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Review Article

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Effect of calcium hydroxide on inflammatory root resorption and ankylosis in replanted teeth compared with other intracanal materials: a review

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ABSTRACT

Calcium hydroxide (CH) is the gold-standard intracanal dressing for teeth subjected to traumatic avulsion. A common complication after the replantation of avulsed teeth is root resorption (RR). The current review was conducted to compare the effect of CH with that of other intracanal medications and filling materials on inflammatory RR and replacement RR (ankylosis) in replanted teeth. The PubMed and Scopus databases were searched through June 2018 using specific keywords related to the title of the present article. The materials that were compared to CH were in 2 categories: 1) mineral trioxide aggregate (MTA) and endodontic sealers as permanent filling materials for single-visit treatment, and 2) Ledermix, bisphosphonates, acetazolamide, indomethacin, gallium nitrate, and enamel matrix-derived protein (Emdogain) as intracanal medicaments for multiple-visit management of avulsed teeth prior to the final obturation. MTA can be used as a single-visit root filling material; however, there are limited data on its efficacy due to a lack of clinical trials. Ledermix and acetazolamide were comparable to CH in reducing RR. Emdogain seems to be an interesting material, but the data supporting its use as an intracanal medication remain very limited. The conclusions drawn in this study were limited by the insufficiency of clinical trials.

Keywords: Calcium hydroxide; Root resorption; Tooth ankylosis; Tooth avulsion; Tooth replantation

INTRODUCTION

The lifetime prevalence of traumatic tooth avulsion, which is more frequent in the maxillary central teeth [1], has been reported to be up to 16% [2]. A complication after the replantation of avulsed teeth is root resorption (RR), which can be classified as external and internal RR. External RR, which is more prevalent, is categorized in descending order of frequency as replacement RR (RRR or ankylosis; 51%), inflammatory RR (IRR; 23.2%), and surface RR (SRR; 13.3%) [3]. Because of the good prognosis, low incidence, and reversibility of SRR [4,5], the main focus of the current review article is on IRR and ankylosis. IRR involves erosion of cementum or dentin accompanied by inflammatory cells in the adjacent

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periodontal area [6,7]. Ankylosis takes place in traumatized teeth with a dried, destroyed, or removed periodontal ligament, giving rise to tooth fusion with the alveolar bone [8,9].

The success rate of replanted teeth has been reported to vary from 4% to 50% in different studies [10]. Although replantation of teeth is considered to be a temporary measure, in many such cases, the teeth survive up to 20–40 years with a normal periodontium [11].

Although there is no absolute consensus on the management of avulsed teeth with an extended dry time outside of the socket, treatment of the root surface and root canal is the current protocol [12]. In fact, the root surface should be removed from the remnant periodontal ligament [13,14], for which several solutions and methods have been proposed [14,15]. Of note, removing necrotic periodontal tissue decreases the amount of inflammatory stimuli and in turn, RR [16].

The next step in the treatment of such teeth is root canal debridement. The purpose of this step is to eliminate the toxins arising from bacteria in the necrotic pulp, which lead to inflammation and osteoclast-mediated resorption of replanted teeth [17,18]. For root canal treatment of these teeth, using an intracanal medication is suggested [19]. Calcium hydroxide (CH), with the formula of $Ca(OH)_2$, is by far the most widely used intracanal medication because it has numerous desirable properties [20], most notably inhibition of bacterial enzymes, antimicrobial effects, activation of tissue enzymes such as alkaline phosphatase, and stimulation of mineralization [20,21]. Despite the excellent properties of CH, it has some drawbacks, including the requirement of a long duration of treatment, the need for replacements, and weakening of the tooth structure in cases of long-term application [20,22]. CH may also cause tooth discoloration [23]. Hence, to overcome some of the disadvantages of CH, several studies have been conducted to compare various other intracanal dressings and filling materials with CH [20].

It is debatable whether avulsed teeth should be filled in a single visit or multiple applications of intracanal medicaments should be performed prior to the final filling.

The current review article was conducted to evaluate the effect of various intracanal medications and filling materials in comparison with CH as a traditional gold standard for IRR and ankylosis in replanted teeth.

