Mineral trioxide aggregate and other bioactive endodontic cements: An updated overview- Part I: Vital pulp therapy

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Abstract:

Mineral trioxide aggregate (MTA) is a bioactive endodontic cement (BEC) mainly comprised of calcium and silicate elements. The cement was introduced by Torabinejad in the 1990s and has been approved by the Food and Drug Administration (FDA) to be used in the U.S. in 1997. A number of new Bioactive Endodontic Cements (BECs) have also been introduced to the market, including BioAggregate, Biodentine, BioRoot RCS, calcium enriched mixture (CEM) cement, CAPSEAL, Endo-CPM, Endocem, EndoSequence, EndoBinder, EndoSeal MTA, iRoot, MicroMega MTA, MTA Bio, MTA Fillapex, MTA Plus, Neo MTA Plus, Ortho MTA, Quick-Set, Retro MTA, Tech Biosealer, and TheraCal. It has been claimed that these materials have properties similar to those of MTA without its drawbacks. In this article, chemical composition and the application of MTA and other BECs for vital pulp therapy (VPT) including indirect pulp cap, direct pulp cap, partial pulpotomy, pulpotomy, and partial pulpectomy, have been reviewed and compared. Based on selected key words all papers regarding chemical composition and VPT applications of BECs had been reviewed.

Most of the materials had calcium and silicate in their composition. Instead of referring to the cements based on their chemical compositions, we suggest the term “bioactive endodontic cements (BECs),” which seems more appropriate for these materials because, in spite of differences in their chemical compositions, bioactivity is a common property for all of them. Numerous articles were found regarding use of BECs as VPT agents for indirect pulp capping, partial pulpotomy, and cervical pulpotomy. Most of these investigations used MTA for VPT.

In most studies, newly introduced materials have been compared to MTA. Some of the BECs have shown promising results; however, the number of their studies compared to investigations on MTA is very limited. Most studies have had several methodological shortcomings. Future investigations with rigorous methods and materials are needed.

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Introduction

Mineral trioxide aggregate (MTA) has been evaluated extensively (Enkel et al. 2008, Parirokh & Torabinejad 2010a, b, Torabinejad & Parirokh 2010, Trope et al. 2015, Wang 2015, Shen et al. 2015, Naik et al. 2015). In laboratory studies it has been reported to have excellent biocompatibility and sealing ability, as well as being associated with desirable clinical outcomes when used for: repair of perforations, vital pulp therapies, root-end fillings, root fillings, and when used as an apical plug (Parirokh & Torabinejad 2010b, Torabinejad & Parirokh 2010). However, long setting time, tooth discoloration, high cost (Tanlap et al. 2012, Foley 2013, Walker et al. 2013, Kahler & Rossi-Fedele 2016), and difficult handling characteristics have emerged as potential drawbacks (Parirokh & Torabinejad 2010b, von Arx 2011, Tanlap et al. 2012).

In a previous review, papers on the properties and clinical applications of MTA since its introduction were included (Parirokh & Torabinejad 2010a, b, Torabinejad & Parirokh 2010). However, a later scientometric evaluation reported there were limited numbers of reports on the use of MTA for clinical applications (Asgary et al. 2013a).

In order to overcome the drawbacks of MTA, a range of bioactive endodontic cements (BECs) have been developed, with manufacturers claiming they have similar characteristics to MTA but without its shortcomings. This has led to a large number of publications that has made it challenging to understand fully the properties of these new materials and thus their potential for use in place of or alongside MTA.

The term “bioactive endodontic cement” is used in this overview because the new materials have a variety of chemical compositions; however, they all have one common capability, i.e. bioactivity.

This implies: releasing calcium ions, electroconductivity, production of calcium hydroxide, formation of an interfacial layer between the cement and dentinal wall, and formation of apatite crystals over the surface of the material in a synthetic tissue fluid environment such as phosphate buffer saline (Parirokh & Torabinejad 2010a, b, 2014).

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Scope of the review

The aim of this article is to review CLINICAL investigations using MTA and other BECs. All articles in English published in peer-reviewed journals from October 2009 to March 2017 were searched. Where relevant, previous reviews (Parirokh & Torabinejad 2010a, b, Torabinejad & Parirokh 2010) have been cited and not the original papers published before October 2009.

Search strategy

An electronic search of PubMed and Cochrane databases was undertaken. Appropriate MeSH keywords including: “mineral, trioxide, aggregate” and the name of all BECs defined in relevant papers (Trope et al. 2015, Wang 2015, Shen et al. 2015) were used to extract papers on clinical applications of BECs. Therefore, all laboratory studies as well as biocompatibility investigations were excluded and only available evidence-based investigations and studies that evaluated clinical applications of BECs in animals and humans were included. In addition, a hand search of the main endodontic journals was conducted from 2010 to 2017, including the Journal of Endodontics, International Endodontic Journal, Australian Endodontic Journal, and Iranian Endodontic Journal. Reference mining of the articles that were identified was used to locate other papers. Indirect pulp cap, pulp capping, partial pulpotomy, and pulpotomy were used as keywords to locate studies that used BECs for clinical applications.

Inclusion and exclusion criteria

Only studies on vital pulp therapies are reported in Part I of this review. Other clinical applications of BECs are reviewed in Part II.

Chemical composition and setting time

For convenience, the chemical composition and setting times of the BECs are listed in Table 1, along with the manufacturers. The focus on setting time links to one of the known drawbacks of MTA that has been a catalyst for the introduction of other materials (Parirokh & Torabinejad 2010b).
Vital pulp therapies

Vital pulp therapies include indirect pulp capping, direct pulp capping, partial (superficial) pulpotomy and complete (cervical) pulpotomy. They have gained prominence in recent years for several reasons (Opal et al. 2014, Akhlaghi & Khademi 2015, Komabayashi et al. 2016):

- High success rates when MTA has been used in animal studies (Parirokh & Torabinejad 2010b, Luotonen et al. 2014);
- High success rate when BECs, particularly MTA, have been used in traumatic and cariously exposed pulps in humans, (Stangvaltaite et al. 2016);
- High prevalence of apical periodontitis on a global scale and the challenges of providing high quality root canal treatment (Dutta et al. 2014, Oginni et al. 2015, Huumonen et al. 2017, Van der Veken et al. 2017);
- Cost-effectiveness of using vital pulp therapies compared to root canal treatment (Schwendicke & Stolpe 2014, Schwendicke et al. 2015a).

Calcium hydroxide has been used as a cavity liner and pulp capping agent for nearly a century. However, dentists have not routinely used vital pulp therapies as an alternative to root canal treatment in teeth with reversibly inflamed pulps (Schwendicke & Stolpe 2014, Schwendicke et al. 2015a). Failure of vital pulp therapies when using calcium hydroxide are associated with: lack of a bond to dentine with a resulting susceptibility to leakage, dissolution over time in a moist environment thus leaving a void beneath the restoration, and tunnel defects in dentine bridges (Asgary et al. 2008, Mohammadi & Dummer 2011).

A. Indirect pulp capping

Indirect pulp capping has been recommended for both primary and permanent teeth (Ghoddusi et al. 2014, Parisay et al. 2015).

Primary teeth: The Hall technique (sealing all carious dentine beneath a crown), has been reported to be the most cost-effective method in treating carious primary molars compared to conventional treatment, that is, removing all caries and restoration of the cavity (Schwendicke et al. 2015b).
Interestingly, the Hall technique was more cost-effective than pulpotomy with ProRoot MTA when provided under the regulations of the German healthcare system (Schwendicke et al. 2015b). Two randomized clinical trials (Menon et al. 2016, Mathur et al. 2016) reported successful clinical (no pain, absence of sinus tract) and radiographic (no sign of external and internal resorption, presence of calcified bridge) outcomes following use of MTA and TheraCal LC when used for indirect pulp capping in primary teeth. However, a shortcoming of these studies was their short term follow-up. In addition, taking two cone beam computed tomography images within six months in one of these studies goes against the principles of ALARA and the need to restrict irradiation of patients, especially young patients, to a minimum. The authors also reported that exposing cone beam computed tomography images in children was difficult because they tended to move during the long exposure time (Mathur et al. 2016).

**Permanent teeth:** Several reports have illustrated successful outcomes using CEM cement as an indirect pulp capping agent (Torabzadeh & Asgary 2013, Asgary et al. 2014c). Randomized clinical trials and cohort investigations reported successful outcomes following the use of MTA, medical Portland cement, Biodentine and TheraCal as indirect pulp capping agents in permanent teeth (Leye Benoist et al. 2012, Petrou et al. 2014, Hashem et al. 2015, Mathur et al. 2016). The time of follow-up is an important factor after indirect pulp capping. A clinical and radiographic investigation reported significantly higher success rates for MTA compared to calcium hydroxide as an indirect pulp capping material three months following treatment (Leye Benoist et al. 2012). However, no significant difference was found between the materials at six months in terms of calcified bridge thickness. Several predictive factors were identified that may have influenced the outcome, including the use of MTA and the presence of disto-occlusal cavities. Use of MTA was a positive predictive factor, whereas disto-occlusal cavities were an unfavorable predictive factor (Leye Benoist et al. 2012).
In conclusion, there are only a small number of investigations on BECs as indirect pulp capping materials. Most did not mention the level of caries activity in terms of the colour or texture of the carious dentine (Bjørndal et al. 2014), had short follow-up periods, and no analysis of caries depth. Since all these factors influence the outcome of indirect pulp capping, further studies are required to determine the suitability of BECs for indirect pulp capping.

