A review of the literature on the efficacy of mineral trioxide aggregate in conservative dentistry

Noriyasu HOSOYA1, Tomoyoshi TAKIGAWA2, Taku HORIE3, Hidefumi MAEDA4, Yuko YAMAMOTO1, Yasuko MOMOI5, Kazuyo YAMAMOTO6 and Takashi OKIJI7

1 Department of Endodontology, Tsurumi University School of Dental Medicine, 2-1-3 Tsurumi, Tsurumi-ku, Yokohama 230-8501, Japan
2 Department of Operative Dentistry, Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan
3 Department of Operative Dentistry, School of Dentistry, Aichi Gakuin University, 2-11 Suemori-dori, Chigusa-ku, Nagoya 464-8651, Japan
4 Department of Endodontology and Operative Dentistry, Division of Oral Rehabilitation, Faculty of Dental Science, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
5 Department of Operative Dentistry, Osaka Dental University, 8-1 Kuzuhanazono-cho, Hirakata 573-1121, Japan
6 Department of Pulp Biology and Endodontics, Division of Oral Health Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan
7 Department of Endodontology, Tsurumi University School of Dental Medicine, 2-1-3 Tsurumi, Tsurumi-ku, Yokohama 230-8501, Japan

The aim of this literature review was to assess the clinical performance of MTA to establish the evidence level for its effectiveness in vital pulp therapy, perforation repair, and retrograde root canal filling. A comprehensive literature survey was performed via electronic databases of PubMed/MEDLINE. A total of 58 papers were reviewed in this study, of which 2 were systematic reviews/meta-analysis, 9 were randomized controlled trials (RCTs), and the rest were fallen into other categories. Mineral trioxide aggregate (MTA) provided better pulp protection as a direct capping material when compared with calcium hydroxide. As perforation repair materials, MTA demonstrated an excellent sealing ability in vitro. For periodontal tissues around a perforation, MTA provided normal healing processes in clinical trials. It is therefore concluded that MTA has a high potential in repairing perforations. MTA is the most promising material when used for retrograde root canal filling demonstrating normal healing in short/long term clinical outcomes.

Keywords: Mineral trioxide aggregate (MTA), Pulp capping, Perforation repair, Retrograde filling

INTRODUCTION
Mineral trioxide aggregate (MTA) was developed in the early 1990s by Torabinejad. It is a biofunctional inorganic material with excellent physical and biological properties, with its main ingredients including CaO, SiO2, Al2O3, and Fe2O3. It was approved by the United States Food and Drug Administration (FDA) in 1998 and launched on the market as a commercial product under the brand name ProRoot® MTA (Dentsply Tulsa Dental, Johnson City, TN, USA). It rapidly became used worldwide for a broad variety of applications, including direct pulp capping, perforation repair, retrograde and other types of root canal filling, vital pulpotomy, and apexification. As MTA became commercialized, a variety of studies were performed, and its good biocompatibility, action in promoting hard tissue formation, and marginal sealing ability was demonstrated in numerous basic studies, together with other properties including its antibacterial effects. Many studies also reported excellent clinical outcomes that are equivalent or better than those of calcium hydroxide, which is frequently used for the same purposes. However, some issues still required improvement, including setting time, handling property, and tooth discoloration. Researchers and manufacturers have made progress in overcoming these problems in recent years, and new and improved products are becoming available. We have therefore carried out a review of the literature describing clinical and basic studies of direct pulp capping, perforation repair, and retrograde root canal filling after apicoectomy with the objective of establishing the level of evidence for the effectiveness of MTA in these applications, in order to encourage its use in a greater number of cases and bring its outstanding benefits to more patients. This will both provide a thorough understanding of the current status of MTA and reconfirm the efficacy to help lay the foundations for the broader use of this material.

DATA AND SOURCES
A comprehensive literature search for MTA peer-reviewed journals was performed via electronic databases of PubMed/MEDLINE from November 1993 to October 2017.

STUDY SELECTION
Electronic search was performed using a number of set key words, including MTA, direct pulp capping, perforation repair, apicoectomy, and retrograde filling. Hand search was carried out as well. A total of 58 papers including 1 Japanese paper were reviewed in this study, of which 2 systematic reviews/meta-analysis, 9 randomized controlled trials (RCTs), 2 non-randomized controlled trial studies (NRS),
and 19 human observational studies (16 observational studies\(^{15-30}\) and 3 descriptive studies\(^{31-33}\) were reviewed. In addition, one literature review\(^{34}\) and 25 non-human studies (14 animal experimental studies\(^{35-48}\), 5 basic studies\(^{49-53}\) and 6 tooth model studies\(^{54-56}\) were reviewed.

NOTE: In this review, a general term “MTA” is used. In 58 reviewed articles, some adopted the term MTA in a general sense while others adopted the various commercial name of MTA. Name of products, manufacturers, regions and countries cited in the reviewed articles are listed below.