The authors electronically searched the PubMed and Scopus databases through June 2018 using the following keywords: “calcium hydroxide,” “root resorption,” “external root resorption,” “inflammatory external root resorption,” “external inflammatory root resorption,” “external inflammatory resorption,” “inflammatory external resorption,” “tooth ankylosis,” “replacement root resorption,” “tooth avulsion,” “tooth luxation,” “tooth replantation,” “intrusion,” “intrusive luxation,” “tooth injury,” and “dental trauma.”

The references of each article were also searched in order to identify any articles that were missed during the initial literature search. Only articles relevant to the selected keywords and the topic of the study were included; thus, every study had to compare CH with another intracanal medication or filling material. Case reports were not included. In total, 108 and 128 papers were retrieved from the PubMed and Scopus databases, respectively. After screening the titles and abstracts and applying the inclusion criteria, 17 articles met the criteria for final inclusion. Of these, only one study was a multicenter randomized controlled

trial, while the remaining were animal studies. The details of the retrieved articles are presented in **Table 1**.

Table 1. Characteristics of the selected articles

First author (yr)	Study design	Type of trauma	Intracanal material (No. of teeth)	Replantation time	Details of the procedure	Main result
Panzarini *et al*. [29] (2007)	Animal study on monkeys	Avulsion	CH (6) MTA (6)	Immediate replantation	- Storage: in saline solution for 15 min - Surface treatment: none - Splinting: 14 days - Sacrifice: 180 days - ABA: single dose of benzathine penicillin 320,000 IU	- Ankylosis: NS - IRR: NS
Panzarini *et al*. [32] (2014)	Animal study on monkeys	Avulsion	CH (10) MTA (10)	Delayed replantation	- Storage: 60 min bench-dried - Surface treatment: 10 min in 2% acidulated phosphate sodium fluoride - Splinting: 30 days - Sacrifice: 60 days - ABA: penicillin V (250 mg; 3 drops/day for 7 days)	- Ankylosis: significantly lower in MTA group (p = 0.04) - IRR: NS
Marão *et al*. [33] (2012)	Animal study on Wistar rats	Avulsion	CH (10) MTA (10)	Delayed replantation	- Storage: 60 min bench-dried - Surface treatment: 10 min in 2% acidulated phosphate sodium fluoride - Splinting: not mentioned - Sacrifice: 80 days - ABA: single IM dose of benzathine G penicillin 20,000 IU	- Ankylosis: NS - IRR: NS
Esteves *et al*. [34] (2015)	Animal study on Wistar rats	Avulsion	Control (8) CH (9) MTA plug & CH filling (10)	Delayed replantation	- Storage: 60 min bench-dried - Surface treatment: 10 min in 2% acidulated phosphate sodium fluoride - Splinting: not mentioned - Sacrifice: 60 days - ABA: single IM dose of penicillin G benzathine 20,000 IU	- Ankylosis: NS - IRR: significantly lower in MTA group (p = 0.0006)
Vogt *et al*. [31] (2016)	Animal study on Wistar rats	Avulsion	Control (12) CH (12) MTA (12) MTA Fillapex (12)	Delayed replantation	- Storage: 30 min bench-dried - Surface treatment: 30 min in 1% sodium hypochlorite and 20 min in 2% sodium fluoride solution - Splinting: none - Sacrifice: 10 and 60 days - ABA: single IM dose of penicillin G benzathine 20,000 IU	- At 10 days: NS regarding IRR - At 60 days: only ankylosis extension showed a statistically significant difference between the MTA Fillapex and the control (p < 0.05)
Ferreira *et al*. [35] (2017)	Animal study on Wistar rats	Avulsion	CH MTA Fillapex	Delayed replantation	- Storage: 60 min bench-dried - Surface treatment: 10 min in 2.72% acidulated phosphate sodium fluoride - Splinting: performed by silk 3/0 but the duration was not mentioned - Sacrifice: 8 weeks - ABA: not mentioned	- Ankylosis: NS - IRR: NS
Negri *et al*. [17] (2008)	Animal study on Wistar rats	Avulsion	CH-based paste* (8) Sealapex (8) Endofill (8)	Delayed replantation	- Storage: 60 min bench-dried - Surface treatment: 10 min in 2% acidulated phosphate sodium fluoride - Splinting: none - Sacrifice: 60 days - ABA: single IM dose of penicillin G benzathine 20,000 IU	- Ankylosis: NS - IRR: NS