B. Direct pulp capping

Direct pulp capping is a procedure for covering healthy or reversibly inflamed pulps that have been exposed mechanically or during the removal of caries. Current guidelines only support that mechanically exposed pulps, i.e. those that are healthy, should be considered for direct pulp capping (Frisk et al. 2013, American Academy of Pediatric Dentistry’s (AADP) guideline for vital pulp therapy 2014).

Animal studies

Primary teeth: There are a limited number of studies using BECs for direct pulp capping in the primary teeth of animals. Shayegan et al. (2012) concluded that there were no significant differences between Dycal, tooth coloured ProRoot MTA and Biodentine as direct pulp capping materials in the primary teeth of pigs in terms of calcified bridge formation and degree of inflammation at the end of the experiment. However, one of the important concerns in most animal studies is the fact that the response of sound intact pulps is measured and this is not necessarily the same as the response of pulps that have some degree of inflammation because of caries. Furthermore, it is not always known whether the animal model reflects the potential outcome in human teeth.

Permanent teeth: Several animal investigations have evaluated MTA and other BECs as direct pulp capping agents in baboons, dogs, rodents, pigs and rats. Most of these investigations compared ProRoot MTAs (grey or tooth coloured) or MTA Angelus with hard setting calcium hydroxide liners such as Dycal. They concluded that grey ProRoot MTA, tooth coloured ProRoot MTA and white MTA Angelus were either similar or superior to calcium hydroxide in terms of hard tissue formation, pulp inflammation and pulp necrosis (Asgary et al. 2006, 2008, Dammaschke et al. 2010a, b, Al-Hezaimi et al. 2011a, Leites et al. 2011, Louwakul et al. 2015).

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When grey ProRoot MTA, tooth coloured ProRoot MTA and white Portland cement were used as pulp capping agents in dogs there was no significant difference between them in terms of hard tissue formation and pulp inflammation (Parirokh et al. 2005, Bidar et al. 2014).

Comparison of ProRoot MTA with calcium hydroxide, platelet-rich plasma (PRP), autologous bone marrow mesenchymal stem (BMMS) cells with the scaffold of hydroxyapatite tricalcium phosphate, a combination of corticosteroid and β-glycerophosphate and Vitamin D, and enamel matrix derivative in dogs and rats as pulp capping materials found no significant differences in the development of odontoblast-like cells and reparative dentin (Orhan et al. 2012, Obeid et al. 2013, Moazzami et al. 2014). However, a combination of human placental extract and tooth coloured MTA in rats provided significantly better outcomes compared to the material alone in terms of dentine bridge, odontoblast layer, and dentinal tubule formation, as well as lower inflammatory cell responses (Chang et al. 2016).

Several investigations added various ingredients to MTA to either improve its physical properties or in an attempt to downgrade the inflammatory response following pulp capping. Adding CaCl₂, chlorhexidine, or BMP-2 to ProRoot MTA did not significantly improve the pulp response to the materials (Ko et al. 2010, Parirokh et al. 2011, Manochehrifar et al. 2016). However, placing emdogain (Straumann AG, Basel, Switzerland) beneath tooth coloured ProRoot MTA as well as ProRoot MTA and Portland cement improved the quality of reparative dentine formed at the capping site in terms of absence of tunnel defects and presence of tubular calcified bridges (Al-Hezaimi et al. 2011b, Bollu et al. 2016).

Two non-collagenous glycoproteins of pulpal extracellular matrix are expressed during dentinogenesis, namely fibronectin and tenasin. Fibronectin can induce cell adhesion, growth, differentiation and migration, while tenasin induces odontoblast differentiation. A study that used ProRoot MTA as a pulp capping agent in dogs’ teeth reported that expression of fibronectin and tenasin were significantly increased throughout the study, whereas pulps that were capped with glass ionomer had no increase in the production of fibronectin and tenasin at any time interval (Moradi et al. 2015).
An investigation comparing the combination of low-power laser irradiation and direct pulp capping with ProRoot MTA to the traditional treatments of placing the capping material on the exposure site reported that laser irradiation did not improve pulp responses to ProRoot MTA in terms of hard tissue formation (continuity, morphology and thickness) and inflammatory reactions (type, intensity and extension), and histopathologic change in pulp tissue (necrosis, odontoblastic layer formation and calcification); however, the authors did not compare their results statistically (Bidar et al. 2016).


Both Biodentine and ProRoot MTA had significantly thicker calcified bridges following direct pulp capping in rats compared to BioAggregate; however, all three BECs had a comparable optimal pulp reaction in terms of hard tissue formation, inflammation, and presence of necrosis (Kim et al. 2016). The heat generated by light-cured pulp capping materials is a matter of concern (Smail et al. 1988). However, one of the advantages of TheraCal as a light cure agent (compared to currently used light-cured calcium hydroxide-based materials) is the lower temperature change in dentin it induces when irradiated (Savas et al. 2014). However, the study only evaluated temperature change under laboratory conditions and not in vivo.

It has been reported that biomimetic carbonated apatite (BCA) forms over ProRoot MTA when the material is kept in a synthetic tissue fluid (Parirokh et al. 2009, Parirokh & Torabinejad 2010b). One may assume that BCA may have the same ability as MTA when used as a pulp capping agent. However, an investigation reported that tooth coloured ProRoot MTA provided a better outcome in
terms of calcified bridge formation and degree of pulpal inflammation compared to BCA in a direct pulp capping procedure in dogs (Danesh et al. 2012).

Direct pulp capping materials might be extruded into pulp tissue during the procedure (Lee et al. 2012). An investigation using Ortho-MTA as a pulp capping material reported that using the material with electrospun poly (e-caprolactone) fibre (PCL-F) meshes increased the thickness of calcified bridges formed beneath the capping material (Lee et al. 2012). It has been reported that the use of the mesh has two advantages, preventing extrusion of the capping agent into the pulp during placing of the material and preventing further tooth discoloration (Lee et al. 2012, 2015a).

It should be emphasized that one of the major flaws of most animal studies is their short study duration with the result that the long-term effects of the materials are not known. In addition, studies on animals mostly evaluate responses of healthy pulps to the capping materials that is different to the normal clinical situation where caries produces a chronic response in pulps prior to their exposure.

Several flaws in studies performed on experimental animal have been identified, including: no positive or negative controls, no bacterial staining for evaluating the presence of bacteria, using unsuitable coronal restorations with no barrier between the capping materials and the final restoration, not comparing the experimental materials with well-known materials acting as gold standards, short-term evaluation, improper methods of pulp fixation, no explanation of the criteria for histological evaluation, no statistical analysis and small sample size.

In conclusion, ProRoot MTA and tooth coloured ProRoot MTA and MTA Angelus have either a similar or significantly more favorable pulp response as a direct pulp capping agent compared to Dycal. Several investigations that used BECs reported promising results; however, there are only a small numbers of investigations on the new BECs, for example, MTA Bio, MTA Plus, Neo MTA Plus, Endosequence MTA, MicroMega MTA, TechBioSealer capping, RetroMTA. Thus, more investigations with sophisticated methods and materials are needed particularly for BECs that have not been evaluated as direct pulp capping materials.
Pulp capping in animals with specific conditions

A study on dogs suggested that pulp capping with ProRoot MTA may not be a reasonable procedure when the animals receive immunosuppressive medication. In contrast to control animals, the dogs that received mycophenolate mofetil, sirolimus, or cyclosporine A had substantial pulp necrosis as well as slight or moderate inflammatory cell infiltration in the pulp tissue and incomplete hard tissue formation at the exposure site (Mahmoud et al. 2010).

No significant difference was reported in pulp healing between normal and diabetic rats when white MTA Angelus was used. In contrast, the use of CEM cement as a direct pulp capping material was associated with significantly more extensive pulp inflammation in diabetic rats compared to normal control animals (Madani et al. 2014).

The importance of having controls in all experiments for vital pulp therapies was demonstrated in an experiment in which pulp inflammation occurred in the control teeth of both healthy and diabetic rats at the end of the study. In fact, the pulps of intact teeth from healthy rats had signs of mild inflammation (Madani et al. 2014).

