

Will mineral trioxide aggregate replace calcium hydroxide in treating pulpal and periodontal healing complications subsequent to dental trauma? A review

REVIEW ARTICLE

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Abstract – Mineral trioxide aggregate (MTA) has over the last two decades begun to take the place of calcium hydroxide (CH) in the treatment of a variety of pulpal and periodontal healing complications following dental trauma. These conditions include teeth with: (i) exposed pulps, (ii) immature roots and pulp necrosis, (iii) root fractures and pulp necrosis located in the coronal part of the pulps, and (iv) external infection-related (inflammatory) root resorption. The main reasons for replacing CH with MTA in these situations have generally been the delayed effect when using CH to induce hard tissues, the quality of such induced hard tissues, and finally the dentin weakening effect of CH, which in some instances lead to cervical root fractures in immature teeth. MTA appears, from a relatively few clinical studies, to overcome these shortcomings of CH. The lack of long-term clinical studies, however, may warrant a certain reservation in an unrestricted replacement of CH with MTA. A definite need for randomized clinical studies comparing CH and MTA in trauma healing situations is urgently needed.

Calcium hydroxide (CH) has for many decades been the main material used to treat a variety of pulpal healing complications in dental traumatology, such as in teeth with exposed pulps (pulp capping, pulpotomy), in teeth with incomplete root formation and pulp necrosis (apexification), in teeth with root fractures and pulp necrosis located in the coronal part of the pulps, and in teeth with infection-related external root resorption (1). In spite of its successful outcome in many of the above-mentioned trauma healing complications, a number of shortcomings have been noted with respect to its use in dental traumatology. These problems can be summarized as follows:

- 1 *Length of time for induction of coronal or apical hard tissue barriers.* This typically ranges from 2–3 months in the case of pulp capping (2) and 6–18 months in the case of apexification procedures (3–5) with an average of 9 months for the latter (6). Such lengths of time, apart from delaying completion of treatment, also represent a risk of failure in patient compliance with subsequent appointments.
- 2 *Induction of initial zones of sterile pulp necrosis.* These zones represent the contact area between calcium hydroxide and vital pulp tissue; they may become infected at a later time through micro-leakage under restorations, leading to pulpitis and subsequent pulp necrosis (7).

- 3 *Incomplete coronal and apical hard tissue barriers because of vascular inclusions.* This is a phenomenon that may allow bacterial invasion through such vascular tunnels (8, 9).

- 4 *CH-related changes in the physical structure of dentin.* These changes are related to the loss of inorganic and organic components of the dentin (10–18). Such changes have been found to lead rather frequently to cervical root fractures (5, 19, 20).

In 1993, a new endodontic material, mineral trioxide aggregate (MTA) was developed by Torabinejad and co-workers, primarily for the purpose of making a bacteria tight and biocompatible material to, among other applications, seal accidental perforations of the root canal (21). Subsequently, the material was shown to also be ideal as root-end filling material and a material for use in pulp capping and pulpotomy cases (22–27). Later, MTA found its way into treatment of traumatized immature teeth with pulp necrosis (apexification), as some of the shortcomings of CH seemed to be overcome with the use of MTA (28).

Comparison of treatment modalities: CH and MTA

In an effort to compare the use of CH and MTA, the reported effects of these two materials on pulp, dentin,

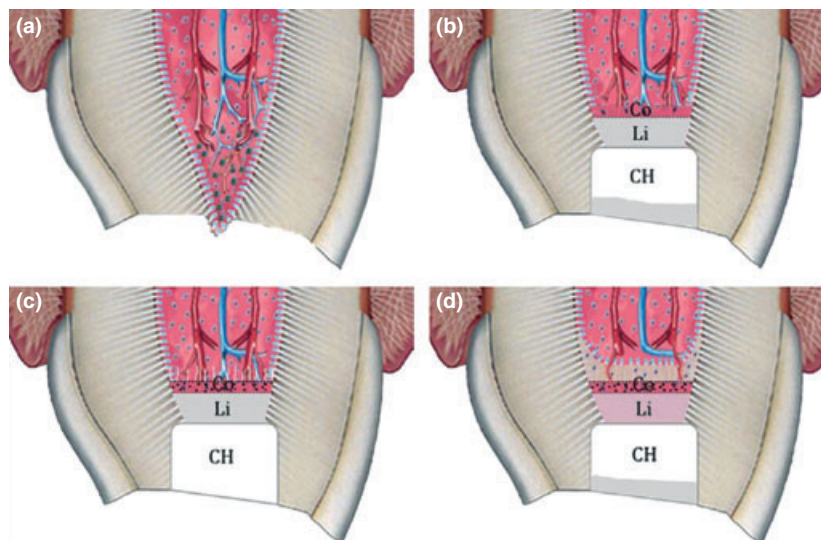


Fig. 1. Calcium hydroxide induced pulp changes after pulpotomy. (a) Exposed pulp. (b) Pulpotomy with application of CH. Because of its high pH effect on dentin, calcium hydroxide (CH) causes the release of a number of wound healing signals (growth factors), and for some time, the high pH also may prevent bacteria from entering the amputation site. The high pH of CH generates a zone of liquefaction necrosis (Li) and a zone of coagulation necrosis (Co) (approximately 1 mm combined width, in case of non-setting CH). In the case of hard setting CH cements (e.g., Dycal[®]), a very narrow or absent liquefaction zone is formed (9, 90, 91). (c) The coagulation zone seems to be an initiator of a wound healing response starting with spherical foci of calcification, which coalesce to form a calcification zone and next to that collagen is formed. (d) Bone-like tissue is deposited containing cells and vascular inclusions (67–69). After approximately 2–3 weeks, new odontoblast-like cells appear subjacent to the initial hard tissue bridge and normal dentin begins to be formed.

and periodontium in various applicable dental trauma situations are described.