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Table 1. (Continued) Characteristics of the selected articles

First author (yr)	Study design	Type of trauma	Intracanal material (No. of teeth)	Replantation time	Details of the procedure	Main result
Day *et al*. [36] (2012)	Multicenter randomized controlled trial	Avulsion	CH (15 teeth/12 patients) Ledermix (12 teeth/10 patients)	Delayed or immediate replantation	- Storage: a maximum of 20 min dry extra-alveolar storage time, or the aforementioned scenario plus a maximum of 60 min extra-alveolar time, kept in milk or another appropriate storage media - RCT procedure: pulp extirpated and dressed with CH or Ledermix within 7–10 days, at days 60–90 re-dressed with CH, at month 6 obturated if no sign of active resorption, at year 1 definite diagnosis or patient continued to be reviewed until healing - Splinting: 7–10 days - Clinical visits: 60–90 days, 6 months ± 14 days, 1 year ± 14 days - ABA: amoxicillin, if allergic another suitable antibiotic	- Ankylosis: NS - Periodontal healing: NS
Thong *et al*. [37] (2001)	Animal study on monkeys	Avulsion	Control (12) CH (11) Ledermix (12)	Immediate replantation	- Storage: 15 min bench-dried - Surface treatment: none - Splinting: none - Sacrifice: after 8 weeks - ABA: not mentioned	- Ankylosis: significantly lower in Ledermix group than in CH group ($p < 0.05$), but NS when the untreated control was compared with either treatment group - IRR: NS between CH and Ledermix, but significantly lower in both treatment groups than in the control group ($p < 0.05$)
Bryson *et al*. [38] (2002)	Animal study on mongrel dogs	Avulsion	CH (15) Ledermix (14)	Delayed replantation	- Storage: 60 min bench-dried - Surface treatment: not mentioned - Splinting: none - Sacrifice: 4 months - ABA: not mentioned	- Favorable healing (presence of cementum over the dentin surface whether previously resorbed or not), and poor healing (including IRR or ankylosis): Ledermix exhibited a significantly greater amount of favorable healing ($p = 0.004$)
Mori *et al*. [43] (2007)	Animal study on Wistar rats	Avulsion	CH (15) Alendronate (15)	Delayed replantation	- Storage: 30 min bench-dried - Surface treatment: 30 min in 1% hypochlorite solution and 20 min in 2% acidulated phosphate sodium fluoride - Splinting: none - Sacrifice: 15, 30, and 60 days - ABA: single IM dose of penicillin G benzathine 20,000 IU	- At 15 days: NS - At 30 days: IRR, RRR, and ankylosis were greater in the CH group ($p < 0.05$) - At 60 days: NS
Thong *et al*. [7] (2009)	Animal study on monkeys	Avulsion	Control (plaque) (5) CH (7) Bisphosphonate (etidronate disodium) (11)	Delayed replantation	- Storage: 60 min bench-dried - Surface treatment: - Splinting: none - Sacrifice: 8 weeks - ABA: not mentioned	- Ankylosis: was the least in the control and the greatest in the bisphosphonate-treated group ($p < 0.05$); the difference was NS between the CH and bisphosphonate groups, but both had significantly higher ankylosis occurrence than the untreated control ($p = 0.01$) - IRR: was significantly greater in the control than in the 2 treatment groups ($p = 0.02$), but was NS between the CH and bisphosphonate groups
Mori *et al*. [45] (2006)	Animal study on Wistar rats	Avulsion	CH Acetazolamide solution	Delayed replantation	- Storage: 30 min bench-dried - Surface treatment: 30 min in 1% hypochlorite solution and 20 min in 2% acidulated phosphate sodium fluoride - Sacrifice: 15, 30, and 60 days - Splinting: none - ABA: single IM dose of penicillin G benzathine 20,000 IU	- At 15 days: NS - At 30 days: ankylosis and RRR were greater in the CH group ($p < 0.05$) - At 60 days: RRR and IRR were greater in the CH group ($p < 0.05$)