- MTA (Loma Linda University, CA, USA)
- MTA (Dentsply Tulsa Dental, Okla)
- white MTA (Pro Root\(^{®}\); Dentsply-Tulsa Dental, Johnson City, TN, USA)
- ProRoot MTA (Dentsply Tulsa Dental Specialities, Tulsa, OK)
- MTA (Pro Root, Tulsa Dental, Tulsa, OK, USA)
- MTA (ProRoot MTA White; Dentsply Tulsa Dental, Tulsa, OK)
- MTA (White Pro Root, Dentsply, Tulsa Dental, Tulsa, OK, USA)
- MTA (Pro Root\(^{®}\); Dentsply Tulsa, Tulsa, OK, USA)
- MTA (ProRoot MTA; Dentsply Maillefer, Ballaigues, Switzerland)
- MTA (Mineral Trioxide Aggregate, Dentsply Tulsa Dental, Tulsa OK, USA)
- MTA (ProRoot MTA; Dentsply Tulsa Dental)
- MTA (ProRoot MTA White; Dentsply, Johnson City, TN)
- MTA (ProRoot MTA, gray version; Dentsply-Maillefer, Ballaigues, Switzerland)
- MTA (ProRoot\(^{TM}\) MTA; Dentsply Maillefer, Weybridge, UK)
- white MTA (ProRoot MTA; Dentsply, Tulsa, OK)
- MTA (ProRoot; Dentsply Maillefer, Ballaigues, Switzerland)
- MTA (ProRoot MTA; Dentsply Maillefer, Ballaigues, Switzerland)
- MTA (Pro Root; Dentsply Tulsa Dental, Tulsa, OK)
- MTA (ProRoot MTA; Dentsply Maillefer, Ballaigues, Switzerland; gray and white versions)
- Gray ProRoot MTA cement (Maillefer, Ballaigues, Switzerland)
- MTA (Dentsply Tulsa\(^{®}\), Tulsa, OK)
- MTA (Dentsply/ Tulsa Dental, Tulsa, OK)
- Mineral Trioxide Aggregate (PRO ROOT\(^{TM}\) MTA: Dentsply)
- MTA (Pro Root MTA, Dentsply Tulsa Dental, Tulsa, OK, USA; #9990903)
- MTA (Pro Root MTA, Dentsply/Tulsa Dental, Tulsa, OK)
- MTA (white MTA; Angelus, Londrina, Brazil)
- Mineral trioxide aggregates (MTA; Dentsply, York, PA)
- MTA (ProRootMTA, Dentsply Tulsa)
- MTA (ProRoot MTA, Dentsply Tulsa Dental, Tulsa, OK)
- Mineral trioxide aggregation (ProRoot tooth colored MTA, Dentsply Maillefer)
- MTA (ProRoot, Dentsply/Tulsa)
- ProRoot MTA (Maillefer, Dentsply, Switzerland)
- MTA-Angelus (Angelus, Londrina, PR, Brazil)

Direct pulp capping material

1. Background

Methods of pulp capping as a vital pulp therapy can be divided into direct and indirect capping techniques. Scientific evidence for the efficacy of indirect pulp capping, in which some of the infected tooth substance is left in situ, has been described in the clinical guidelines or reviews for treating caries\(^{59}\), and this technique is already widely used in clinical practice. However, the success rate for direct pulp capping, in which the pulp of the carious tooth is exposed, has varied widely in different studies, with rates from 30% to 80% being reported\(^{8,15,16,60,61}\), and good long-term outcomes are not always obtained. This variation may be due to the choice of patients and pulp capping methods. In this section, we investigated the scientific evidence for the efficacy of MTA as a material for direct pulp capping of either pulp at the stage of reversible pulpitis from pulp hyperemia or clinically healthy pulp, which has been exposed either after the removal of infected dentin or accidentally as a result of tooth fracture or cavity preparation.

2. Histopathological evaluations

Calcium hydroxide (CH) has often been used as the material for direct pulp capping. In this section, we compared the efficacy of MTA with that of CH. We reviewed studies including both basic research and clinical studies related to MTA to investigate the evidence underpinning its broader clinical application.

Prior to clinical studies of direct pulp capping, many basic studies of the use of CH or MTA were performed using the mechanically exposed pulp of teeth in monkeys or dogs. Ford et al.\(^{37}\) used a #1 round bur to expose the pulp of upper canine teeth in monkeys, and used CH or MTA as a pulp-capping material in 6 teeth each. After 5 months’ follow-up, there was no inflammation in 5/6 teeth capped using MTA, and complete hard tissue deposition (a dentin bridge) had formed in 6/6. An inflammatory reaction was evident in 6/6 teeth capped using CH, and hard tissue deposition was present in only 2/6. Faraco and Holland\(^{40}\) created areas of exposed pulp 0.5 mm in diameter on the labial side of 30 teeth in dogs, and capped 15 each with CH and MTA. After 2 months’ follow-up, tubular dentin bridge formation was present in all the MTA-capped teeth, with no inflammatory findings. Dentin bridge formation was present in 5/15 of the CH-capped teeth, but inflammation was evident in 12/15. The authors concluded that MTA was a more effective pulp capping material than CH.