Calcium hydroxide and its capacity to induce hard tissues in relation to pulp capping and pulpotomy

The effects of CH on pulpal and periapical tissues have been studied for many years (2, 7, 29, 30) (Fig. 1). The hard tissue eliciting effect on adjacent soft tissue appears to be related to a necrotizing effect of CH because of its high pH (pH = 12.5) (29, 31). This effect takes a few hours and results in a zone of liquefaction necrosis subjacent to the CH and a deeper zone of coagulation necrosis next to the vital pulp tissue. This latter zone appears to stimulate a bone-like hard tissue bridge formation between it and the vital pulpal tissue (29, 31).

Recently, it has been demonstrated that CH and MTA may solubilize growth factors sequestered in dentin during tooth development (35–37). The release of these factors and other bioactive cell signaling molecules may cause the recruitment of undifferentiated pulpal cells to the wound site leading to production of a hard tissue bridge.

It is thought that the release of wound healing signals (i.e., growth factors) activate progenitor cells in the pulp to proliferate and form the initial bridge (9, 38, 39). This bridge formation has been found in humans to take place in about 2–4 weeks in case of non-setting CH (7, 9, 29, 40). During this process vessels may become included in the bridge formation (7–9, 29, 31, 41, 42), a situation that later may become a problem if the sealing of the pulp capping or pulpotomy area is not optimal. Because of the

unavoidable *dissolution* of the CH, during which it loses its antibacterial effect and allows bacteria to use these vascular channels to enter the pulp, pulpitis may occur (8, 43–45).

A desirable feature of CH (at its normally high pH level) is its excellent antibacterial property (46, 47). This may establish a bacteria-free environment at the amputation site during the critical time when the hard tissue bridge is formed. Furthermore, its dissolving effect of necrotic tissue remnants (48, 49) promotes healing. The average healing rate in three clinical studies on the use of CH in pulpotomies is 95% (range 94–96%) (Table 1).

Mineral trioxide aggregate and its capacity to induce hard tissues in relation to pulp capping and pulpotomy

The effect of MTA on pulpal and periapical tissues has certain similarities to that produced by CH (Fig. 2). The mixture of MTA with water results in the formation of calcium hydroxide (50, 51). MTA is biocompatible and has antibacterial properties and an ability to induce the release of bioactive dentin matrix proteins (36). The initiation of hard tissue bridges (coronally or apically)

Table 1. Healing of the exposed pulp in crown-fractured teeth after pulpotomy with calcium hydroxide

Authors	No of teeth	Healing (%)
Cvek (94)	60	58 (96)
Fuks et al. (95)	63	59 (94)
Cvek (96)	178	169 (95)
Total	301	286 (95)

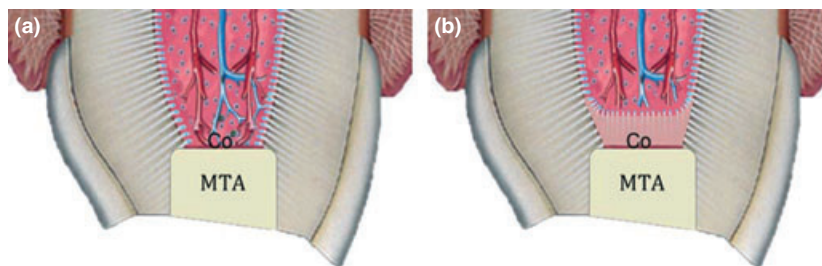


Fig. 2. Mineral trioxide aggregate induced pulp changes after pulpotomy. (a) Mineral trioxide aggregate (MTA) induces, by its high pH an effect on dentin, a release of wound healing signals (growth factors) and a chemical bond between MTA and dentin (a layer of hydroxyapatite) that prevents or reduces oral bacterial penetration to the pulp amputation site. (b) MTA induces by its pH effect a very narrow zone of coagulation necrosis (Co). Next to that zone, a reparative dentinogenesis zone is found. (c) Subsequently, a dentinal bridge is formed faster than in case of CH and with fewer vascular inclusions (9, 39).

appears to be by stimulation of cell proliferation (32) and cell migration with subsequent differentiation (33, 34). The exact mechanism whereby MTA induces a hard tissue bridge is only partly understood. Tziafas et al. observed a homogenous zone of crystalline formed along the pulp-MTA interphase after 1 week; next to that zone, pulpal cells were arranged in close proximity to the crystals. A regular hard tissue barrier with cellular inclusion was seen after 2 weeks, and after 3 weeks, cellular dentin was formed (39). Apart from that, MTA forms a very tight seal where it contacts the dentin walls coronally and apically (22, 23, 52, 53), most likely due to a physical bond between MTA and dentin (a layer of hydroxyapatite is created as a link) (52). This seal prevents and reduces bacterial penetration to the pulp amputation site (54, 55).

Concerning leakage of MTA used as a coronal plug material, two bacterial leakage investigations comparing MTA and Fuji glass ionomer cement showed no difference between the two types of materials in regard to bacterial penetration (54, 55).

As can be expected, because of the recent introduction of MTA, there are relatively few studies in humans, on the hard tissue inducing effect of MTA when used for pulp capping and pulpotomy in permanent teeth (9, 56). During setting, a high pH (12.5) is created in the area next to the MTA and it will remain high for at least 8 weeks (57). As can be seen from these studies, there seems to be an effect because of the high pH of MTA during setting next to living pulp tissues (50). The hard tissue bridge appears to be formed earlier than under CH, with larger daily dentin increments and few vascular inclusions (9, 39, 58–60).

Only two clinical studies on pulpotomy have been published to date, both with a healing rate of 100%. However, only 10 of the 34 teeth included were pulps exposed by trauma and the rest were pulp exposed by caries (Table 2). A clinical report of MTA used in case of exclusively caries pulp exposures showed 98% outcome (61).