In conclusion, very few studies have investigated the effect of systemic conditions on the efficacy of BECs as pulp capping materials; all were conducted in experimental animals. The major shortcomings of these studies are the lack of a reasonable method for fixing pulp tissue, as well as working on sound, intact teeth free of pulp inflammation prior to the procedure. Based on the limited data available, immunosuppressive medication may have an adverse effect on direct pulp capping outcomes in animals. The type of pulp capping agent also may have an impact on the pulp response to materials in diabetic animals in the short term; however, further work is required to confirm this finding and to demonstrate its relevance in humans.

Human studies

Primary teeth: CEM cement and Bioactive glass were not significantly different compared to ProRoot MTA and tooth coloured ProRoot MTA in terms of clinical and radiographic outcomes of direct pulp capping in primary teeth (Fallahinejad Ghajari et al. 2010, 2013). However, CEM cement induced significantly more calcified bridge formation as well as no pulp inflammation compared to nano-hydroxyapatite (Haghgoo et al. 2015).
Both ProRoot MTA and an antibiotic mixture of Ciprofloxacin, Metronidazole and Cefixime combined with Simvastatin (3Mixtatin) were significantly superior clinically (no tenderness to percussion, absences of sinus tract, no pain) and radiographically (absence of resorption, hard tissue formation beneath the capping material, absence of radiolucency) compared to the Simvastatin and the triple antibiotic mixture alone (Asl Aminabadi et al. 2016). Results of a systematic review and meta-analysis revealed no significant differences in clinical and radiographic outcomes between calcium hydroxide and both ProRoot MTA and tooth coloured ProRoot MTA as direct pulp capping agents in primary teeth; however, the number of studies included in the analysis was limited (Schwendicke et al. 2016).

**Permanent teeth - histological studies:** ProRoot MTA had similar to significantly better outcomes in terms of complete calcified bridge formation and reducing inflammation compared to Dycal (Parolia et al. 2010, Eskandarizadeh et al. 2011, Swarup et al. 2014, Nowicka et al. 2015).

Comparison between tooth coloured ProRoot MTA and ProRoot MTA revealed no significant difference in terms of the thickness of calcified bridge formation and inflammation (Eskandarizadeh et al. 2011).

Various powder-to-liquid ratios of tooth coloured MTA (0.28, 0.33 and 0.40 water/powder ratios) had no significant effect after one month when used as a pulp capping agents in terms of intensity and type of inflammation, presence of pulp necrosis, as well as continuity, morphology and thickness of calcified bridges (Shahravan et al. 2011).

No significant difference has been reported between Biodentine and tooth coloured ProRoot MTA as pulp capping agents in terms of formation of complete calcified bridges (Nowicka et al. 2013, 2015). Nano-hydroxyapatite and CEM cement were also reported as potential direct pulp capping agents with comparable results to MTA Angelus in terms of inducing complete calcified bridges as well as favorable cellular and vascular responses (Zarrabi et al. 2010, Swarup et al. 2014).

Placement of a poly (ε -caprolactone) fibre mesh as a barrier beneath OrthoMTA and ProRoot MTA as pulp capping materials in humans (Lee et al. 2015a) confirmed the results of an animal study in dogs (Lee et al. 2012). In addition, other benefits such as significantly more rapid and thicker hard
tissue barrier formation, as well as no tooth discoloration were observed when compared to the ProRoot MTA control (Lee et al. 2015a).

MTA was associated with significantly thicker calcified bridges when compared to gentamycin and betamethasone as direct pulp capping agents (AlShwaimi et al. 2016). Both MTA Angelus and CEM cement have been reported to increase tenascin and fibronectin levels soon after pulp capping in human teeth (Zarrabi et al. 2011).

From a histological standpoint, the time for hard tissue barrier formation beneath capping materials varies. In animal studies the formation of a complete hard tissue barrier at the capping site occurs as soon as one week following treatment (Parirokh et al. 2005, Liu et al. 2015). However, in human studies, no barriers have been reported to form in less than two weeks (Swarup et al. 2014, AlShwaimi et al. 2016). In fact, in most studies, the time needed for hard tissue barrier formation in humans has been reported to be from 30 to 42 days (Eskandarizadeh et al. 2011, Shahravan et al. 2011, Yoshia et al. 2012, Banava et al. 2015).

One of the most important limitations of human studies is the fact that the researchers capped healthy pulps in sound, intact teeth, whereas in reality pulps are only capped in carious or traumatized teeth that are exposed to microorganisms. In carious exposures, it is particularly critical because the pulp has already been influenced by the bacteria and their byproducts and the extent of pulp inflammation as well as the severity of pulp reaction is not clear or standardized (Parirokh & Torabinejad 2010b).

In conclusion, other than the white and grey varieties of ProRoot MTA and MTA Angelus, few histological studies have been conducted in human teeth using BECs as pulp capping agents. Several previous investigations reported favorable outcomes in animal models but this does not predict similar responses in humans (Hebling et al. 1999, Hörsted-Bindslev et al. 2003, Accorinte et al. 2005). One of the major shortcomings for histological studies has been the use of intact teeth with healthy pulps and the measurement of the thickness of calcific barriers and other surrogate measures that are not necessarily linked to the real outcome of direct pulp capping. Therefore, more investigations should be conducted on teeth with carious lesions to provide an environment close to real clinical conditions; they should also focus on measuring the real outcome and not focus on surrogate measures.

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The following variables are discussed in the literature as possible factors influencing the outcome of direct pulp capping: age, gender, type of direct pulp capping material, tooth location, type of tooth, type of restoration, time duration between pulp capping to placement of final restoration, site of exposure, type of pulp exposure (mechanical or carious), type of caries (primary or secondary), size of exposure, class of restoration, quality of coronal restoration at the follow-up visit, treatment providers, duration of the follow-up period, removal of caries with an excavator or bur and recall time (Mente et al. 2010, 2014, Dogan et al. 2013, Hilton et al. 2013, Cho et al. 2013, Marques et al. 2015, Çalışkan & Güneri 2017).

Several reports did not reveal a significant impact of these factors on the final outcome and survival rate of teeth after direct pulp capping (Çalışkan & Güneri 2017). In contrast, others reported that several of these factors may have had a significant impact and should be considered when direct pulp capping is used (Accorinte et al. 2005, Mente et al. 2010, 2014, Cho et al. 2013, Marques et al. 2015). For instance, an investigation that compared calcium hydroxide (Merck, Darmstadt, Germany) mixed with distilled water to ProRoot MTA as direct pulp capping agents in teeth with cariously exposed pulps did not find a significant difference between the materials in terms of the final outcome of treatment (Çalışkan & Güneri 2017). However, Kundzina et al. (2016) reported significantly better outcomes for tooth coloured ProRoot MTA compared to Dycal in terms of pulp survival rates.

Prognostic factors may be influenced by sample size and duration of follow-up. The studies conducted by Mente et al. (2010, 2014) are good examples for revealing the effect of sample size as well as duration of follow-up as factors that may affect the outcomes of direct pulp capping. In their first study on 122 teeth that received direct pulp capping with either ProRoot MTA or calcium hydroxide, two prognostic factors, including time elapsed between pulp capping and final restoration, as well as the practitioners’ experience had a significant influence on the treatment outcome when a non-setting
calcium hydroxide (Hypocal SN; Merz Dental, Lutjenburg, Germany) was used; however, neither of these prognostic factors had a significant influence on the success rate of ProRoot MTA (Mente et al. 2010). In their second study (Mente et al. 2014) with larger sample size and longer follow-up, ProRoot MTA (as a direct pulp capping agent) was associated with a significantly greater success rate compared to the non-setting calcium hydroxide (Hypocal SN) in terms of clinical (absence of clinical signs or symptoms, no need to receive root canal treatment subsequent to direct pulp capping, having function, or pulp survival long term following the procedure) and radiographic outcomes (condensing apical periodontitis, internal root resorption, and periapical index <2). Another important result of their study was the fact that the teeth restored permanently more than two days following the capping procedure had significantly higher failure irrespective of the type of the direct pulp capping material used (Mente et al. 2014).

Two studies (Accorinte et al. 2005, Mente et al. 2010), reported that the experience of treatment providers had a significant influence on the outcomes of direct pulp capping. However, the results of a later study by Mente et al. (2014) with a larger sample size and a longer follow-up period concluded that the experience of the treatment providers had no influence on the final outcome of treatment.

Several investigations have emphasized that occlusal exposures (Cho et al. 2013, Schwendicke & Stolpe 2014) and patients under 40 years of age had better outcomes following direct pulp capping treatment when either Dycal (Cho et al. 2013) and tooth coloured ProRoot MTA were used as pulp capping agents (Cho et al. 2013, Marques et al. 2015).

Placing a moist cotton pellet over MTA improves its physical properties (Parirokh & Torabinejad 2010a). In addition, the practitioner can check the setting of the material at the second visit and have confidence in the method and technique of mixing and placement. Therefore, using the material in two visits has been recommended (Parirokh & Torabinejad 2010a). However, some practitioners prefer to use it in a one-visit treatment (Parirokh & Torabinejad 2010b), which has been confirmed by Banava et al. (2015) who reported no significant difference between one- or two-visit treatments with tooth coloured ProRoot MTA as pulp capping material in terms of clinical (sensitivity to cold) and histologic criteria (hard tissue formation and pulp inflammatory response).