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Table 1. (Continued) Characteristics of the selected articles

First author (yr)	Study design	Type of trauma	Intracanal material (No. of teeth)	Replantation time	Details of the procedure	Main result
Mori *et al*. [46] (2013)	Animal study on Wistar rats	Avulsion	CH Acetazolamide paste	Delayed replantation	- Storage: 30 min bench-dried - Surface treatment: 20 min in 1% hypochlorite solution and 20 min in 2% acidulated phosphate sodium fluoride - Splinting: none - Sacrifice: at 15 and 60 days - ABA: single IM dose of penicillin G benzathine 20,000 IU	- Ankylosis: NS - RRR: at 60 days, was greater in the CH group ($p < 0.05$) - IRR: NS
Zanetta-Barbosa *et al*. [50] (2014)	Animal study on dogs	Avulsion	Control (6) CH (6) Indomethacin (6) CH + indomethacin (6)	Delayed replantation	- Storage: 50 min bench-dried - Surface treatment: 10 min in 0.9% physiologic saline, or CH solution (50 mg/mL), or indomethacin solution (50 mg/mL), or CH + indomethacin solution (25 mg/mL of each) - Splinting 15 days - Sacrifice: on day 120 - ABA: single dose of penicillin G procaine 300,000 IU and sodium penicillin G 100,000 IU	- Ankylosis: NS - IRR: NS
Mori *et al*. [56] (2006)	Animal study on Wistar rats	Avulsion	CH Gallium nitrate	Delayed replantation	- Storage: 30 min bench-dried - Surface treatment: 30 min in 1% hypochlorite solution and 20 min in 2% acidulated phosphate sodium fluoride - Splinting: none - Sacrifice: at 15, 30, and 60 days - ABA: single IM dose of penicillin G benzathine 20,000 IU	- At 15 days: NS - At 30 days: ankylosis and RRR were greater in the CH group ($p < 0.05$) - At 60 days: NS
de Oliveira *et al*. [59] (2013)	Animal study on Wistar rats	Avulsion	CH (8) Enamel Matrix-derived protein (Emdogain) (8)	Delayed replantation	- Storage/surface treatment: 45 min in saturated solution of sodium chloride - Splinting: not mentioned - Sacrifice: 25 days - ABA: none	- Emdogain-treated teeth showed a lower percentage of surface resorption (31.58%) than the CH group (80.48%) ($p = 0.0006$)

Notation: in the studies performed by Mori et al. [43,45,46,56], the authors reported distinct results for "ankylosis" and "RRR". However, we failed to find any distinguished meaning for these terms described in Mori's articles. Commonly in the literature, these terms are synonymous.
CH, calcium hydroxide; MTA, mineral aggregate trioxide; ABA, antibiotic administration; IU, international unit; IRR, inflammatory root resorption; RRR, replacement root resorption; NS, not significant; IM, intramuscular; RCT, root canal treatment.
*5 mL of propylene glycol, 5 g of CH, 2 g of zinc oxide, and 0.015 g of colophony.

REVIEW

Calcium hydroxide in comparison with mineral trioxide aggregate

Although the use of CH paste as a temporary intracanal medication is mostly employed in replanted teeth, the importance of periodic dressing changes to maintain its action has been highlighted [24]. Therefore, clinicians are seeking a material with advantageous characteristics similar to those of CH that can be used as a single-visit filling material. Mineral trioxide aggregate (MTA) has been considered for this purpose because it has similar properties to those of CH [25,26], as well as favorable physical characteristics [27]. It is believed that medications with an alkaline pH that continuously release CH are effective in controlling IRR [28].