Calcium hydroxide and its capacity to induce hard tissues in immature teeth with pulp necrosis

A substantial amount of research exists on the effect of CH on apical healing events after pulp necrosis in young

Table 2. Healing of the pulp in carious and crown-fractured teeth after pulpotomy with mineral trioxide aggregate

Examiner	No of teeth	Healing (%)
Ei-Meligy and Avery (97)	15 ¹	15 (100)
Witherspoon et al. (98)	19 ²	19 (100)
Total	34	34 (100)

¹Only four trauma affected teeth.
²Only six trauma affected teeth.

teeth with immature roots (1, 62, 63) (Table 3) (Fig. 3). The essential features appear to be, as in the coronal use of CH, a bacteria-killing effect as well as a hard tissue inducing effect, the latter related to the initiation of zones of liquefaction and coagulation necrosis next to the apical vital tissue. This results in the development of hard tissue at the apex (apexification), usually as a cementum-like structure (63–71). The drawback of this hard tissue bridge is that numerous vascular channels, which could lead to bacterial invasion into these channels, perforate it (63). Three large clinical studies have shown an average healing rate of 95% (range 77–98%) (Table 3).

Mineral trioxide aggregate and its capacity to induce hard tissues in immature teeth with pulp necrosis

MTA has been shown to be a very biocompatible material, in fact more biocompatible than Super EBA and IRM (72) (Fig. 4). The success in use of this material

Table 3. Periapical healing following initial treatment with calcium hydroxide and subsequent gutta-percha root filling in teeth with pulp necrosis and immature roots

Examiner	No of teeth	Healing (%)
Kerekes et al. (99)	66	62 (94)
Vojinovic (100)	100	98 (98)
Mackie et al. (3)	112	108 (96)
Yates (4)	48	37 (77)
Merglova (101)	33	31 (94)
Cvek (5)	328	314 (96)
Total	687	650 (95)

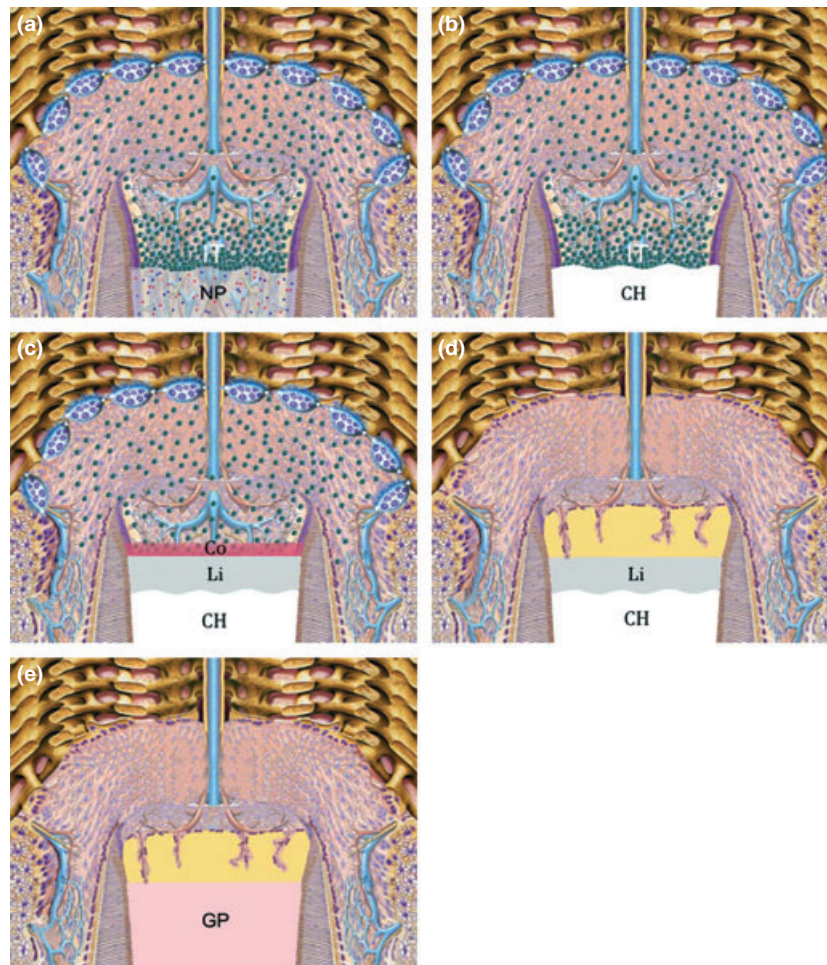


Fig. 3. Calcium hydroxide induced apical closure changes after pulp necrosis. (a) Infected pulp necrosis (NP) plus inflammation (IT) in the apical part of the root canal. (b) Dressing with calcium hydroxide (CH). (c) Because of its high pH effect upon dentin, calcium hydroxide (CH) causes the release of a number of wound healing signals (growth factors), and for some time, the high pH also may prevent bacteria from entering the wound healing site. CH induces by its high pH effect apical liquefaction (Li) and a coagulation zones (Co) of necrosis. (d) The response to the coagulation necrosis appears to be recruitment of new hard tissue forming cells from the apical tissues, these are usually of cementoblastic origin, but may also be osteoblasts. During this process, vascular inclusions may occur. After 6–18 month, a hard tissue barrier is formed. (e) Status after root filling with gutta-percha (GP).

in immature teeth with pulp necrosis is possibly related to two features:

- 1 The extraordinary cementum and PDL-inducing potential of MTA.
- 2 The bacteria tight sealing capacity of MTA when placed in the apical part of the root canal.

This combination of a bacteria tight seal in the apical foramen of the root canal and formation of new cementum and PDL makes this technique a very biologically acceptable method for closing a root canal with an open apex (44). In a recent review article, on the mechanism of action of MTA on pulpal and periodontal tissues, the following actions are described: when placed, MTA immediately releases calcium ions activating cell attachment and proliferation, and at the same time, the high pH creates an antibacterial environment. Furthermore, MTA modulates cytokine production and encourages differentiation and migration of hard tissue producing cells whereby hydroxyapatite is formed on the MTA surface, and a biologic seal is created (59).