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ProRoot MTA compared with Endocem (Song et al. 2015, Jang et al. 2015) as well as grey MTA
Angelus compared with Biodentine (Katge & Patil 2017) as direct pulp capping materials revealed no
significant difference between the materials in terms of the teeth being asymptomatic, sensitive to a
sensibility tests, no internal and external resorption, and no periapical radiolucency. However, all
these studies had the usual shortcomings of small sample size and short-term follow-up.
TheraCal and Dycal were not significantly different in terms of the outcome following use as direct
pulp capping agents in cariously exposed pulps in permanent teeth; however, a combination of
irradiating the exposure site by erbium, chromium-doped yttrium, scandium, gallium, and garnet
(Er,Cr:YSGG) laser with either of the direct pulp capping agents was associated with significantly
less pulp necrosis and fewer clinical symptoms (tenderness to percussion, reaction to thermal stimuli,
and spontaneous pain) (Cengiz & Yilmaz 2016).
Use of corticosteroids beneath the capping material may reduce inflammation associated with pulp
exposure. Direct pulp capping of mechanical exposure using dexamethasone beneath tooth coloured
ProRoot MTA induced less inflammation while there was no significant difference in calcified bridge
formation and connective tissue response when MTA was used alone (Mousavi et al. 2016). The
major shortcoming of studies using laser or medicaments such as corticosteroid that reduce
inflammation is their short term follow-up, thus, the long-term effects of using these treatments is
unknown.
From an economic standpoint, cost-effectiveness of dental treatment is an important issue. Modeling
the cost-effectiveness of direct pulp capping and root canal treatment in teeth with vital and
asymptomatic pulps revealed that when the axial wall was exposed, or in patients older than 50 years
of age, root canal treatment was more cost-effective than direct pulp capping. However, when the
teeth had an occlusal exposure site and belonged to younger patients, direct pulp capping was more
cost-effective compared to root canal treatment (Schwendicke & Stolpe 2014).
In another investigation by the same group (Schwendicke et al. 2015a) treatment with MTA was more
cost-effective than calcium hydroxide because the need for additional future expensive treatments
would be prevented.
The success rate of pulp capping following use of MTA in teeth with open and closed apices has been a matter of controversy in several investigations. Based on a systematic review and meta-analysis of results in teeth with carious exposures, those with closed apices were associated with a significantly higher failure rate compared to teeth with open apices after direct pulp capping (Aguilar & Linsuwanont 2011).

Another important issue in pulp capping studies is the follow-up period. Some investigators reported tooth coloured ProRoot MTA and Dycal had lower long-term success (Cho et al. 2013), whereas others reported that ProRoot MTA had a constant number of cases with success and even had higher success rates when followed-up for more than 3 years (Mente et al. 2010). Methods and materials of investigations are important issues that may affect the outcome of pulp capping procedures. For instance, in the study of Miles et al. (2010) the lowest success rate of pulp capping outcomes with ProRoot MTA was associated with treatment performed by undergraduate students and when caries was not excavated completely following pulp exposure.

Early failure following direct pulp capping has a strong relationship with the pulp condition prior to the procedure. However, long-term failure may be influenced by the ability of the material to provide an environment for the development of odontoblast-like cells as well as calcified bridge formation with no necrosis or inflammation that may affect pulp health. It has been recommended that at least a 1-year follow-up is necessary when direct pulp capping materials are compared to each other (Jang et al. 2015); however, most studies reported different success rates over longer periods for direct pulp capping (Mente et al. 2010, 2010, Cho et al. 2013).

Using the correct statistical methods of analysis are important when comparing the outcome of treatments. When different forms of vital pulp therapies are compared it is important to compare them by indirect comparisons to measure the effect of the treatments and compare them to each other.

Statistical direct comparisons of the results of these studies may be a methodological flaw because the inclusion criteria and the treatment protocols are different (Aguilar & Linsuwanont 2011). A systematic review and meta-analysis reported no significant differences between calcium hydroxide and MTA as pulp capping materials when compared directly. However, statistical indirect comparison
of weighted pooled success rate revealed that MTA was significantly superior to calcium hydroxide for direct pulp capping (Aguilar & Linsuwanont 2011).

Two systematic reviews and meta-analyses that evaluated the clinical and radiographic outcomes of pulps that were directly capped with either various types of MTA or calcium hydroxide reported significantly higher success rates for MTA (Li et al. 2015, Zhu et al. 2015). In fact, the frequency of success in both randomized clinical trials and retrospective non-randomized studies in MTA-capped pulps was significantly higher than calcium hydroxide. From a histological standpoint, MTA was associated with significantly less inflammation and more frequent calcified bridge formation compared to calcium hydroxide. The shortcomings of these systematic reviews were the inclusion of teeth with and without caries, including primary and permanent teeth, including teeth with a history of primary and secondary caries, and the inclusion of retrospective studies in the meta-analysis. In addition, including both types of ProRoot MTA and tooth coloured ProRoot MTA (Zhu et al. 2014) as well as all types of ProRoot MTA, tooth coloured ProRoot MTA and MTA Angelus (Li et al. 2015) is another shortcomings of these systematic reviews and meta-analyses. Another systematic review reported that there was insufficient evidence to support the superiority of MTA over calcium hydroxide in terms of promoting hard tissue formation following direct pulp capping. Heterogeneity among the studies made it difficult for the authors to include a reasonable number of investigations in their systematic review and perform a meta-analysis. For instance, various forms of MTA and calcium hydroxide have been used for pulp capping (Fransson et al. 2016). The lack of randomized clinical trials with rigorous methodology was a major concern for the investigators that undertook the systematic reviews and meta-analyses on carious teeth with vital pulps (Bergenholtz et al. 2013). A recent systematic review and meta-analysis (Schwendicke et al. 2016) reported that the risk of failure was significantly lower when MTA was used as a direct pulp capping agent in permanent teeth; however, more randomized clinical trials should be performed to confirm the absolute superiority of one material over others. One of the shortcomings of the meta-analysis was including both types of ProRoot MTA and tooth coloured ProRoot MTA (Schwendicke et al. 2016). Many clinical studies on direct pulp capping using BECs had shortcomings including no valid inclusion criteria, no rigorous exclusion criteria, small sample size, no method for determining the sample size,
no reasonable method of randomization for different sites or materials of pulp capping, no description regarding method of randomization, high numbers of lost cases during follow-up, mixing of MTA with local anaesthetic solution instead of distilled water, no caries excavation after pulp exposure that may affect the treatment outcome, a long period of time between the pulp capping procedure and placing the final restoration, short follow-up period, no objective evaluation method, no calibration prior to clinical and radiographic evaluation, no inter- and intra-examiner reliability, no report of Kappa score reporting, no comparison with other currently used pulp capping agents, teeth being restored with various permanent restorations in the same investigation, no information regarding experience, skill and training of the practitioners prior to the treatment as well as lack of data on the individual clinicians experience of working with the capping materials (Maltz & Alves 2013). Other than that, there are also several variables that may influence the outcome vital pulp therapies including: site of pulp exposure (Bogen & Chandler 2008, Cho et al. 2013), whether removing caries with burs or excavators (Dogan et al. 2013), type of pulp capping materials (Aguilar & Linsuwanont 2011), type of irrigants used for rinsing the pulpal wound (Akcay & Sari 2014), age of the patient, type of pulp capping procedure (Aguilar & Linsuwanont 2011, Gudkina et al. 2012). It has been reported that occlusal exposures have a better prognosis than axial wall exposures following direct pulp capping (Bogen & Chandler 2008, Cho et al. 2013); therefore, stratified randomization between the materials is necessary to eliminate bias when various exposure sites are encountered (Fleming et al. 2014).

In conclusion, it has been reported that direct pulp capping with ProRoot MTA and tooth coloured ProRoot MTA is more cost-effective compared to root canal treatment in younger patients in teeth with reversible pulpitis. The trend of published clinical trials demonstrates the superiority of ProRoot MTA and tooth coloured ProRoot MTA compared to calcium hydroxide. However, in order to have better levels of evidence through systematic review and meta-analysis, more rigorous randomized clinical trials with better reporting are required. In addition, in order to prevent further common errors, those planning a systematic review and meta-analysis as well as cost-effectiveness studies should consider the type of MTA and calcium hydroxide as significant variables and not simply pool them into one group during the analysis. Several investigations evaluated other BECs as pulp capping

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agents with short-term follow-up. More research with longer-term follow-up is needed in order to evaluate alternative pulp capping materials to MTA. In addition to the material used for direct pulp capping, there are several other factors that may influence the final outcome; therefore, these variables should be controlled in future studies.

