 buffer= 0.5% sucrose, 2.5% glycine, 5mM L-glutamatic acid, 5Mm NaCl, 0.01% polysorbate 80 pH 4.5; rHBMP-12= Bone morphogenetic protein-12; NaOCl= Sodium hypochlorite; GaAlAs laser= Gallium-Aluminium-Arsenide laser; $CaOH_{2=}$ Calcium hydroxide; FFA= Acidulated phosphate fluoride; ODN= Odanacatib.