When MTA is used as an apical plug in cases of pulp necrosis, studies in dogs and monkeys where apical osteitis was induced showed that MTA can form a biologic seal and the MTA becomes covered with cementum and a normal PDL attachment (28, 73–75). Several studies have shown that when used as a root-end filling material MTA demonstrates a good resistance to bacterial penetration as well as to endotoxin (76). In eight *clinical studies*, an average healing rate of 89% was found (range 77–100%) (Table 4).

Based on the available information, one can state that MTA is suitable for induction of an apical hard tissue barrier in immature incompletely developed teeth with pulp necrosis.

Calcium hydroxide and its ability to induce hard tissue in root fractures with coronal pulp necrosis

The methodology was first described by Cvek (77) and consisted of placing CH in the coronal part of the pulp in

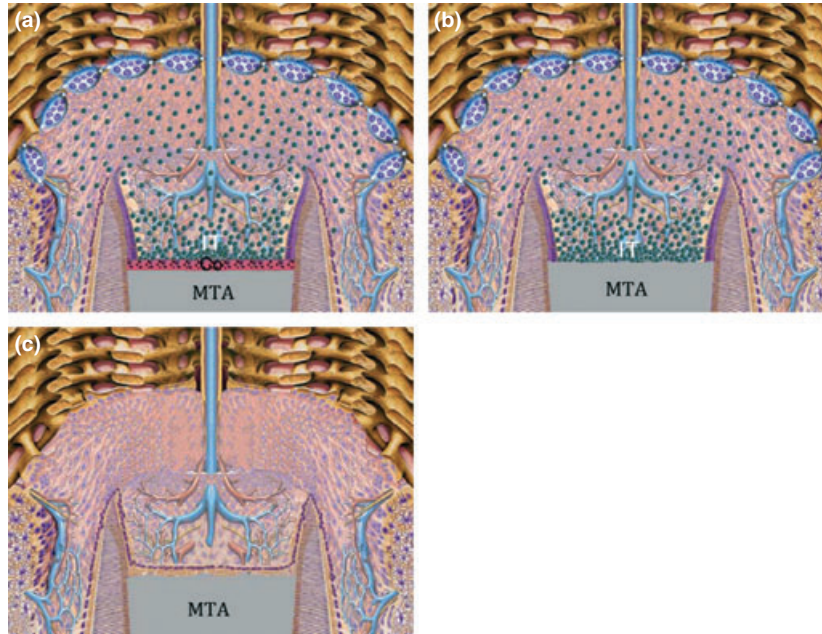


Fig. 4. Mineral trioxide aggregate induced apexification changes after pulp necrosis. (a) Mineral trioxide aggregate (MTA) induces, by its high pH effect upon dentin, a release of wound healing signals (growth factors). Subsequent to this a physical bond between MTA and dentin provides a barrier against bacterial penetration (22, 23, 72, 92, 93). MTA induces by its high pH effect a very narrow zone of coagulation necrosis (Co). Next to that zone, a reparative cementum zone is formed. (c) Subsequently, the hard tissue barrier is associated with formation of normal PDL attachment to the cementum layer. MTA should not be placed directly against an area with inflammatory tissue fluid as the low pH will prevent setting of the MTA. If fluid is present, it makes sense to place CH for a short period of time to 'dry' the area before placing the MTA.

Table 4. Periapical healing following treatment with mineral trioxide aggregate (MTA) in teeth with pulp necrosis and immature roots

Examiner	No of teeth	Healing (%)
El-Meligy and Avery (102, 103)	15	15 (100)
Pradhan et al. (104)	10	10 (100)
Pace et al. (105)	11	10 (91)
Simon et al. (106)	57	46 (81)
Sarris et al. (107)	17	13 (77)
Holden et al. (108)	20	17 (85)
Witherspoon et al. (109)	116	106 (92)
Moore et al. (110)	22	21 (96)
Total	268	238 (89)

root-fractured teeth until a hard tissue bridge was formed at the fracture site. It was later shown in a large clinical study of 68 root fractures to result in healing in 86% of the cases (78). A drawback of this treatment scenario appears to be the relatively long treatment time it takes to induce a hard tissue barrier at the fracture site, typically around 6 months.

Mineral trioxide aggregate and its ability to induce hard tissue in root fractures with coronal pulp necrosis

The use of MTA in root fractures has only been described in a few case reports (79–84). Therefore, it is too early to make a comparison of MTA as an alternative to CH and gutta-percha.

Calcium hydroxide and its effect on external infection-related root resorption

This effect of CH external infection-related root resorption was first described in 1971 by Andreasen (85), and this observation has since been supported by a number of clinical studies demonstrating that CH is able to arrest 98% of infection-related resorptions in luxated teeth and 90% in avulsed and later replanted teeth (85–87). The drawback of this method has been the weakening effect of CH on the dentin, leading to the risk of cervical root fractures (5, 20).

MTA and its effect on external infection-related root resorption

This effect of MTA is not well known. Its use has only been described in a few case reports (88). One experimental study in monkeys shows that MTA used 1 week after intentional replantation could to a large extent prevent infection-related resorption (89). It is still too early to evaluate whether MTA can be considered a predictable replacement for CH in the management of infection-related root resorption.

Conclusion

The studies described may lead one to consider whether the time has come to replace CH with MTA in certain dental trauma situations such as pulp capping, pulpotomy, and apexification. Before reaching a conclusion in that regard, it is necessary to look at the amount of clinical data

related to the long-term outcomes of the two methods. In the case of CH, a number of long-term studies have demonstrated a healing rate of 95% for pulpotomy (Table 1) and 95% for apexification (Table 3). With respect to MTA, there are only a few clinical studies with relatively few subjects for either pulpotomy or apexification (Tables 2 and 4). That underscores that clinical MTA studies should be encouraged, optimally as randomized clinical studies (RCT), comparing CH and MTA. Until then, MTA should be used with the knowledge that it is a new material without a long-term usage background. This is particularly important with respect to its use in teeth with root fractures and coronal pulp necrosis and in teeth with infection-related external root resorption.