C. Partial pulpotomy

Animal studies

Both ProRoot MTA and RetroMTA were associated with high quality calcified bridges and, in most specimens, the pulp tissue was free of inflammation. In contrast, TheraCal had poor quality calcified bridges and diffuse inflammation (Lee et al. 2015b).

Human studies


A new term, “miniature pulpotomy,” has been introduced that refers to the limited removal of vital pulp tissue following exposure (Asgary & Ahmadyar 2012, Asgary & Fazlyab 2014, Asgary et al. 2014c). However, there is no real difference between this term and superficial/partial pulpotomy, and the latter remains the recommended terminology. Two cases with spontaneous pain and periapical rarefaction illustrated successful clinical and radiographic outcomes of so-called miniature pulpotomy through resolution of periapical pathosis and formation of calcified tissue beneath the capping material, as well as no pain and positive response to pulp sensibility tests (Asgary et al. 2016).

Several studies through clinical and radiographic evaluation reported high success rates of grey ProRoot MTA as a pulp capping agent after partial pulpotomy (Parirokh & Torabinejad 2010b, Caprioglio et al. 2014).
Randomized clinical trials comparing RetroMTA, iRoot BP and OrthoMTA with tooth coloured ProRoot MTA as pulp capping agents revealed similar responses in both sound intact (Azimi et al. 2014) and cariously exposed pulps (Kang et al. 2017). Clinical and radiographic evaluation of ProRoot MTA and Dycal for partial pulpotomy in young permanent teeth with carious exposures revealed no significant difference between the materials in terms of unsuitable clinical signs and symptoms (pain, swelling, sinus tract, tenderness to percussion) and radiographic outcome (evidence of periradicular or furcation pathosis, root resorption or a lack of continuation of root development in immature teeth) (Chailertvanitkul et al. 2014).

A systematic review and meta-analysis on cariously exposed pulps reported significantly greater success after using calcium hydroxide as a partial pulpotomy agent compared to MTA (Aguilar & Linsuwanont 2011). However, a recent systematic review concluded that there was insufficient evidence to support the superiority of MTA over calcium hydroxide in terms of promoting hard tissue formation following partial pulpotomy (Fransson et al. 2016).

In conclusion, few investigations have compared BECs as partial pulpotomy agents. Therefore, it is not possible to claim superiority of one material over another. More randomized clinical trials are required.

D. Complete pulpotomy

Animal studies

**Primary teeth:** Both tooth coloured ProRoot MTA and Biodentine were associated with significantly less inflammation and more calcified bridge formation compared to formocresol in the primary teeth of pigs up to 90 days following the procedure (Shayegan et al. 2012).

**Permanent teeth:** Several investigations compared MTA with other BECs using histologic evaluation in rats and dogs. CEM cement, iRoot BP Plus, MTA Plus and Biodentine, as well as ProRoot MTA and tooth coloured ProRoot MTA, were reported to have successful outcomes following pulpotomy in terms of limited inflammation and successful calcified bridge formation (Tabarsi et al. 2010, De Rossi et al. 2014, Kramer et al. 2014, Liu et al. 2015). A radiographic and histologic investigation revealed significantly thicker calcified bridge formation in the Biodentine.

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group compared to tooth coloured ProRoot MTA as pulpotomy agents in dogs’ teeth (De Rossi et al. 2014). Comparing Endocem Zr to ProRoot MTA as pulpotomy agents revealed no significant difference between the materials in terms of calcified barrier formation and inflammation; however, the maturity of hard tissues formed in response to the materials was significantly in favour of ProRoot MTA (Lee et al. 2017).

Two studies on Quick-Set revealed no significant difference with ProRoot MTA (Kramer et al. 2014) and tooth coloured ProRoot MTA for calcified bridge formation (Woodmansey et al. 2015); however, Quick-Set induced a significantly more intense pulp inflammatory response (Woodmansey et al. 2015).

Evaluating nociceptive responses is a new approach for evaluating animal behavior following dental procedures by measuring the duration of animal meals (Kramer et al. 2010). ProRoot MTA, Quick-Set and MTA Plus significantly reduced the length of animal meal times following pulp capping (Kramer et al. 2014).

In conclusion, a few animal studies have compared new BECs to ProRoot MTA. Some of these studies have been well designed; however, others have had shortcomings including lack of statistical comparisons, small sample size, loss of the cement in a large number of the teeth, no controls, no bacteriological staining and short-term follow-up periods. In future, investigations should be performed with more sophisticated designs.

**Human studies**

**Primary teeth:** Numerous articles with varying levels of evidence have been published on pulpotomies in primary molar teeth using various BECs including Portland cement, ProRoot MTA, MTA Angelus, Biodentine and CEM cement (Conti et al. 2009, Emine & Tuba 2011, Mehrdad et al. 2013, Oliveira et al. 2013).

Despite there being no significant difference in the outcome when using Portland cement and grey MTA Angelus following pulpotomy in primary molars (Sakai et al. 2009), it should be emphasized that using Portland cement is not advisable, as the material may contain heavy metal elements that could be harmful, particularly in children (Parirokh & Torabinejad 2010a).
Two studies reported that MTA was associated with significantly better outcomes compared to ferric sulfate (Doyle et al. 2010, Goyal et al. 2016), whereas others reported no significant difference between the materials in terms of radiographic findings (internal resorption as well as furcation and periapical radiolucency) and clinical sign and symptoms (no pain, tenderness to percussion, swelling, absence of sinus tract, pathologic mobility (Erdem et al. 2011, Odabaş et al. 2012, Frenkel et al. 2012, Yildiz & Tosun 2014). MTA also had significantly fewer clinical sign and symptoms (less pain, sinus tract formation, and mobility) and radiographic evidence of pathosis (furcation radiolucency, internal and external resorption, periodontal widening, canal obliteration) compared to buffered glutaraldehyde up to 6 months following treatment (Goyal et al. 2016).

Both MTA Angelus and ProRoot MTA had significantly greater clinical and radiographic success rates compared to calcium hydroxide following pulpotomy in primary molar teeth (Liu et al. 2011, Celik et al. 2013). However, another clinical investigation reported no significant difference between radiographic and clinical outcomes when ProRoot MTA and calcium hydroxide were used as pulpotomy agents in primary molars (Yildiz & Tosun 2014).


No significant difference was found between tooth coloured ProRoot MTA and ProRoot MTA as pulpotomy agents in primary teeth (Frenkel et al. 2012, Cardoso-Silva et al. 2011). Substantial clinical and radiographic success for CEM cement as a pulpotomy agent has been reported for primary molars up to 12 months following treatment. However, the authors admitted that they had small sample sizes and their patients may not have been able to report pain objectively following the procedure due to their young age (Memarpour et al. 2016). However, others have reported that CEM
cement was not significantly different in outcome compared to electrosurgery +ZOE (Khorakian et al. 2014).

Clinical trials comparing Biodentine, CEM cement, RetroMTA and OrthoMTA to tooth coloured MTA, ProRoot MTA, and MTA Angelus as pulpotomy materials in primary molar teeth reported no significant differences in clinical and radiographic outcomes (Malekafzali et al. 2011, Kang et al. 2015, Kusum et al. 2015, Niranjani et al. 2015, Cuadros-Fernández et al. 2016, Rajasekharan et al. 2017, Togaru et al. 2016). In addition, no significant difference was found between pain felt by children following pulpotomy of primary molars using either CEM or tooth coloured ProRoot MTA (Shafie et al. 2017).

There was no significant difference between Biodentine and formocresol up to 6 months following pulpotomy in terms of clinical (no pain or swelling, absence of abscess, sinus tract, mobility, and tenderness to percussion), and radiographic success (absence of periapical or furcation radiolucency as well as internal and external resorption and presence of a normal periodontal ligament space) (El Meligy et al. 2016). There was also a significant increase in dentin bridge thickness when Biodentine compared to calcium hydroxide (Pulpdent) as pulpotomy agents in primary molars (Grewal et al. 2016).

Several BECs such as tooth coloured ProRoot MTA, ProRoot MTA, Portland cement, Biodentine, and CEM cement were associated with canal obliteration following pulpotomy in primary molars (Sakai et al. 2009, Parirokh & Torabinejad 2010b, Rajasekharan et al. 2017, Memarpour et al. 2016, Godhi et al. 2016). However, Biodentine was associated with significantly more extensive root canal obliteration compared to tooth coloured ProRoot MTA (Rajasekharan et al. 2017).

No significant differences in clinical sign and symptoms (presence of pain, sensitivity on percussion and palpation, discoloration, swelling, sinus tract, mobility, lymphadenopathy related to the site of treatment) and radiographic observations (periodontal widening, periapical and furcation radiolucency, external and internal resorption, canal obliteration) were found between diode laser and enamel matrix derivatives with ProRoot MTA (Yildirim et al. 2016) and MTA after pulpotomy in primary molars (Uloopi et al. 2016).