3. Clinical assessment

Numerous randomized comparative clinical trials of direct pulp capping with MTA have been reported. In one study by Aeinehchi et al.\(^{19}\), the pulp of 14 healthy upper wisdom teeth was intentionally exposed and
capped directly with either CH or MTA, and the state of the pulp was examined histologically up to 6 months later. They found that teeth capped with MTA exhibited mild inflammation and a thick dentin bridge had formed. However, they pointed out that longer-term studies with more subjects were required to compare the ultimate state of new hard tissue formation. Cho et al.\textsuperscript{23} used CH or MTA to carry out direct capping of pulp exposed after removal of infected dentin from carious teeth in different sites, and found that after a maximum of 3.7 years’ follow-up (median 11.1 months) the pulp survival rate was significantly higher for MTA than for CH. In a multicenter randomized comparative trial reported in 2013 by Hilton et al.\textsuperscript{10} pulp exposed either after the removal of infected dentin or accidentally was capped directly with either CH or MTA. The authors found that the probability of failure after up to 2 years’ follow-up was significantly lower for MTA compared with CH. Mente et al.\textsuperscript{14} used CH or MTA as capping material for pulp exposed after the removal of infected dentin, followed them for up to 11 years, and found that MTA achieved better results than CH. In a randomized comparative trial reported in 2016 by Kundzine et al.\textsuperscript{12} direct pulp capping with CH or MTA was used to treat pulp exposed after the removal of infected dentin, and patients were followed up to a maximum of 3 years. Although pain was expressed with equivalent frequency 1 week after the procedure, the pulp survival rate was significantly higher for MTA, and the authors concluded that MTA is more effective than CH as a pulp-capping material for pulp exposed after the removal of infected dentin in adults. These studies demonstrated that MTA is more effective than CH, the material conventionally used for direct pulp capping.

4. Summary
In this survey, we found that MTA has been shown to be highly effective in conserving pulp as a direct pulp capping material, and its proactive use may help to decrease the need for pulp extirpation.

Perforation repair material
1. Background
Perforation of the root canal wall results in an unnatural route of communication between the root canal and the surrounding periodontal tissue or the oral cavity. In most cases, it is formed iatrogenically during access cavity preparation or root canal preparation, but it may also occur pathologically for reasons such as advanced caries or root resorption. The presence of a perforation is often cited as a risk factor for a poor outcome from endodontic treatment\textsuperscript{18,21,24,62}, and it is considered to be a factor that requires particular attention when attempting to preserve an endodontically affected tooth. When attempting to preserve a tooth in which a perforation is present, the use of an appropriate sealing material to repair the perforation and seal off the route of communication with the periodontal tissue is essential\textsuperscript{18,31,60}. A number of perforation repair materials are currently in use, including amalgam, gutta-percha, CH, glass ionomer cement, reinforced zinc oxide-eugenol cement [o-ethoxybenzoic acid (EBA) cement], and adhesive resin\textsuperscript{59}. Recently, however, the sealing ability and biocompatibility of MTA have been drawing attention as an agent that is potentially capable not only of blocking the infection route but of encouraging wound healing and tissue repair. In this section, we investigated the evidence for the efficacy of MTA as a perforation repair material from the perspectives of its sealing ability in vitro, the reaction of periodontal tissue around the perforation in vivo, and clinical outcomes.

2. Sealing ability for perforations
The sealing ability of MTA has been analyzed in numerous in vitro studies, and the general consensus is that it is better than that provided by other materials\textsuperscript{50}. The first study of simulated perforation repair using perforations made in the roots of extracted human teeth was published by the developers as the first paper to describe MTA\textsuperscript{1}. Dye leakage tests confirmed that the sealing ability of MTA was significantly better than those of both amalgam and reinforced zinc oxide-eugenol cement. Studies of perforations in the pulp chamber floor using extracted human teeth have also found that MTA provides better sealing performance than amalgam\textsuperscript{54}, resin-modified glass ionomer cement\textsuperscript{58}, or intermediate reinforced material (IRM) cement (Dentsply Sirona, York, PA, USA), a zinc oxide-eugenol cement\textsuperscript{50}. However, fluid filtration tests of the sealing ability of MTA for perforations of the floor of the pulp chamber of extracted human teeth that included analysis over time found that after 24 h its performance was somewhat worse than those of Super EBA (Harry Bosworth, Skokie, IL, USA)\textsuperscript{50}, a reinforced zinc oxide-eugenol cement, and One-up Bond (Tokuyama Dental, Tokyo, Japan)\textsuperscript{57}, a one-step bonding agent, although it was subsequently equivalent. These results reflect the fact that the MTA setting reaction proceeds gradually and takes some time to complete. All of the above studies may be interpreted as providing basic data suggesting that MTA has good sealing ability when used for perforation repair though MTA’s sealing ability may not reach the desired level a short time after mixing.

3. Histopathological evaluations
The histological reaction of periodontal tissue after perforation repair with MTA has been analyzed in a range of animal experiments\textsuperscript{5,55,39,41,43-45,47,48,53}. The first paper published from this perspective was written by the developers\textsuperscript{50}, who created experimental perforations in the pulp chamber floor of dog mandibular premolars and analyzed the histological reaction 4 months after sealing. They found that signs of inflammation were present for all the teeth sealed with amalgam, whereas for those sealed with MTA, there was a high rate of healing with cementum-like hard tissue deposition on the surface of the sealing material. In subsequent animal experiments on dog premolars, healing associated with cementum-like hard tissue deposition on the surface of the sealing material when freshly made perforations
were immediately repaired with MTA\textsuperscript{20,41,43,45,47,48,53}, and comparisons with other sealing materials also showed that inflammation persisted for longer and there was less new hard tissue deposition than when MTA was used\textsuperscript{10,41,43,45,47,48}. Compared with MTA, chronic inflammation was more frequent after the use of a CH-based root canal sealer (Sealapex, Kerr, Romulus, MI, USA)\textsuperscript{39}; after the use of Super EBA, scar-like connective tissue was formed and there was no new hard tissue formation\textsuperscript{41,43}; and the use of zinc oxide-eugenol cement provoked a severe inflammatory reaction\textsuperscript{48}. In a rat molar model of pulp chamber floor perforation repair, inflammation and alveolar bone resorption were found to be milder when MTA was used compared with zinc oxide-eugenol cement\textsuperscript{47}. However, when MTA was used to seal perforations in dog premolars that had opened to the oral environment to induce contamination with saliva, there was less deposition of new hard tissue than when perforations had been sealed immediately\textsuperscript{45}, and there was no significant difference in the severity of inflammation compared with the use of amalgam\textsuperscript{44}. The results of these studies suggest that when fresh perforations are immediately repaired with MTA the histological reaction is less severe than that generated by other materials, and that healing and new hard tissue deposition can be anticipated. However, MTA may not be as useful as stated above for old, contaminated perforations.