Particular problems regarding the use of MTA should be noted. One concern has to do with whether or not MTA exerts the same weakening effect upon dentin as CH. Two *in vitro* studies seem to indicate such a risk as MTA was found to maintain a high pH level in the root canal for many months, and the structural strength of dentin appeared to be weakened (12, 17). On the other hand, Hatibović-Kofman et al. (16) showed that the use of MTA did not seem to weaken dentin over a 3-month to 1-year period. Both additional *in vitro* and *in vivo* studies should be performed to determine whether such a risk is actually present.

Another problem has been an apparent staining effect of MTA when used for pulp capping, pulpotomy, and apexification in anterior teeth (59). That question needs to be addressed as MTA is increasingly being used for anterior tooth pulpotomies. The frequency and severity of this effect is presently unknown.

It may be concluded from this review that MTA appears to be a promising successor to CH for a variety of pulpal and periodontal healing complications after trauma. There is, however, presently a definitive lack of long-term clinical studies to demonstrate the safety and effectiveness of this new procedure. Randomized clinical studies need to be carried out to compare CH and MTA in the treatment of pulp and periodontal healing complications after trauma.

References

- Cvek M. Endodontic management and the use of calcium hydroxide in traumatized permanent teeth. In: Andreassen JO, Andreassen FM, Andersson L, editors. Textbook and color atlas of traumatic injuries to the teeth, 4th edn. Oxford: Blackwell; 2007. p. 598–657.
- Olsson H, Petersson K, Rohlin M. Formation of a hard tissue barrier after pulp cappings in humans. A systematic review. *Int Endod J* 2006;39:429–42.
- Mackie IC, Bentley EM, Worthington HV. The closure of open apices in non-vital immature incisor teeth. *Br Dent J* 1988;165:167–73.
- Yates JA. Barrier formation time in non-vital teeth with open apices. *Int Endod J* 1988;21:313–9.
- Cvek M. Prognosis of luxated non-vital maxillary incisors treated with calcium hydroxide and filled with gutta percha. *Endod Dent Traumatol* 1992;8:45–55.
- Kinirons MJ, Srinivasan V, Welbury RR, Finucane D. A study in two centres of variations in the time of apical barrier detection and barrier position in non-vital immature permanent incisors. *Int J Paediatr Dent*, 2001;11:447–51.
- Schröder U, Granath LE. Early reaction of intact human teeth to calcium hydroxide following experimental pulpotomy and its significance to the development of hard tissue barrier. *Odontol Revy* 1971;22:379–96.
- Cox C, Subay R, Ostro E, Suzuki S, Suzuki SH. Tunnel defects in dental bridges: their formation following direct pulp capping. *Oper Dent* 1996;21:4–11.
- Nair PNR, Duncan HF, Pitt Ford TR, Luder HU. Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: a randomized controlled trial. *Int Endod J* 2008;41:128–50.
- Grigoratos D, Knowles J, Ng YL, Hulabivala K. Effect of exposing dentine to sodium hypochlorite and calcium hydroxide on its flexural strength and elastic modulus. *Int Endod J* 2001;34:113–9.
- Andreassen JO, Farik B, Munksgaard EC. Long-term calcium hydroxide as a root canal dressing may increase risk of root fracture. *Dent Traumatol* 2002;18:134–7.
- White JD, Lacefield WR, Chavers LS, Eleazer PD. The effect of three commonly used endodontic materials on the strength and hardness of root dentin. *Endod J* 2002;28:828–30.
- Doyon GE, Dumsha T, Von Fraunhofer JA. Fracture resistance of human root dentine exposed to intracanal calcium hydroxide. *J Endod* 2005;31:895–7.
- Yoldaş O, Doğan C, Seydaoğlu G. The effect of two different calcium hydroxide combinations on root dentine microhardness. *Int Endod J* 2004;37:828–31.
- Rosenberg B, Murray PE, Namerow K. The effect of calcium hydroxide root filling on dentin fracture strength. *Dent Traumatol* 2007;23:26–9.
- Hatibović-Kofman S, Raimundo L, Zheng L, Chong L, Friedman M, Andreassen JO. Fracture resistance and histological findings of immature teeth treated with mineral trioxide aggregate. *Dent Traumatol* 2008;24:272–6.
- Twati WA, Wood DJ, Liskiewicz TW, Willmott NS, Duggal MS. An evaluation of the effect of non-setting calcium hydroxide on human dentine: a pilot study. *Eur Arch Paediatr Dent* 2009;10:104–9.
- Sahebi S, Moazami F, Abbott P. The effects of short-term calcium hydroxide application on the strength of dentine. *Dent Traumatol* 2010;26:43–6.
- Störmer K, Jacobsen I, Attramadal A. Hvor funksjonsdyktige bliver rottfylte unge permanente inciserer? Nordisk forening for pedodonti. Bergen, Norway: Aarsmøte; 1988.
- Al-Jundi SH. Type of treatment, prognosis and estimation of time spent to manage dental trauma in late presentation cases at a dental teaching hospital: a longitudinal and retrospective study. *Dent Traumatol* 2004;20:1–5.
- Lee SJ, Monsef M, Torabinejad M. Sealing ability of a mineral trioxide aggregate for repair of lateral root perforations. *J Endod* 1993;19:541–4.
- Torabinejad M, Hong CU, McDonald F, Pitt Ford TR. Physical and chemical properties of a new root-end filling material. *J Endod* 1995;21:349–53.
- Torabinejad M, Hong CU, Lee SJ, Monsef M, Pitt Ford TR. Investigation of mineral trioxide aggregate for root-end filling in dogs. *J Endod* 1995;21:603–8.
- Pitt Ford TR, Torabinejad M, Abedi HR, Bakland LK, Kariyawasam SP. Using mineral trioxide aggregate as a pulp-capping material. *J Am Dent Assoc* 1996;127:1491–4.
- Roberts HW, Toth JM, Berzins DW, Charlton DG. Mineral trioxide aggregate material use in endodontic treatment: a review of the literature. *Dent Mater* 2008;24:149–64.
- Torabinejad M, Pariokh M. Mineral trioxide aggregate: a comprehensive literature review-Part II: leakage and biocompatibility investigations. *J Endod* 2010;36:190–202.
- Pariokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review – Part III: clinical applications,