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The number of patients with malignant diseases is increasing around the world (WHO 2017).

Evaluating the record of healthy children who received pulpotomy with either MTA or formocresol compared to children who were under active cancer treatment and received the same dental treatment revealed no significant difference in radiographic and clinical success up to six months following treatment (Halperson et al. 2014). In addition, none of the patients in the cancer group had bacteremias and systemic complications related to the dental treatment they received. The shortcomings of the study were a small sample size, short term follow up period, and a wide range of dental treatments that the patients received, including various types of pulpotomy materials, no explanation for the type of MTA used, mode of chemotherapy, duration of the chemotherapy and/or radiation.

It can be debated that teeth with mechanical exposures are not a suitable model for evaluating pulpotomy agents. ProRoot MTA and formocresol were not significantly different in the success rates of the materials in carious and mechanical exposures (Ozdemir et al. 2015, Celik & Sari 2016). However, calcium hydroxide had a significantly higher success rate in intact sound primary teeth compared to those that were cariously exposed. An interesting point was the level of pro-inflammatory cytokines as the predictor of success and failure in the pulpotomy procedure. Pro-inflammatory cytokines, namely IL-1α, IL-6 and IL-8, were significantly higher in the coronal pulp prior to the capping procedure of the failed teeth compared to the successful ones (Ozdemir et al. 2015).

An important point regarding use of a material as a pulp capping agent in primary teeth is its safety for permanent successor teeth. No adverse effect in terms of discoloration, hypomineralization, structure or malposition and no delay in the eruption time of the successor teeth has been reported (Mendoza-Mendoza et al. 2014).

Several shortcomings have been found in studies evaluated pulpotomies in primary teeth such as small sample size, short term follow-up, and including teeth with natural root resorption (Gokhale et al. 2016, El Meligy et al. 2016).

In a systematic review, Anthonappa et al. (2013) reviewed 22 studies that used various types of MTA as a pulpotomy material in primary teeth. They concluded that there was insufficient evidence to support the superiority of MTA over other currently used materials. They also emphasized the need to plan high quality investigations in the future because current reports had serious methodological shortcomings.

Another systematic review performed by Lin et al. (2014) reported that despite the superiority of MTA compared to calcium hydroxide and formocresol in the early follow-up period (9-12 months), longer time evaluation (18-24 months) revealed that formocresol, ferric sulfate and MTA had significantly better clinical and radiographic outcomes compared to calcium hydroxide and laser irradiation for pulpotomy in primary molars (Lin et al. 2014). A review of the Lin et al. (2014) study criticized it for including articles with high heterogeneity and few restrictions in the inclusion criteria (Omar 2015).

Using calcium hydroxide as a pulpotomy agent in primary molars has not been supported by several systematic reviews and meta-analyses (Shirvani et al. 2014, Stringhini Junior et al. 2015).

Two systematic reviews and meta-analyses reported no significant difference between formocresol and MTA as pulpotomy materials in primary molars with at least 24-month follow-ups (Lin et al. 2014, Marghalani et al. 2014). In contrast, several systematic reviews and meta-analyses reported significantly greater clinical and radiographic success rates for MTA compared to formocresol as pulpotomy agents in primary molars (Peng et al. 2006, Shirvani et al. 2014, Shirvani & Asgary 2014, Stringhini Junior et al. 2015). Yet another systematic review reported that formocresol and MTA had better outcomes compared to other pulpotomy agents (Simancas-Pallares et al. 2010).

The duration of follow-up may affect the results of systematic reviews when pulpotomy agents are compared (Lin et al. 2014, Asgary et al. 2014b). A systematic review and meta-analysis revealed that despite similar outcomes up to 12 months, at the two-year evaluation ProRoot MTA had a
significantly greater success rate compared to ferric sulfate when used as a pulpotomy agent in primary molars (Asgary et al. 2014b).

A Cochrane review on primary teeth with extensive caries reported that there was insufficient evidence to support a single superior material for all vital pulp therapy procedures (Smail-Faugeron et al. 2014). However, based on the evidence, the authors mentioned two preferable materials, including ferric sulfate and MTA as pulpotomy agents. The main problem with announcing superiority of one material over another for pulpotomy in primary molars is the fact that the quality of current evidence is not sufficient to support such conclusions because of shortcomings in methodology, small sample size and short-term follow-up. However, it seems that MTA may be a reasonable choice for pulpotomy in primary molars.

In conclusion, despite several systematic reviews and meta-analyses that have announced MTA is a superior pulpotomy material in primary teeth compared to other currently used materials (Shirvani et al. 2014, Shirvani & Asgary 2014, Asgary et al. 2014b, Stringhini Junior et al. 2015), there are major concerns regarding the quality of the randomized clinical trials included in the analysis, e.g. insufficient sample sizes and short duration of follow-up. In addition, some systematic reviews and meta-analyses did not use strict inclusion criteria. This ignores the heterogeneity among the randomized clinical trials and the results should be considered with caution (Omar 2015). Future randomized clinical trials should be designed carefully with a large number of cases and long-term follow-up to provide sufficient evidence for making decisions on the best techniques as well as the most appropriate materials for pulpotomy in primary molar teeth. In addition, in most of these systematic reviews and meta-analyses the type of MTA was not considered as an important variable yet it could have a major impact on the outcomes.

**Human studies**

**Permanent teeth:** Several case reports and case series have illustrated the successful treatment of permanent teeth with immature apices following pulpotomy using ProRoot MTA, tooth coloured ProRoot MTA, Endocem, CEM cement, and Biodentine (Asgary & Ehsani 2009, Nosrat & Asgary 2010a, b, Barngkgei et al. 2013, Subay et al. 2013, Harandi et al. 2013, Kim et al. 2014, Martens et
Successful treatment outcomes have been reported when cariously and traumatically exposed permanent teeth with open apices were treated by either MTA or ZOE as pulpotomy agents (Ghoddusi et al. 2012).

Two investigations reported successful outcomes in teeth with partial irreversible pulpitis and apical periodontitis (Qudeimat et al. 2017, Taha et al. 2017). In a preliminary report, pulpotomy with ProRoot MTA or tooth coloured ProRoot MTA in molar teeth in young patients resulted in clinical and radiographic success even when the teeth had signs of symptomatic (probably partial) irreversible pulpitis with symptomatic apical periodontitis prior to the treatment (Qudeimat et al. 2017). Another investigation reported a successful outcome up to three years following grey MTA Angelus placement as the pulpotomy agent in teeth with both reversible and (partial) irreversible pulpitis. The teeth had radiographic signs of apical periodontitis or no periapical involvement (Taha et al. 2017).

Platelet-rich fibrin is considered an autologous healing biomaterial consisting of leukocytes, platelets and a wide range of key healing proteins in a dense fibrin matrix. In fact, platelet-rich fibrin can be assumed to provide the slow and continuous release of various signaling molecules in a regenerative or capping process. These signaling molecules consist of growth factors that promote odontoblast-like cell differentiation and angiogenic growth factors for capillary formation as well as adjustment of inflammatory reactions (Fouad & Nosrat 2013). In a case report, a novel intervention using platelet-rich fibrin as a pulp capping agent and ProRoot MTA was illustrated (Hiremath et al. 2012b).

However, two randomized clinical trials reported no significant difference when using ProRoot MTA, tooth coloured ProRoot MTA and platelet-rich fibrin as pulpotomy materials in cariously exposed molar teeth in terms of clinical signs and symptoms and radiographic evaluation. The authors recommended platelet-rich fibrin as a more economic method for pulp capping (Keswani et al. 2014, Kumar et al. 2016).
Successful treatment following use of ProRoot MTA and tooth coloured ProRoot MTA, white Portland cement, and CEM cement as pulpotomy materials in either intact or cariously involved human permanent teeth has been reported by several investigations (Simon et al. 2013, Nosrat et al. 2013a, b, Alqaderi et al. 2014, Bhagat et al. 2016).

In a multi-centre randomized clinical trial, CEM cement was compared to tooth coloured ProRoot MTA as pulpotomy agents in 413 patients with a history of pain and with at least some area of irreversible pulpitis. Results revealed that pain reported by the patients in the seven days following treatment was not different between the materials. Moreover, no significant difference was found between the materials in terms of clinical and radiographic outcomes up to 12 months (Asgary & Eghbal 2013).

A multi-centered investigation reported that patients with at least some area of irreversible pulpitis who received either pulpotomy with CEM cement or root canal treatment suffered significantly more post-operative pain when receiving the latter treatment (Asgary & Eghbal 2010).