4. Clinical assessment
Siew et al.\textsuperscript{3} carried out a systematic review and meta-analysis of the treatment outcomes of perforation repair using different materials. They found that the combined success rate using data from 12 papers was 72.5% for all teeth [confidence interval (CI) 61.9–81.0%] and 80.9% (CI 67.1–89.8%) for teeth repaired with MTA. Although this difference was not statistically significant, the use of MTA did tend to improve the success rate. A non-randomized clinical trial of the outcomes of secondary root canal treatment performed at the University of Toronto (4–6 years follow-up)\textsuperscript{21} found that 14 patients exhibited a perforation associated with preoperative radiolucency, and that the four teeth repaired with MTA were all judged to have healed, whereas only three of ten teeth healed after repair with resin-modified glass ionomer cement. In a non-randomized clinical trial of the outcomes of non-surgical endodontic treatment (including both primary and secondary treatment) carried out at the University of London (2–4 years follow-up)\textsuperscript{29}, 81 perforations were repaired by using various different materials (MTA, glass ionomer cement, EBA cement, IRM cement, gutta-percha, or amalgam), but there were no differences in the rates of healing between any of these materials. Pontius et al.\textsuperscript{26} carried out a multicenter retrospective cohort study (mean, 37 months follow-up) and found that 92% (32/37) of perforation repairs with MTA were successful, but that a high success rate of 85% (11/13) was also obtained when other materials were used, and no significant difference was observed. Case series studies (prospective studies) of perforation repair with MTA included a series of 110 patients over 8 years analyzed by Gorni et al.\textsuperscript{39}. According to this study, the results within 2 years of the procedure were judged to be good for 101 patients (92%), with a probability of progressing at 5 and 8 years of 18% (95% CI 9–27%) and 33% (95% CI 16–47%), respectively. In a retrospective case series study, Main et al.\textsuperscript{17} reported the treatment outcomes of 16 patients who underwent perforation repair with MTA and found that after 12–45 months (mean, 25 months) no patient exhibited radiolucency or periodontal pockets of 3 mm or more in depth regardless of presence/absence of preoperative radiolucency. Pace et al.\textsuperscript{33} carried out a retrospective study of 10 patients with perforation of the pulp chamber floor and reported that good results were obtained in nine cases 5 years after repair with MTA. Mente et al.\textsuperscript{20} carried out a retrospective case series study of 26 patients and found that the success rate 12–65 months (mean, 33 months) after perforation repair with MTA was 81%. They subsequently added further cases to this series and carried out a retrospective case series study of a total of 64 patients\textsuperscript{20}, in which they found that the success rate was 86% after 12–107 months follow-up (mean, 27.5 months). The operator’s experience and postoperative post placement significantly affected the outcome. Krupp et al.\textsuperscript{27} reported a retrospective case series study of the outcomes of 90 cases of perforation repair with MTA and found that the success rate after 1–10 years (mean, 3.4 years) was 73% and that the presence of preoperative radiolucency near to the perforation site and communication between the perforation and the oral cavity both affected the outcome. The case series studies described above suggested that the use of MTA for perforation repair provided highly predictable results. Thus, the clinical use of MTA is considered to improves the success rate in comparison with other materials though studies with high evidence level are not sufficient.

5. Summary
The value of MTA as a perforation repair material has been demonstrated in in vitro studies of its sealing ability, in vivo studies of the reaction of periodontal tissue surrounding perforations, and clinical studies. At this point, MTA may thus be considered to be one of the most reliable perforation repair materials available. The gathering of further clinical evidence is required.

Retrograde root canal filling material
1. Background
Amalgam has long been used as a retrograde root canal filling material, but its clinical usage has rapidly declined due to concerns about mercury content. Super EBA, a reinforced zinc oxide-eugenol cement, is now often used in its place. The use of calcium silicate cements has also recently been increasing. MTA, which was first developed and marketed over 20 years ago, is now widely known for its reliable efficacy in clinical use. In this section, we describe the scientific evidence for the use of MTA as a retrograde root canal filling material.
on the basis of histological evaluations of animal models and clinical outcomes.