- drawbacks, and mechanism of action. *J Endod* 2010;36:400–13 (Review).
28. Shabahang S, Torabinejad M. Treatment of teeth with open apices using mineral trioxide aggregate. *Pract Periodontics Aesthet Dent* 2000;12:315–20.
 29. Schröder U. Reaction of human dental pulp to experimental pulpotomy and capping with calcium hydroxide. *Odontol Revy* 1973;24(Suppl. 25):1–25.
 30. Hilton TJ. Keys to clinical success with pulp capping: a review of the literature. *Oper Dent* 2009;34:615–25.
 31. Schröder U. Effects of calcium hydroxide-containing pulp-capping agents on pulp cell migration, proliferation, and differentiation. *J Dent Res* 1985;64:541–8.
 32. Moghaddame-Jafari S, Mantellini MG, Botero TM, McDonald NJ, Nör JE. Effect of ProRoot MRA on pulp cell apoptosis and proliferation in vitro. *J Endod* 2005;31:387–91.
 33. Kuratate M, Yoshida K, Shigetani Y, Yoshida N, Ohshima H, Okiji T. Immunohistochemical analysis of nestin, osteopontin, and proliferating cells in the reparative process of exposed dental pulp capped with mineral trioxide aggregate. *J Endod* 2008;34:970–4.
 34. Masuda-Murakami Y, Kobayashi M, Wang X, Yamada Y, Kimura Y, Hossain M et al. Effects of mineral trioxide aggregate on the differentiation of rat dental pulp cells. *Acta Histochem* 2010;112:452–8.
 35. Graham L, Cooper P, Cassidy N, Nor JE, Sloan AJ, Smith AJ. The effect of calcium hydroxide on solubilisation of bio-active dentine matrix components. *Biomaterials* 2006;27:2865–73.
 36. Tomson PL, Grover LM, Lumley PJ, Sloan AJ, Smith AJ, Cooper PR. Dissolution of bio-active dentine matrix components by mineral trioxide aggregate. *J Dent* 2007;35:636–42.
 37. Ferracane JL, Cooper PR, Smith AJ. Can interaction of materials with the dentin-pulp complex contribute to dentin regeneration. *Odontology* 2010;98:2–14.
 38. Lesot H, Smith AJ, Tziafas D, Begue-Kirn C, Cassidy N, Ruch JV. Biologically active molecules and dental tissue repair: a comparative review of reactionary and reparative dentinogenesis with the induction of differentiation in vitro. *Cells Mater* 1994;4:199–218.
 39. Tziafas D, Pantelidou O, Alvanou A, Belibasakis G, Papadimitriou S. The dentinogenic effect of mineral trioxide aggregate (MTA) in short-term capping experiments. *Int Endod J* 2002;35:245–54.
 40. Sekine N, Asai Y, Nakamura Y, Tagami T, Nagakubo T. Clinico-pathological study of the effect of pulp capping with various calcium hydroxide pastes. *Bull Tokyo Dent Coll* 1971;22:149–73.
 41. Goldberg F, Massone EJ, Spielberg C. Evaluation of the dentinal bridge after pulpotomy and calcium hydroxide dressing. *J Endod* 1984;10:318–20.
 42. Ulmanky M, Sela J, Sela M. Scanning electron microscopy of calcium hydroxide induced bridges. *J Oral Pathol* 1972;1:244–8.
 43. Holland R, de Souza V, de Mello W, Nery MJ, Bernabé PFE, Filho JAO. Permeability of the hard tissue bridge formed after pulpotomy with calcium hydroxide: a histologic study. *J Am Dent Assoc* 1979;99:472–5.
 44. Bakland LK. New procedures using mineral trioxide aggregate (MTA) for teeth with traumatic injuries. In: Andreasen JO, Andreasen FM, Andersson L, editors. *Textbook and color atlas of traumatic injuries to the teeth*, 4th edn. Oxford: Blackwell; 2007. p. 658–68.
 45. Kitasako Y, Ikeda M, Tagami J. Pulpal response to bacterial contamination following dentin bridging beneath hard-setting calcium hydroxide and self-etching adhesive resin system. *Dent Traumatol* 2008;24:201–6.
 46. Byström A, Claesson R, Sundqvist G. The antibacterial effect of camphorated paramonochlorophenol, camphorated phenol and calcium hydroxide in the treatment of infected root canals. *Endod Dent Traumatol* 1985;1:170–5.