In a series of articles, the radiographic and clinical outcomes of a multi-centre (23 health-care centres) investigation on 407 patients with different follow-up periods were presented (Asgary et al. 2013b, 2014a, 2015). Patients having molars with at least some area of irreversible pulpitis who received either root canal treatment or pulpotomy with CEM cement by general practitioners were followed-up for up to five years. In the first paper, the authors reported no significant difference in clinical success for teeth that received either pulpotomy or root canal treatment when followed up for six months and one year, whereas the CEM cement pulpotomy group had a significantly higher radiographic success rate compared to root canal treatment (Asgary et al. 2013b). Results of the second and third papers revealed that after 27 months and 60 months of follow-up, no significant difference was found between the two procedures in terms of clinical and radiographic success (Asgary et al. 2014a, 2015).

Based on these studies (Asgary & Eghbal 2010, Asgary et al. 2013b, 2014a), a health technology assessment investigation has claimed that vital pulp therapy with CEM cement is more efficient, affordable and effective in mature permanent molar teeth with at least some area of irreversible pulpitis compared to root canal treatment when the treatment was performed by general practitioners. Their claim was based on short-term (pain rated one week following the treatment) as well as
intermediate-term outcomes (six months to two years of follow-up) of the previous investigations that compared CEM cement to root canal treatment (Yazdani et al. 2014). It should be noted that all treatment procedures were performed by general practitioners. A recent investigation on a large number of teeth (487,476) that received root canal treatment confirmed that when molar teeth received root canal treatment by endodontic specialists compared to the general practitioners, the survival rate of the teeth was high (greater than 85%) after long-term follow-up (Burry et al. 2016). Other than the material used for vital pulp therapies the methodology of the treatment procedure may influence the treatment outcome. For instances, it has been reported that in primary teeth, when removing caries with burs, there was a significantly better outcome following pulp capping (either by direct pulp capping or pulpotomy) compared to removing caries with an excavator (Dogan et al. 2013). Therefore, heterogeneity in the literature makes it difficult to determine an absolute advantage of one material over another without considering these differences among investigations on vital pulp therapies (Bogen & Chandler 2008, Elkhadem et al. 2014).

Several investigations presented results of treatment carried out in private dental clinics. This results in high internal validity but low external validity. Another commonly observed shortcoming is the evaluation of cases in follow-up visits by the same operator who carried out the treatment (Marques et al. 2015). This may lead to performance bias, detection bias, and attrition bias (Fleming et al. 2014). Presence of an apical radiolucency has been assumed as a contraindication for performing vital pulp therapies in permanent teeth; however, a retrospective investigation reported a high percentage of success even in teeth that received MTA pulpotomy (Linsuwanont et al. 2017). However, it should be noted that in young permanent molar teeth the apical papilla might be confused with a periapical radiolucency.

From clinical and radiographic standpoints, using NaOCl prior to placement of the pulpotomy material improved the success rate of calcium hydroxide; however, it had a slight but insignificant adverse effect on the success rate of MTA (Akcay & Sari 2014).

A systematic review on vital pulp therapy on cariously exposed pulps reported that both partial pulpotomy and complete pulpotomy were associated with higher success rates than direct pulp capping (Aguilar & Linsuwanont 2011). There was no significant difference between calcium
hydroxide and MTA after full pulpotomy. This study had limitations, such as including both case series and cohort studies in the meta-analysis. In addition, studies included in the meta-analysis exhibited heterogeneity in their methodology. Therefore, the authors recommend that their results should be considered with caution (Aguilar & Linsuwanont 2011).

An important limitation for current systematic reviews and meta-analyses are the limited number of investigations that could be included. A recent review article (Zanini et al. 2016) has emphasized the importance of using valid criteria to identify success and failure of pulpotomies. The authors believe that by using their criteria it would be easier to compare the results of various investigations and use their data in future systematic reviews and meta-analyses. Their criteria for future clinical investigations on pulpotomy are based on functionality as well as clinical (subjective and objective) criteria and radiographic findings (Zanini et al. 2016).

In conclusion, using MTA as a pulpotomy agent was associated with a higher successful outcome compared to most of other pulpotomy agents; however, to date, most of the clinical trials have had several biases and shortcomings. More investigations with rigorous methodology are needed.

Partial pulpectomy

There are a limited number of low-level evidence-based reports on whether to maintain some tissues of the pulp after partial pulpectomy followed by coronal placement of a BEC (Asgary & Kemal Çalışkan 2015). However, this method has an advantage of preserving pulp in teeth with open apices.

Summary

ProRoot MTA and tooth coloured ProRoot MTA have several drawbacks such as long setting time, difficult handling, discoloration potential, high cost and induction of pulp calcification (Parirokh & Torabinejad 2010a, b, Yang et al. 2010, Cardoso-Silva et al. 2011, Chin et al. 2016, Komabayashi et al. 2016). Most of these drawbacks are also true for MTA Angelus. Despite these drawbacks, ProRoot MTA and tooth coloured ProRoot MTA and MTA Angelus have been associated with successful outcomes as vital pulp therapy agents, particularly when pulps have been exposed mechanically.

There are several reports that confirm dentists are avoiding using BECs for managing deep caries because they are either not aware of the potential of these materials, not trained and/or because BECs...
are more difficult to handle than conventional liners (Chin et al. 2016, Ha et al. 2016). Thus, the training of undergraduate and postgraduate students and dentists to use BECs must be emphasized in both dental schools and continuing education programmes (Foley 2011, 2013, Chin et al. 2016).

From an evidence-based perspective, the number of investigations that demonstrate MTA has absolute superiority over calcium hydroxide for all vital pulp therapy procedures is low. At the same time, several BECs have been introduced and their manufacturers claim their superiority over MTA in terms of setting time, handling properties and discoloration potential. However, there are only limited numbers of evidence-based investigations regarding their efficacy as vital pulp therapy agents. In addition, long-time follow-up after using these new BECs is unavailable. Furthermore, the quality of most of these investigations has not been sufficient to support the assertions of the manufacturers. Therefore, future investigations must have rigorous methodologies, particularly sufficient sample size, long-term follow-up and qualified methods and materials based on CONSORT guidelines (Lucena et al. 2017).

One of the common shortcomings in clinical investigations has been to ignore the specific type of material used for vital pulp therapy. For instance, several investigations only reported ‘MTA’ as the capping material without specifying the type (grey or white) and the manufacturer (Dentsply Sirona or Angelus) who produced the product (Hilton et al. 2013, AlShwaimi et al. 2016, Godhi et al. 2016). The same is also true for calcium hydroxide; most investigations used Dycal as the hard-setting calcium hydroxide product; however, there are also investigations that used calcium hydroxide powder (Çalışkan & Güneri 2017) or Hypocal (Mente et al. 2010, 2014). When systematic reviews and meta-analyses or cost-effectiveness analyses have been performed they often ignore the heterogeneity among studies and undertake an analysis without considering the differences between the materials (Aguilar & Linsuwanont 2011, Swarup et al. 2014, Smail-Faugeron et al. 2014, Schwendicke et al. 2015a, Li et al. 2015). Therefore, it is essential that future systematic reviews and meta-analyses consider the type of materials used for vital pulp therapy and undertake analyses that account for the type of material.
Another important factor is the type of irrigant used for rinsing pulpal wounds following exposure. There are only a few reports on the use of irrigants to control bleeding of pulp wounds during vital pulp therapy (Silva et al. 2006, Accorinte et al. 2007, Tüzüner et al. 2012, Akcay & Sari 2014). One investigation reported the adverse effect of using sodium hypochlorite before placement of calcium hydroxide as a pulp capping material (Accorinte et al. 2007), whereas others reported no significant difference in outcome of the treatment after using antibacterial irrigants such as chlorhexidine and sodium hypochlorite (NaOCl) compared to normal saline (Silva et al. 2006, Tüzüner et al. 2012, Akcay et al. 2015).

One of current dilemmas among researchers is the terminology used for describing irreversible pulpitis. The pulp status during treatment may not completely be explained by the symptoms that are declared by the patients. Pulps may be necrotic at the exposure site; however, pulp tissues in root canals may be reversibly inflamed (Ricucci et al. 2014). Based on this fact it is recommended that the term “partial irreversible” pulpitis is used instead of “irreversible pulpitis” to provide a better definition of pulp status at the time of performing vital pulp therapies (Seltzer 1972).

**Conflict of Interest statement**

Dr. Torabinejad reports other from Dentsply International, outside the submitted work.

The other authors have stated explicitly that there are no conflicts of interest in connection with this article.
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trioxide aggregate for partial pulpotomies in cariously exposed pulps of permanent molars.


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*Endodontic Topics* 32, 86-96.