2. Histopathological evaluations
A number of histological evaluations of healing of periapical tissue when MTA has been used as a retrograde root canal filling material in animal models of apical periodontitis have been performed, addressing this from the perspectives of inflammatory reaction, new cementum deposition, and bone regeneration. Torabinejad et al.30 used a canine model of apical periodontitis to examine the healing of periapical tissue after retrograde root canal filling with MTA or amalgam. After 18 weeks, inflammatory cell infiltration of periapical tissue was present around all the root canals filled with amalgam, whereas cell infiltration was only seen in 30% of those filled with MTA. None of those filled with amalgam exhibited any new cementum deposition covering the filling material, whereas new cementum deposition was present on all those filled with MTA. Torabinejad’s group carried out similar experiments in a monkey model of apical periodontitis, and performed histological evaluations of periapical tissue after 5 months38). They found that signs of inflammation were evident around all the roots filled with amalgam, whereas for MTA such signs were only present for 17% of teeth. Only fibrous tissue was formed on the surface of the filling of all the roots filled with amalgam, whereas new cementum deposition was present on the filling surface of 83% of the roots filled with MTA. Interestingly, this newly formed cementum contained fibrous tissue resembling Sharpey’s fibers, like the cementum on the root surface. In a detailed study using a canine model of apical periodontitis, Baek et al.72 prepared undecalcified specimens and compared healing after the use of amalgam, Super EBA, or MTA as a retrograde root canal filling material. After 5 months, the results for MTA were significantly better than those for both amalgam and Super EBA in terms of inflammatory reaction in periapical tissue, abscess formation, cementum formation, cancellous bone formation, and the level of bone maturation. With respect to inflammatory reaction in particular, there was major infiltration by lymphocytes and neutrophils for both amalgam and Super EBA, but for MTA only a small amount of lymphocyte infiltration was present, and no neutrophil infiltration at all. Lymphocytes and neutrophils are known to secrete inflammatory cytokines including tumor necrosis factor (TNF) and interleukins (IL), and cytokines such as TNF-α, IL-1β, and IL-6 are not only known to promote osteoclast differentiation but have also been reported to inhibit osteoblast differentiation.9,51-52. In a quantitative comparison using microscopic radiography for new bone formation after the use of amalgam, Super EBA, or MTA as a retrograde root canal filling material in a canine model of apical periodontitis, the mean distance between the newly formed bone surface and the central surface of the filling material was 1.290±0.386 mm for amalgam, 0.756±0.581 mm for Super EBA, and 0.397±0.278 mm for MTA. Surprisingly, the distance for MTA was similar to the mean thickness of normal periodontal ligament tissue in dogs (0.386±0.025 mm)49. This suggested that when MTA is used as a retrograde root canal filling material, it promotes bone formation in the periapical tissue, but does not induce excess bone formation, acting to encourage the ultimate regeneration of the natural tissue structure. Maeda et al.30 reported that in vitro MTA releases Ca²⁺ ions, encouraging the expression of bone morphogenetic protein-2 (BMP2) and calcified substrate formation in periodontal ligament cells in humans, suggesting that when used as a retrograde root canal filling material it may act to encourage new cementum formation. From those studies, it appears that thanks to its high biocompatibility, MTA may minimize the inflammatory reaction by inhibiting leukocyte and neutrophil infiltration, encourage post-apicoectomy tissue healing, and act to promote new cementum deposition on the MTA surface via BMP2 and thus to regenerate the tissue structure of a healthy apex by periodontal ligament tissue formation.

3. Clinical assessment
The results of numerous in vitro studies and the in vivo studies of animal models described above demonstrated that MTA induces good healing of periapical tissue when used as a retrograde root canal filling material, and in the late 1990s it started to come into clinical use as a retrograde root canal filling material. The first clinical results were reported in 1999 by Torabinejad and Chivian32, who confirmed that periapical radiolucency disappeared 15 months after treatment of a maxillary left central incisor using MTA as a retrograde root canal filling material. Since that report, MTA has been used as a retrograde root canal filling material in a very large number of patients, and studies of its clinical outcomes have been published. One study of the outcomes of 276 teeth that underwent retrograde root canal filling with MTA found that the rate of healing after 18 months was 88.8%52. Another study showed the outcomes for 39 teeth after 6 years that underwent retrograde root canal filling with MTA and showed that the rates of healing were 96 and 52%, respectively7. Furthermore, in another study the outcomes for 39 teeth after 6 years showed that the rates of healing were 86% in the MTA group and 55% in the GP group and a significant difference between the two groups was observed11. This indicated that retrograde root canal filling with MTA led to much better clinical outcomes than when root-end resection alone was performed. Other studies have compared the rates of healing when MTA was used as a retrograde root canal filling material with those for other materials. An investigation of the rates of healing of 108 teeth 1 year and 2 years after retrograde root canal filling with either MTA or IRM cement found that the success rates for MTA were 84% after 1 year and 92% after 2 years, whereas for IRM cement, they were 76% after 1 year and
87% after 2 years\(^5\). Another study by a different group of the use of MTA or IRM cement as a retrograde root canal filling material for 100 teeth similarly found that the healing rate after 1 year was 92% for MTA and 86% for IRM cement\(^6\). In a study by von Arx et al. of 191 teeth treated by retrograde root canal filling with either MTA, resin, or Super EBA, the rate of healing after 1 year was highest for MTA (90.2%) followed by resin (84.7%) and Super EBA (76.4%)\(^7\). These studies also suggested that the rate of healing when MTA was used as a retrograde root canal filling material was something over 90%. However, it was difficult to draw any reliable conclusions on the basis of these individual comparative studies. Tsesis\(\text{et al.}\)\(^8\) identified only the studies in which “modern retrograde root canal filling techniques” such as microscopy or ultrasonic retrotips were used and reported between 1966 and 2012 and carried out a meta-analysis of those papers that reported results after at least 1 year. They combined the results of 18 studies and calculated the overall healing success rates for each type of retrograde root canal filling material. The healing success rate was highest for MTA (90.8%), followed by Super EBA (89%), gutta-percha (88.5%), and zinc oxide-eugenol cement (84.7%). MTA was significantly better than the other types of filling materials, but there was no significant difference between either Super EBA or zinc oxide-eugenol cement and gutta-percha. Surprisingly, as there was no significant difference between Super EBA and gutta-percha and between IRM cement and gutta-percha, these findings suggested that Super EBA and IRM cement as retrograde fillings led no better healing outcome, compared with gutta-percha with no retrograde filling. As the healing process after retrograde root canal filling is complex and longer time is required for complete healing to be achieved, and it is difficult to calculate the healing rate accurately in studies of short-term outcomes. A study of outcomes during a 4-year period after retrograde root canal filling found that recurrent apical lesions subsequently developed in 9% of cases that were judged to have healed after 1 year\(^9\), and long-term follow-up of outcomes is essential in order to evaluate the rate of healing accurately. In addition to reporting the 1-year healing rates when retrograde root canal filling was carried out using MTA, resin, or Super EBA, von Arx et al. also reported the rates of healing after 5 years\(^10\). They found that after 5 years, similarly to after 1 year, the highest healing rate was obtained when MTA was used (86.4%), followed by resin (75.3%) and Super EBA (67.3%), and that the difference between MTA and Super EBA was significant. In another study of the 1-year and 5-year healing rates of 271 teeth after retrograde root canal filling with either MTA or resin\(^29\), the rates of healing after 1 year were 96.7% for MTA and 90.7% for resin, a difference that was not significant, whereas a significant difference was shown after 5 years; the rates were 92.5% for MTA and 76.6% for resin. These studies suggested that the long-term healing rate for patients treated with MTA remained over 80% even after 5 years or more, and that MTA is a more effective material for encouraging healing compared with Super EBA, resin, and gutta-percha. All these findings from histological analysis and animal experiments lead us to the conclusion that of the materials currently used for retrograde root canal filling, MTA is outstandingly effective in terms of encouraging healing and achieving good outcomes in clinical use.