 47. Stuart KG, Miller CH, Brown CE Jr, Newton CW. The comparative antimicrobial effect of calcium hydroxide. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1991;72:101–4.
 48. Andersen M, Lund A, Andreasen JO, Andreasen FM. In vitro solubility of human pulp tissue in calcium hydroxide and sodium hypochlorite. *Endod Dent Traumatol* 1992;8:104–8.
 49. Yang SR, Rivera EM, Baumgardner KR, Walton RE, Stanford C. Anaerobic tissue-dissolving abilities of calcium hydroxide and sodium hypochlorite. *J Endod* 1995;21:613–6.
 50. Camilleri J, Montesin FE, Di Silvio L, Pitt Ford TR. The chemical constitution and biocompatibility of accelerated Portland cement for endodontic use. *Int Endod J* 2005;38:834–42.
 51. Camilleri J. Characterization of hydration products of mineral trioxide aggregate. *Int Endod J* 2008;41:408.
 52. Sarkar NK, Caicedo R, Ritwik P, Moiseyeva R, Kawashima I. Physicochemical basis of the biologic properties of mineral trioxide aggregate. *J Endod* 2005;31:97–100.
 53. Luketić SF, Malčić A, Jukić S, Anić I, Segović S, Kalenić S. Coronal microleakage of two root-end filling materials using a polymicrobial marker. *J Endod* 2008;34:201–3.
 54. Tselnik M, Baumgartner JC, Marshall JG. Bacterial leakage with mineral trioxide aggregate or a resin-modified glass ionomer used as a coronal barrier. *J Endod* 2004;30:782–4.
 55. John AD, Webb TD, Imamura G, Goodell GG. Fluid flow evaluation of Fuji Triage and gray and white ProRoot mineral trioxide aggregate intraorifice barriers. *J Endod* 2008;34:830–2.
 56. Iwamoto CE, Adachi E, Pameijer CH, Barnes D, Romberg EE, Jefferies S. Clinical and histological evaluation of white ProRoot MTA in direct pulp capping. *Am J Dent* 2006;19:85–90.
 57. Fridland M, Rosado R. MTA solubility: a long term study. *J Endod* 2005;31:376–9.
 58. Faraco IM Jr, Holland R. Response of the pulp of dogs to capping with mineral trioxide aggregate or a calcium hydroxide cement. *Dent Traumatol* 2001;17:163–6.
 59. Parirokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review-part I: chemical, physical, and antibacterial properties. *J Endod* 2010;36:16–27.
 60. Accorinte Mde L, Holland R, Reis A, Bortoluzzi MC, Murata SS, Dezan E Jr et al. Evaluation of mineral trioxide aggregate and calcium hydroxide cement as pulp-capping agents in human teeth. *J Endod* 2008;34:1–6.
 61. Bogen G, Kim JS, Bakland LK. Direct pulp capping with mineral trioxide aggregate. An observation study. *J Am Dent Assoc* 2008;139:305–15.
 62. Rafter M. Apexification: a review. *Dent Traumatol* 2005;21:1–8.
 63. Cvek M, Sundström B. Treatment of non-vital permanent incisors with calcium hydroxide. V. Histologic appearance of roentgenographically demonstrable apical closure of immature roots. *Odontol Revy* 1974;25:379–92.
 64. Steiner JC, Van Hassel HJ. Experimental root apexification in primates. *Oral Surg Oral Med Oral Pathol* 1971;31:409–15.
 65. Dylewski JJ, Arbor A. Apical closure of nonvital teeth. *Oral Surg Oral Med Oral Pathol* 1971;32:82–9.
 66. Ham JW, Patterson SS, Mitchell DF. Induced apical closure of immature pulpless teeth in monkeys. *Oral Surg Oral Med Oral Pathol* 1972;33:438–49.
 67. Binnie WH, Rowe AHR. A histological study of the periapical tissues of incompletely formed pulpless teeth filled with calcium hydroxide. *J Dent Res* 1973;52:1110–6.
 68. Torneck CD, Smith JS, Grindall P. Biologic effects of endodontic procedures on developing incisor teeth. IV. Effect of debridement procedures and calcium hydroxide-camphorated parachlorophenol paste in the treatment of experimentally induced pulp and periapical disease. *Oral Surg Oral Med Oral Pathol* 1973;35:541–54.
 69. Holland R, de Souza V, Tagliavini L, Milanezi LA. Healing process of teeth with open apices: histological study. *Bull Tokyo Dent Coll* 1971;12:333–8.