Our search yielded 5 animal studies comparing CH with MTA using replanted teeth (**Table 1**). First, in 2007, Panzarini *et al.* [29] compared CH with MTA in monkey teeth that underwent immediate replantation. In the extra-alveolar period, the teeth were kept in saline solution. After 7 days, the teeth underwent root canal debridement and the root canals were irrigated

with a saturated solution of CH with the aim of making the dentin alkaline [30]. Since there was no significant difference between the study groups regarding IRR and ankylosis, it was concluded that both MTA and CH are suitable root canal filling materials for immediately replanted teeth. Vogt *et al.* [31] also evaluated the effect of these 2 materials on replanted teeth exposed to a dry environment for 30 minutes. They analyzed the groups at 10 and 60 days. MTA-treated teeth displayed IRR and ankylosis similar to those observed in CH-treated teeth at both 10 and 60 days. However, the CH-treated group showed significantly lower inflammation scores than the negative control group at 10 days.

Three animal studies were performed to assess delayed replantation (with a dry time of 60 minutes). In 2014, Panzarini *et al.* [32] compared CH with MTA in cases of delayed replantation. In general, they did not find inflammatory cells in the periodontium of the teeth when either CH or MTA was used (except for one specimen in the apical foramen in the CH-treated group). However, in the MTA group, the incidence of ankylosis was significantly lower than in the CH group. In contrast, Marão *et al.* [33] did not find any significant difference in terms of ankylosis between the 2 groups.

Esteves *et al.* [34] compared a CH-treated group with a group in which the root canal apices were sealed with an MTA plug and then filled with CH paste. Periapical healing was significantly higher in the MTA-treated group, and although the incidence of ankylosis was not significantly different between the groups, the MTA-treated group was significantly less affected by IRR. The latter effect might be attributed to the fact that the MTA plug blocks the leakage and dissolution of CH paste in the root apex, consequently keeping the CH in the root canal. This enables continuous disinfection of the dentinal walls without contact with periapical tissue fluids [34].

In summary, when CH or MTA was used in cases of immediate replantation of avulsed teeth with long-term placement of intracanal materials (180 days), there was no significant difference in the occurrence of IRR and ankylosis [29]. However, in cases of delayed replantation, the occurrence of IRR or ankylosis in the MTA-treated groups was similar to or lower than that of the CH-treated groups (**Table 1**) [32-34].

Calcium hydroxide in comparison with endodontic sealers

Two animal studies compared CH with MTA Fillapex in terms of the occurrence of ankylosis in replanted teeth [31,35]. They did not find any significant differences between the 2 groups. However, in one of the studies, when compared to the MTA-treated group, the extent of ankylosis was significantly superior in the MTA Fillapex-treated group at a 60-day follow-up [31]. Negri *et al.* [17] also compared Sealapex and Endofill with CH and found no significant difference in the occurrence of ankylosis in teeth that underwent delayed replantation. In general, filling the root canals with the aforementioned MTA-based sealers did not provide better results.

Calcium hydroxide in comparison with Ledermix

Ledermix is a commercial water-soluble paste containing 1% triamcinolone, a corticosteroid, and 3% demeclocycline, a tetracycline. It seems that the corticosteroid in this substance plays an active role in reducing IRR [18]. The only randomized controlled trial found in our search was a study by Day *et al.*, [36] who conducted a multicenter study (at 5 specialist pediatric dentistry centers). They utilized a standardized protocol, including calibration across centers, and did not find any significant difference in periodontal healing and ankylosis

between the CH and Ledermix-treated groups. In 2001, Thong *et al.* [37] conducted an animal study and did not find any differences in IRR between the CH and Ledermix-treated groups when the teeth underwent immediate replantation. However, the incidence of IRR was lower in both treatment groups than in a control group. In their study, ankylosis was significantly lower in the Ledermix group than in the CH group, but the untreated control group did not differ significantly from either treatment group. This finding might have been related to the duration of extraoral storage of the extracted teeth (15 minutes), as well as the lack of contamination. In fact, it is possible that not all pulps became contaminated following extraction, and revascularization of the pulps was noted in 2 control teeth that were excluded from the analysis [37].