4. Summary

When MTA is used as a retrograde root canal filling material, it has a greater healing effect on tissue compared with other materials, and its continuous clinical performances are highly evaluated.

CONCLUSIONS

In the field of endodontics, a highly trusted material and/or medicament providing favorable prognosis for direct pulp capping, perforation repair, retrograde root canal filling has long been much-needed. As yet, there is no standardized material and/or medicament which obtained a solid scientific evidence, and conventional restorative materials and/or resin-based adhesives still remain in use today. Since the advent of MTA, it has become widely used over the last two decades, and MTA is currently almost accepted as one of the most versatile materials with various clinical applications. The outstanding properties of MTA might help many patients whose teeth could not otherwise be preserved or who would have no choice but to undergo pulp extirpation. However, compared to conventional material/medicament, MTA has some disadvantages to overcome which include discoloration potential, difficult handling properties, extended setting time and prolonged maturation phase. As MTA is still in the stage of improvements, changes in its compositions are expected to enhance its physical and biological properties. Further clinical research with well controlled study design needs to be conducted for MTA in order to improve patients’ quality of life through their better oral health.

REFERENCES

1) Lee SJ, Monsef M, Torabinejad M. Sealing ability of a mineral trioxide aggregate for repair of lateral root perforations. J Endod 1993; 19: 541-544.
2) Tsesis I, Rosen E, Taschieri S, Telishevsky Strauss Y, Ceresoli V, Del Fabbro M. Outcomes of surgical endodontic treatment performed by a modern technique: an updated meta-analysis of the literature. J Endod 2013; 39: 332-339.
3) Siew K, Lee AHC, Cheung GSP. Treatment outcome of repaired root perforation: a systematic review and meta-analysis. J Endod 2015; 41: 1795-1804.
4) Kvist T, Reit C. Results of endodontic retreatment: a randomized clinical study comparing surgical and nonsurgical procedures. J Endod 1999; 25: 814-817.
5) Chong BS, Pitt Ford TR, Hudson MB. A prospective clinical study of mineral trioxide aggregate and IRM when used as root-end filling materials in endodontic surgery. Int Endod J 2003; 36: 520-526.
6) Lindeboom JA, Frenken JW, Kroon FH, van den Akker HP. A comparative prospective randomized clinical study of MTA and IRM as root-end filling materials in single-rooted teeth in endodontic surgery. Oral Surg Oral Med Oral Pathol Oral
Radiol Endod 2005; 100: 495-500.
7) Christiansen R, Kierkevang LL, Horsted-Bindslev P, Wenzel A. Randomized clinical trial of root-end resection followed by root-end filling with mineral trioxide aggregate or smoothing of the orthograde guta-percha root filling 1-year follow-up. Int Endod J 2009; 42: 105-114.
8) Bjørnadal L, Reit C, Bruun G, Markvart M, Kjældgaard M, Nasman P, et al. Treatment of deep caries lesions in adults: randomized clinical trials comparing stepwise vs. direct complete excavation, and direct pulp capping vs. partial pulpotomy. Eur J Oral Sci 2010; 118: 290-297.
9) von Arx T, Hanni S, Jensen SS. 5-year results comparing mineral trioxide aggregate and adhesive resin composite for root-end sealing in apical surgery. J Endod 2014; 40: 1077-1081.
10) Hilton TJ, Ferracane JL, Mancl L. Comparison of CaOH with MTA for direct pulp capping: a PBRN randomized clinical trial. J Dent Res 2013; 92: 16-22.
11) Kruse C, Spin-Neto R, Christiansen R, Wenzel A, Kierkevang LL. Periapical bone healing after apicectomy with and without retrograde root filling with mineral trioxide aggregate: A 6-year follow-up of a randomized controlled trial. J Endod 2016; 42: 533-537.
12) Kundzina R, Stangvaltaite L, Eriksens HM, Kerosuo E. Capping carious exposures in adults: a randomized controlled trial investigating mineral trioxide aggregate versus calcium hydroxide. Int Endod J 2017; 50: 924-932.
13) Aeinehchi M, Esfami B, Ghanbariha M, Saffar AS. Mineral trioxide aggregate (MTA) and calcium hydroxide as pulp-capping agents in human teeth: a preliminary report. Int Endod J 2002; 36: 225-231.