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<table>
<thead>
<tr>
<th>Materials</th>
<th>Manufacturer</th>
<th>Composition</th>
<th>Setting time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ProRoot Mineral trioxide aggregate (Grey)</td>
<td>Dentsply Tulsa Dental Specialties, Johnson City, TN, USA</td>
<td>tricalcium silicate, dicalcium silicate, bismuth oxide, tricalcium aluminate, calcium sulfate dihydrate (gypsum), and calcium aluminoferite Liquid: distilled water</td>
<td>Initial setting time has been reported from 70 to 74 minutes, while the final setting time is 210 to 320 minutes</td>
</tr>
<tr>
<td>2 Tooth coloured ProRoot Mineral trioxide aggregate (White)</td>
<td>Dentsply Tulsa Dental Specialties, Johnson City, TN, USA</td>
<td>tricalcium silicate, dicalcium silicate, bismuth oxide, tricalcium aluminate, calcium sulfate dihydrate or gypsum Liquid: distilled water</td>
<td></td>
</tr>
<tr>
<td>3 Angelus MTA</td>
<td>Angelus, Londrina, PR, Brazil</td>
<td>tricalcium silicate, dicalcium silicate, bismuth oxide, tricalcium aluminate, calcium oxide, aluminum oxide, silicon dioxide Liquid: distilled water</td>
<td>The initial setting time of WAMTA has been reported to be about 8.5 ± 2.4 min; however, other studies reported 130 to 230 minutes as the setting time for AMTA</td>
</tr>
<tr>
<td>4 BioAggregate</td>
<td>Innovative BioCeramix, Vancouver, BC, Canada</td>
<td>tricalcium silicate, dicalcium silicate, calcium phosphate monobasic, amorphous silicon oxide and tantalum pentoxides Liquid: deionized water</td>
<td>Based on the manufacturer data sheet, BA has a setting time of 240 minutes</td>
</tr>
<tr>
<td>5 Biodentine</td>
<td>Septodont, Saint-Maur-des-Fosse’s Cedex, France</td>
<td>tricalcium silicate, dicalcium silicate, calcium carbonate, zirconium oxide, calcium oxide, iron oxide, Liquid: calcium chloride, a hydrosoluble polymer, and water</td>
<td>The setting time of BD has been reported as 6.5 to 45 minutes</td>
</tr>
<tr>
<td>6 Calcium enriched mixture (CEM) cement</td>
<td>BioniQueDent, Tehran, Iran</td>
<td>Calcium oxide, silicon dioxide, Al₂O₃, MgO, SO₃, P₂O₅, Na₂O, Cl, and H&amp;C Liquid: water-based solution</td>
<td>50 minutes</td>
</tr>
<tr>
<td>7 EndoBinder</td>
<td>Binderware, Sao Carlos, SP, Brazil</td>
<td>Al₂O₃ and CaO</td>
<td>60 minutes</td>
</tr>
<tr>
<td>8 Endocem MTA</td>
<td>Maruchi, Wonju, Korea</td>
<td>CaO, Al₂O₃, SiO₂, MgO, Fe₂O₃, SO₃, TiO₂, H₂O/CO₂, bismuth oxide</td>
<td>4.5 to 15 minutes</td>
</tr>
<tr>
<td>9 Endocem Zr</td>
<td>Maruchi, Wonju, Korea</td>
<td>calcium oxide, silicon dioxide, aluminum oxide, magnesium oxide, ferrous oxide, zirconium oxide</td>
<td></td>
</tr>
<tr>
<td>10 EndoSequence RRM, RRP</td>
<td>Brasseler, Savannah, GA, USA</td>
<td>zirconium oxide, calcium silicates, tantalum oxide, calcium phosphate monobasic, and filling and thickening agents</td>
<td>The setting time of EndoSequence putty is 61.1 ± 2.5 minutes and the final setting time is 208 ± 10 minutes</td>
</tr>
<tr>
<td>ID</td>
<td>Product Name</td>
<td>Manufacturer/Location</td>
<td>Composition</td>
</tr>
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</tr>
<tr>
<td>11</td>
<td>MicroMega MTA</td>
<td>MicroMega, Besancon, France</td>
<td>Tricalcium silicate, dicalcium silicate, tricalcium aluminate, bismuth oxide, calcium sulfate dehydrate, and magnesium oxide</td>
</tr>
<tr>
<td>12</td>
<td>MTA Bio</td>
<td>Angelus; Londrina, or Angelus Solucoes Odontologicas, PR, Brazil</td>
<td>Portland cement and bismuth oxide</td>
</tr>
<tr>
<td>13</td>
<td>MTA Plus (White)</td>
<td>Avalon Biomed Inc., Bradenton, FL</td>
<td>Tricalcium silicate, 2CaO.SiO₂, Bi₂O₃, 3CaO.Al₂O₃, and CaSO₄</td>
</tr>
<tr>
<td>14</td>
<td>MTA Plus (Gray)</td>
<td>Avalon Biomed Inc., Bradenton, FL</td>
<td>Tricalcium silicate, Dicalcium silicate, bismuth oxide, Tricalcium aluminium oxide, Calcium sulfate, and Ca₂(Al,Fe)₂O₅</td>
</tr>
<tr>
<td>15</td>
<td>Neo MTA Plus</td>
<td>Avalon Biomed Inc, Bradenton, FL</td>
<td>Tricalcium silicate, dicalcium silicate, tantalite, calcium sulfate, and silica</td>
</tr>
<tr>
<td>16</td>
<td>OrthoMTA</td>
<td>BioMTA, Seoul, Korea</td>
<td>Tricalcium silicate, dicalcium silicate, tricalcium aluminate, tetracalcium aluminoferrite, free calcium oxide, and bismuth oxide</td>
</tr>
<tr>
<td>17</td>
<td>Quick-Set</td>
<td>Avalon Biomed Inc, Bradenton, FL, patent pending</td>
<td>Monocalcium aluminate powder that contains bismuth oxide (as a radiopacifier) and hydroxyapatite</td>
</tr>
<tr>
<td>18</td>
<td>RetroMTA</td>
<td>BioMTA, Seoul, Republic of Korea</td>
<td>Calcium carbonate, silicon oxide, aluminum oxide, and hydraulic calcium zirconia complex</td>
</tr>
<tr>
<td>19</td>
<td>iRoot has been introduced to the market in four forms of iRoot SP, iRoot FS, iRoot BP and iRoot BP Plus</td>
<td>Innovative BioCeramix Inc., Vancouver, Canada</td>
<td>iRoot SP: Zirconium oxide, calcium silicates, calcium phosphate, calcium hydroxide, filler and thickening agents. iRoot FS: Calcium silicates, zirconium oxide, tantalum oxide and calcium phosphate monobasic. iRoot BP (BioCeramix Inc.) and EndoSequence BC sealer (Brasseler USA) have had the same formula including zirconium oxide, calcium silicates, tantalum oxide, calcium phosphate monobasic, and filler and thickening agents.</td>
</tr>
<tr>
<td>20</td>
<td>Tech Biosealer</td>
<td>(Isasan, Como, Italy)</td>
<td>Mixture of white CEM, calcium sulfate, calcium chloride, bismuth oxide, montmorillonite</td>
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<tr>
<td>21</td>
<td>Aureoseal MTA</td>
<td>(Giovanni Ogna and Figli, Muggiò, Milano, Italy)</td>
<td>The powder consists of Portland cement, bismuth oxide, setting-time controllers, plastifying agents and radiopaque substances. The liquid is distilled water</td>
</tr>
<tr>
<td>22</td>
<td>Portland cement</td>
<td>Around the world</td>
<td>The main composition of MTA and PC are very similar in that both consist of tricalcium and dicalcium silicate</td>
</tr>
<tr>
<td>BioRoot RCS</td>
<td>Septodont, Saint-Maur-des-Fosses Cedex, France</td>
<td>Tricalcium silicate, zirconium oxide (opacifier) and excipients in its powder form, and calcium chloride and excipients as an aqueous liquid</td>
<td>Less than 4 hours</td>
</tr>
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</tr>
<tr>
<td>Endo-CPM</td>
<td>EGEO SRL, Buenos Aires, Argentina</td>
<td>MTA, calcium chloride, calcium carbonate, sodium citrate, propylene glycol alginate and propylene glycol.</td>
<td>The initial setting time of End-CPM is 6 to 15 minutes, while the material’s final setting time is 22 to 27 minutes</td>
</tr>
<tr>
<td>EndoSeal MTA</td>
<td>Maruchi, Wonju, Korea</td>
<td>Calcium silicates, calcium aluminates, calcium aluminoferrite, calcium sulfates, radiopacifier and a thickening agent</td>
<td>12.31 minutes</td>
</tr>
<tr>
<td>MTA Fillapex</td>
<td>Angelus Industria de Produtos Odontologicos S/A, Londrina, Brazil</td>
<td>A MTA root canal sealer with nanoparticles of silica</td>
<td>The material’s setting time is 19.3 minutes. In dry conditions, the material fails to set</td>
</tr>
<tr>
<td>TheraCal</td>
<td>Bisco Inc., Schaumburg, IL, USA</td>
<td>CaO, Sr glass, fumed silica, barium sulphate, barium zirconate, Portland cement type III, and resin containing Bis-GMA and PEGDMA.</td>
<td>The setting time has been reported to be 0.3 minutes because of the use of light cure technology</td>
</tr>
</tbody>
</table>