Bryson *et al.* [38] evaluated the effect of CH and Ledermix after 60 minutes of dry storage. Two-rooted premolars were first hemi-sectioned and then extracted and divided into 2 study groups. The authors dichotomized the outcomes into 1) favorable healing (presence of cementum over the dentin surface, whether previously resorbed or not) and 2) poor healing (including IRR or ankylosis). The authors concluded that the Ledermix-treated group exhibited significantly greater healing and less resorption than the CH-treated group.

However, a disadvantage of Ledermix paste is tooth discoloration, which has been reported to be significantly greater than observed with CH paste [39,40].

In summary, in cases of immediate replantation, ankylosis was significantly lower when Ledermix was used compared to CH, although the occurrence of IRR did not differ significantly between the 2 treatments [37]. However, the studies in which CH and Ledermix were used for delayed replantation yielded conflicting results [36,38].

Calcium hydroxide in comparison with bisphosphonates

In 2001, Levin *et al.* [16] soaked extracted dog teeth in an alendronate solution prior to replantation. This method was significantly satisfactory for the elimination of RR and resulted in better healing than when Hanks' Balanced Salt Solution without alendronate was used. This phenomenon might be attributable to the osteoclast inhibitory activity of alendronate [41,42]. Thereafter, in 2007, Mori *et al.* [43] used alendronate as an intracanal therapeutic agent in rat teeth that underwent late replantation. When compared to a CH-treated group, the presence of RR was less evident in the alendronate-treated group at 30 days. However, these differences were not observed at 15 or 60 days. In general, CH and alendronate demonstrated similar behaviors.

In 2009, Thong *et al.* [7] conducted a study of avulsed monkeys' teeth using 2 intracanal medications (CH paste and etidronate disodium, a bisphosphonate) and a negative control group. IRR was significantly greater in the negative control group than in the 2 treatment groups, while ankylosis was significantly lower in the treatment groups; however, no significant difference was found between the CH and bisphosphonate groups. The lower amount of inflammatory resorption and inflammation of the periodontal ligament in the negative control group can be attributed to canal debridement prior to replantation, resulting in the removal of bacteria and pulp tissue debris. Thus, the inflammatory stimulus was less intense in the untreated control group. In the study of Thong *et al.*, [7] the etidronate-treated group showed significantly worse overall outcomes than the CH group. Therefore, the authors concluded that intracanal bisphosphonate treatment did not yield a beneficial effect. The limited effect of bisphosphonate on RR and bone deposition might have resulted from

limited penetration through the dentinal tubules to the root surface. Moreover, etidronate is more soluble than CH; thus, it cannot act as a reservoir for long-term use [7].

Calcium hydroxide in comparison with acetazolamide

In 2002, Mori and Garcia [44] evaluated the possibility of using acetazolamide solution for the surface treatment of rat teeth that underwent intentional avulsion and delayed replantation. However, RR was observed in the specimens. Later, in 2006, Mori *et al.* [45] evaluated the effect of acetazolamide solution at a concentration of 10^{-5} M as an intracanal therapeutic agent in late replanted rat teeth. The results showed that CH paste limited RR, but did not prevent it. On the contrary, no RR was seen after 60 days in the acetazolamide-treated group, confirming the efficacy of acetazolamide in inhibiting RR. Thereafter, in 2013, Mori *et al.* [46] conducted a study with the same design, but with the introduction of acetazolamide in the paste form. The results demonstrated the potential of both intracanal substances—namely, acetazolamide paste and CH—to limit RR, although they were unable to completely prevent it. Replacement resorption lacunae were present in a greater proportion in the CH group at 60 days. It was concluded that the acetazolamide paste was more effective than CH in limiting RR. This can be explained by the mechanism of action of the active substance in the solution. Specifically, acetazolamide is known to be a potent inhibitor of carbonic anhydrase [47,48], an enzyme presents in osteoclasts. This enzyme catalyzes the reaction between carbonic acid and water, leading to the formation of hydrogen ions [49], which are responsible for the decrease in pH in Howship lacunae [49]. Acidic conditions, in turn, liberate and activate other enzymes that participate in the resorption process [49]. Thus, carbonic anhydrase inhibition prevents this decrease in pH, making resorption unlikely.