14) Mente J, Hufnagel S, Michel A, Gebrig H, Panagidis D, Saure D, et al. Treatment outcome of mineral trioxide aggregate or calcium hydroxide direct pulp capping: long-term results. J Endod 2014; 40: 1746-1751.
15) Matsuo T, Nakanishi T, Shimizu H, Ebisu S. A clinical study of direct pulp capping applied to caries-exposed pulps. J Endod 1996; 22: 551-556.
16) Barthel CR, Rosenkranz B, Leuenberg A, Roulet JF. Pulp capping of carious exposures: Treatment outcome after 5 and 10 years; A retrospective study. J Endod 2000; 26: 525-528.
17) Main C, Mirzayan N, Shahbangan S, Torabinejad M. Repair of root perforations using mineral trioxide aggregate: a long-term study. J Endod 2004; 30: 80-83.
18) Farzaneh M, Abitbol S, Friedman S. Treatment outcome in endodontics: the Toronto study. Phases I and II: orthograde retreatment. J Endod 2004; 30: 627-633.
19) Tsesis I, Fuss Z. Diagnosis and treatment of accidental root perforations. Endod Topics 2006; 13: 95-107.
20) von Arx T, Jensen SS, Hanni S. Clinical and radiographic assessment of various predictors for healing outcome 1 year after periapical surgery. J Endod 2007; 33: 123-128.
21) de Chevigny C, Dao TT, Basrani BR, Marquis V, Farzaneh M, Abitbol S, et al. Treatment outcome in endodontics: the Toronto study – phases 3 and 4: orthograde retreatment. J Endod 2008; 34: 131-137.
22) Saunders WP. A prospective clinical study of periradicular surgery using mineral trioxide aggregate as a root-end filling. J Endod 2008; 34: 660-665.
23) Mente J, Hage N, Pfefferle T, Koch MJ, Geletneky B, Dreyhaupt J, et al. Treatment outcome of mineral trioxide aggregate: repair of root perforations. J Endod 2010; 36: 208-213.
24) Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of nonsurgical root canal treatment: part 1: periapical health. Int Endod J 2011; 44: 583-609.
25) Cho SY, Seo DG, Lee SJ, Lee J, Lee SJ, Jung IY. Prognostic factors for clinical outcomes according to time after direct pulp capping. J Endod 2013; 39: 327-331.
26) Pontius V, Pontius O, Braun A, Frankenberger R, Roggendorf MJ. Retrospective evaluation of perforation repairs in 6 private practices. J Endod 2013; 39: 1346-1358.
27) Krupp C, Barghothel C, Brusnaber M, Hülsmann M. Treatment outcome after repair of root perforations with mineral trioxide aggregate: a retrospective evaluation of 90 teeth. J Endod 2013; 39: 1364-1368.
28) Mente J, Lee M, Panagidis D, Saure D, Pfeiferle T. Treatment outcome of mineral trioxide aggregate: repair of root perforations – long-term results. J Endod 2014; 40: 790-796.
29) von Arx T, Hanni S, Jensen SS. Periapical bone healing after apicectomy with and without retrograde root filling with mineral trioxide aggregate. J Endod 2010; 36: 208-297.
30) Murata SS, Dezan E Jr. Reaction of the lateral periodontium to mineral trioxide aggregate or reinforced zinc oxide eugenol cement. Dent Traumatol 2001; 17: 163-166.
31) Ford TR, Torabinejad M, McKayndry DJ, Hong CU, Kariyawasam SP. Use of mineral trioxide aggregate for repair of furcal perforations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 79: 756-763.
32) Torabinejad M, Chivian N. Clinical applications of mineral trioxide aggregate. J Endod 1999; 25: 197-205.
33) Pace R, Giuliani V, Pagavino G. Mineral trioxide aggregate as repair material for furcal perforation: case series. J Endod 2008; 34: 1130-1133.
34) Torabinejad M, Paririkoh M. Mineral trioxide aggregate: A comprehensive literature review—Part II: leakage and biocompatibility investigations. J Endod Dent Traumatol 1998; 12: 253-264.
35) Pitt Ford TR, Torabinejad M, McKenzie DJ, Hong CU, Kariyawasam SP. Histologic assessment of mineral trioxide aggregate as a root-end filling in monkeys. J Endod 1995; 21: 225-228.
36) 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: 603-608.
37) Ford TRP, Torabinejad M, Abedi HR, Backland LK, Kariyawasam SP. Using mineral trioxide aggregate as a pulp-capping material. J Am Dent Assoc 1996; 127: 1491-1494.
38) Torabinejad M, Pitt Ford TR, McKenzie DJ, Abedi HR, Miller DA, Kariyawasam SP. Histologic assessment of mineral trioxide aggregate as a root-end filling in monkeys. J Endod 1997; 23: 225-228.
39) Holland R, Filho JA, de Souza V, Nery MJ, Bernabé PF, Junior ED. Mineral trioxide aggregate repair of lateral root perforations – long-term results. J Endod 2014; 40: 790-796.