70. Holland R, Souza VD, Russo MDC. Healing process after root canal therapy in immature human teeth. *Rev Fac Odont Aracatuba* 1973;2:269–78.
71. Javelet J, Torabinejad M, Bakland L. Comparison of two pH levels for the induction of apical barriers in immature teeth of monkeys. *J Endod* 1985;11:375–8.
72. Fernández-Yáñez Sánchez A, Leco-Berrocal MI, Martínez-González JM. Metaanalysis of filler materials in periapical surgery. *Med Oral Patol Oral Cir Bucal* 2008;13:180–5.
73. Shabahang S, Torabinejad M, Boyne PP, Abedi H, McMillan P. A comparative study of root-end induction using osteogenic protein-1, calcium hydroxide, and mineral trioxide aggregate in dogs. *J Endod* 1999;25:1–5.
74. Ham KA, Witherspoon DE, Gutmann JL, Ravindranath S, Gaith TC, Opperman LA. Preliminary evaluation of BMP-2 expression and histological characteristics during apexification with calcium hydroxide and mineral trioxide aggregate. *J Endod* 2005;31:275–9.
75. Felipe WT, Felipe MCS, Rocha MJC. The effect of mineral trioxide aggregate on the apexification and periapical healing of teeth with incomplete root formation. *Int J Endod* 2006;39:2–9.
76. Tang HM, Torabinejad M, Kettering JD. Leakage evaluation of root end filling materials using endotoxin. *J Endod* 2002;28:5–7.
77. Cvek M. Treatment on non-vital permanent incisors with calcium hydroxide. VI. Periodontal healing and closure of the root canal in the coronal fragment of teeth with intra-alveolar fracture and vital apical fragment. A follow-up. *Odontol Revy* 1974;25:239–46.
78. Cvek M, Mejare I, Andreassen JO. Conservative endodontic treatment of teeth fractured in the middle or apical part of the root. *Dent Traumatol* 2004;20:261–9.
79. Bramante CM, Menezes R, Moraes IG, Bernardinelli N, Garcia RB, Letra A. Use of MTA and intracanal post reinforcement in a horizontally fractured tooth: a case report. *Dent Traumatol* 2006;22:275–8.
80. Yildirim T, Gençoğlu N. Use of mineral trioxide aggregate in the treatment of horizontal root fractures with a 5-year follow-up: report of a case. *J Endod* 2009;35:292–5.
81. Erdem AP, Ozdas DO, Dincol E, Sepet E, Aren G. Case series: root healing with MTA after horizontal fracture. *Eur Arch Paediatr Dent* 2009;10:110–3.
82. Er K, Celik D, Taşdemir T, Yildirim T. Treatment of horizontal root fractures using a triple antibiotic paste and mineral trioxide aggregate: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:63–6.
83. Kusgoz A, Yildirim T, Tanriver M, Yesilyurt C. Treatment of horizontal root fractures using MTA as apical plug: report of 3 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:68–72.
84. Sheikh-Nezami M, Mokhber N, Shamsian K., Saket S. Management of a midroot and complicated crown fracture: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:65–7.
85. Andreassen JO. Treatment of fractured and avulsed teeth. *ASDC J Dent Child* 1971;38:29–35.
86. Cvek M. Treatment on non-vital permanent incisors with calcium hydroxide. II. Effect on external root resorption in luxated teeth compared with effect of root filling with gutta percha. *Odontol Revy* 1973;24:343–54.
87. Andreassen JO, Borum MK, Andreassen FM. Replantation of 400 traumatically avulsed permanent incisors VI – Endodontic procedures related to periodontal healing or progression of root resorption. *Dent Traumatol* 2011;27. In preparation.
88. Oliveira TM, Sakai VT, Silva TC, Santos CF, Abdo RC, Machado MA. Mineral trioxide aggregate as an alternative treatment for intruded permanent teeth with root resorption and incomplete apex formation. *Dent Traumatol* 2008;24:565–8.
89. Panzarini SR, Holland R, de Souza V, Poi WR, Sonoda CK, Pedrini D. Mineral trioxide aggregate as a root canal filling material in reimplanted teeth. Microscopic analysis in monkeys. *Dent Traumatol* 2007;23:262–72.
90. Tronstad L. Reaction of the exposed pulp to Dycal treatment. *Oral Surg* 1974;38:945–53.
91. Brännström M, Nyborg H, Strömberg T. Experiments with pulp capping. *Oral Surg Oral Med Oral Pathol* 1979;48:347–52.
92. Fisher EJ, Arens DE, Miller CH. Bacterial leakage of mineral trioxide aggregate as compared with zinc-free amalgam, intermediate restorative material, and Super-EBA as a root-end filling material. *J Endod* 1998;24:176–9.
93. Adamo HI, Buruiana R, Schertzer L, Boylan RJ. A comparison of MTA, Super-EBA, composite and amalgam as root-end filling materials using a bacterial microleakage model. *Int Endod J* 1999;32:197–203.
94. Cvek M. A clinical report on partial pulpotomy and capping with calcium hydroxide in permanent incisors with complicated crown fracture. *J Endod* 1978;4:232–7.
95. Fuks AB, Chosack A, Klein H, Eidelman E. Partial pulpotomy as a treatment alternative for exposed pulps in crown-fractured permanent incisors. *Endod Dent Traumatol* 1987;3:100–2.
96. Cvek M. Partial pulpotomy in crown-fractured incisors – results 3 to 15 years after treatment. *Acta Stomatol Croat* 1993;27:167–73.
97. El-Meligy OA, Avery DR. Comparison of mineral trioxide aggregate and calcium hydroxide as pulpotomy agents in young permanent teeth (Apexogenesis). *Pediatr Dent* 2006;28:399–404.
98. Witherspoon DE, Small JC, Harris GZ. Mineral trioxide aggregate pulpotomies: a case series outcomes assessment. *J Am Dent Assoc* 2006;137:610–8.
99. Kerekes K, Heide S, Jacobsen I. Follow-up examination of endodontic treatment in traumatized juvenile incisors. *J Endod* 1980;6:744–8.
100. Vojinović O. The endodontic method of treatment of apical periodontitis in immature and young permanent teeth. *J Int Assoc Dent Child* 1981;12:65–72.
101. Merglova V. The treatment of non-vital permanent teeth by filling of root canals with calcium hydroxide. *Eur J Paediatr Dent* 2001;1:38–44.
102. El-Meligy OA, Avery DR. Comparison of mineral trioxide aggregate and calcium hydroxide as pulpotomy agents in young permanent teeth (apexogenesis). *Pediatr Dent* 2006;28:399–404.
103. El-Meligy OA, Avery DR. Comparison of apexification with mineral trioxide aggregate and calcium hydroxide. *Pediatr Dent* 2006;28:248–53.
104. Pradhan DP, Chawla HS, Gauba K, Goyal A. Comparative evaluation of endodontic management of teeth with unformed apices with mineral trioxide aggregate and calcium hydroxide. *J Dent Child* 2006;73:79–85.
105. Pace R, Giuliani V, Pini Prato L, Baccetti T, Pagavino G. Apical plug technique using mineral trioxide aggregate: results from a case series. *Int J Endod* 2007;40:478–84.
106. Simon S, Rilliard F, Berdal A, Machtou P. The use of mineral trioxide aggregate in one-visit apexification treatment: a prospective study. *Int J Endod* 2007;40:186–97.
107. Sarris S, Tahmassebi JF, Duggal MS, Cross IA. A clinical evaluation of mineral trioxide aggregate for root-end closure of non-vital immature permanent incisors in children- a pilot study. *Dent Traumatol* 2008;24:79–85.
108. Holden DT, Schwartz SA, Kirkpatrick TC, Schindler WG. Clinical outcomes of artificial root-end barriers with mineral trioxide aggregate in teeth with immature apices. *J Endod* 2008;34:812–7.
109. Witherspoon DE, Small JC, Regan JD, Nunn M. Retrospective analysis of open apex teeth obturated with mineral trioxide aggregate. *J Endod* 2008;34:1171–6.
110. Moore A, Howley MF, O'Connell AC. Treatment of open apex teeth using two types of white mineral trioxide aggregate after initial dressing with calcium hydroxide in children. *Dent Traumatol* 2011;27:166–73.