Calcium hydroxide in comparison with indomethacin

Indomethacin is a non-steroidal anti-inflammatory medicament that is a potent inhibitor of cyclo-oxygenase, which is the first enzyme in the prostaglandin synthesis pathway. In a study by Zanetta-Barbosa *et al.*, [50] it was hypothesized that indomethacin might serve as a bone resorption inhibitor, with the possible effect of preventing RR when used as an intracanal dressing in delayed tooth replantation. In their study, 24 teeth from 6 adult dogs were extracted, dried, and divided into 4 groups according to the root surface treatment protocols performed before replantation, and the intracanal medication was used after replantation. In group 1 (negative control), the root surfaces were treated by immersion in 0.9% saline solution. In the other groups, the roots were immersed for 10 minutes in CH (group 2), indomethacin (group 3), or a solution of indomethacin with CH (group 4). After 2 weeks, group 1 received a single-visit root canal treatment and obturation with gutta-percha and sealer consisting of zinc oxide and eugenol. The teeth in the other groups received intracanal medications with the same material used for immersion. At 45 and 90 days after replantation, the intracanal therapeutic dressings were changed. There was no significant difference amongst the groups regarding IRR and ankylosis. However, group 1 exhibited significantly more normal periodontal tissue than group 4. Total resorption was significantly greater in group 4 than in group 1. Therefore, based on their results, indomethacin was not recommended as a suitable intracanal dressing for replanted avulsed teeth.

Calcium hydroxide in comparison with gallium nitrate

Several studies have demonstrated that gallium nitrate has the potential to prevent bone resorption [51,52]. Gallium nitrate has an inhibitory effect on osteoclasts [53], and it is incorporated into bone tissue, participating in the formation of fluorapatite; therefore, the newly formed bone becomes further resistant to the action of osteoclastic resorption [51,52].

In 2000, Ghazi *et al.* [54] proposed the use of gallium nitrate as an intracanal dressing. In a quantitative *in vitro* study, they evaluated the amount of gallium nitrate that diffused through dentinal tubes to the periodontal space. The least amount exceeded the 10^{-4} M concentration required to inhibit osteoclastic activity [54,55]. Subsequently, in 2006, Mori *et al.* [56] conducted an experiment to evaluate the effect of gallium nitrate solution as a root canal dressing in avulsed replanted teeth, in comparison to CH paste. They concluded that gallium nitrate solution and CH paste showed similar performance in general.

Calcium hydroxide in comparison with enamel matrix–derived protein

Enamel matrix–derived protein (Emdogain) has been used in periodontal regeneration techniques, and has shown meaningful results in promoting the formation of new bone, periodontal ligament, and cementum [57,58]. The only study comparing CH with enamel Emdogain as an intracanal medication in replanted teeth was conducted by de Oliveira *et al.* [59] Quantification of resorption revealed that Emdogain-treated teeth showed a lower percentage of resorption (31.58%) than CH-treated teeth (80.48%). Elsewhere in the literature, Emdogain has been ascertained to be effective in stimulating the formation of acellular cementum on traumatized root teeth [60]. When applied on the root surface, these proteins resulted in the differentiation of mesenchymal cells into cementoblasts, osteoblasts, and fibroblasts.

CONCLUSIONS

CH is by far the most widely used intracanal medication, and is recommended in clinical guidelines for multiple-visit management of avulsed teeth. However, MTA might present some advantages due to the lack of a requirement for frequent replacements and its ability to be used as a single-visit root filling material; however, there are limited data supporting its use due to a lack of clinical trials. For multiple-visit management, Ledermix and acetazolamide are comparable to CH in terms of reducing RR, but the potential tooth discoloration induced by Ledermix should be taken into account.

Emdogain seems to be an interesting material, but its use as an intracanal medication is supported by very limited data. We found only a single randomized controlled trial relating to the topic of the present study; thus, there is a considerable need for further evaluations of these materials in clinical trials.

Today's dentistry is moving toward less time-consuming, yet higher-quality treatments; thus, it is suggested that future clinical studies compare bioactive filling materials (*e.g.* MTA and new bioceramics) for use in a single visit with various intracanal medicaments that are used in multiple visits.

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