40) Faraco IM Jr, Holland R. Response of the pulp of dogs to capping with mineral trioxide aggregate or a calcium hydroxide cement. Dent Traumatol 1996; 12: 163-166.
41) Suehara M, Morinaga K, Nakagawa K. Tissue reactions of furcal perforations in dog teeth after application of mineral trioxide aggregate or reinforced zinc oxide eugenol cement. Jpn J Conserv Dent 2001; 44: 755-775.
42) Baek SH, Plenk H Jr, Kim S. Periapical tissue responses and cementum regeneration with amalgam, SuperEBA, and MTA as root-end filling materials. J Endod 2005; 31: 444-449.
46) Baek SH, Lee WC, Setzer FC, Kim S. Periapical bone regeneration after endodontic microsurgery with three different root-end filling materials: amalgam, SuperEBA, and mineral trioxide aggregate. J Endod 2010; 36: 1323-1325.
47) da Silva GF, Guerreiro-Tanomaru JM, Sasso-Cerri E, Tanomaru-Filho M, Cerri PS. Histological and histomorphometrical evaluation of furcation perforations filled with MTA, CPM and ZOE. Int Endod J 2011; 44: 100-110.
48) Zairi A, Lambrianidis T, Pantelidou O, Papadimitriou S, Tziafas D. Periradicular tissue responses to biologically active molecules or MTA when applied in furcal perforation of dogs’ teeth. Int J Dent 2012; 257832.
49) Yongchaitrakul T, Lertsirirangson K, Pavasant P. Human periodontal ligament cells secrete macrophage colony-stimulating factor in response to tumor necrosis factor-alpha in vitro. J Periodontol 2006; 77: 955-962.
50) Maeda H, Nakano T, Tomokiyo A, Fuji S, Wada N, Monnouchi S, et al. Mineral trioxide aggregate induces bone morphogenetic protein-2 expression and calcification in human periodontal ligament cells. J Endod 2010; 36: 647-652.
51) Bloemen V, Schoenmaker T, de Vries TJ, Everts V. IL-1beta favors osteoclastogenesis via supporting human periodontal ligament fibroblasts. J Cell Biochem 2011; 112: 1890-1897.
52) Kaneshiro S, Ebina K, Shi K, Higuchi C, Hirao M, Okamoto M, et al. IL-6 negatively regulates osteoblast differentiation through the SHP2/MEK2 and SHP2/Akt2 pathways in vitro. J Bone Miner Metab 2014; 32: 378-392.
53) Bakhtiar H, Mirzaei H, Baghihi MR, Fani N, Mashhadiabbas F, Baghaban Esfahani M, et al. Histologic tissue response to furcation perforation repair using mineral trioxide aggregate or dental pulp stem cells loaded onto treated dentin matrix or tricalcium phosphate. Clin Oral Invest 2017; 21: 1579-1588.
54) Nakata TT, Bae KS, Baumgartner JC. Perforation repair comparing mineral trioxide aggregate and amalgam using an anaerobic bacterial leakage mode. J Endod 1998; 24: 184-186.
55) Weldon JK Jr, Pashley DH, Loushine RJ, Weller RN, Kimbrough WF. Sealing ability of mineral trioxide aggregate and super-EBA when used as furcation repair materials: a longitudinal study. J Endod 2002; 28: 467-470.
56) Daoudi MF, Saunders WP. In vitro evaluation of furcal perforation repair using mineral trioxide aggregate or resin modified glass ionomer cement with and without the use of the operating microscope. J Endod 2002; 28: 512-515.
57) Hardy I, Liewehr FR, Joyce AP, Agee K, Pashley DH. Sealing ability of One-Up Bond and MTA with and without a secondary seal as furcation perforation repair materials. J Endod 2004; 30: 658-661.
58) Hashem AA, Hassanien EE. ProRoot MTA, MTA-Angelus and IRM used to repair large furcation perforations: sealability study. J Endod 2008; 34: 59-61.
59) Momoi Y, Hayashi M, Fujitani M, Fukushima M, Imazato S, Kubo S, et al. Clinical guidelines for treating caries in adults following a minimal intervention policy —evidence and consensus based report. J Dent 2012; 40: 95-105.
60) Shovelton DS, Friend LA, Krik EEJ, Rowe AHR. The efficacy of pulp capping materials. A comparative trial. Br Dent J 1971; 130: 385-391.
61) Haskell EW, Stanley HR, Chelemi J, Stringfellow H. Direct pulp capping treatment; a long-term follow-up. J Am Dent Assoc 1978; 97: 607-612.
62) Sjögren U, Hägglund B, Sundqvist G, Wing K. Factors affecting the long-term results of endodontic treatment. J Endod 1990; 16: 498-504.
63) Clauder T, Shin SJ. Repair of perforations with MTA: clinical applications and mechanisms of action. Endod Topics 2006; 15: 32-55.
64) Lindhe J, Ericsson I. The influence of trauma from occlusion on reduced but healthy periodontal tissues in dogs. J Clin Periodontol 1976; 3: 110-122.