

Mineral Trioxide Aggregate Applications in Endodontics: A Review

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Abstract

A current topic in dentistry concerns the biocompatibility of the materials, and in particular, conservative dentistry and endodontics ones. The mineral trioxide aggregate (MTA) is a dental material with biocompatibility properties to oral and dental tissues. MTA was developed for dental root repair in endodontic treatment and it is formulated from commercial Portland cement, combined with bismuth oxide powder for radiopacity. MTA is used for creating apical plugs during apexification, repairing root perforations during root canal therapy, treating internal root resorption, and pulp capping. The objective of this article is to investigate MTA features from a clinical point of view, even compared with other biomaterials. All the clinical data regarding this dental material will be evaluated in this review article. Data obtained from the analysis of the past 10 years' literature highlighted 19 articles in which the MTA clinical aspects could be recorded. The results obtained in this article are an important step to demonstrate the safety and predictability of oral rehabilitations with these biomaterials and to promote a line to improve their properties in the future.

Keywords

- ▶ dental materials
- ▶ Portland cements
- ▶ dentin
- ▶ pulp exposure
- ▶ pulp capping
- ▶ root canal filling

Introduction

The mineral trioxide aggregate (MTA) is a hydrophilic and bio-compatible endodontic cement, capable of stimulating healing and osteogenesis. It consists of a powder of fine trioxides (tricalcium oxide, silicon oxide, bismuth oxide) and other hydrophilic particles (tricalcium silicate, tricalcium aluminate, responsible for the chemical and physical properties of this aggregate), which hardens in the presence of humidity.¹⁻⁵ The hydration of the powder results in the formation of a colloidal gel with pH 12.5, which solidifies in a structure in about 3 to 4 hours.⁶⁻⁹

In the past 10 years, the MTA found its application in the field of dentistry with specific fit within the conservative and endodontic treatments. A dental trauma is an event that cannot be predicted and usually it is not easy for the clinicians to manage it. The dentist should therefore be prepared to intervene in patient who has suffered a dental trauma. Early intervention is often crucial to improve the prognosis of the trauma itself. In the presence of a coronal fracture with dentine exposure, the primary objective should be to seal dentinal tubules. Especially in a young patient, the size and



number of dentinal tubules are large: even a small amount of exposed dentin therefore allows a large number of plaque bacteria and their metabolites to move to the underlying pulp and cause inflammation. An occurrence of this type could, sometimes in short time, lead to necrosis. When the dental trauma has caused a pulp exposure, the emergency intervention consists with the management of the exposed pulp. One of the treatments, besides the endodontic treatment, is direct capping or partial pulpotomy. Partial pulpotomy could be performed using MTA. The MTA could be applied as cement for its high compatibility, which has a mechanism similar to calcium hydroxide ($\text{Ca}(\text{OH})_2$) (extremely basic) and therefore a powerful antibacterial.

Unlike $\text{Ca}(\text{OH})_2$, however, the MTA hardens, reaching a good consistency; it is, therefore, extremely suitable for any restoration. Fast hardening therefore allows partial pulpotomies performed with MTA to be restored in a definitive manner.⁷

Pulp consisting of a cellular component, vessels and nerves; this tissue is called mature mucosal connective tissue. Endodontic therapy is used if a tooth carious or traumatic injury has caused an irreversible alteration of the pulp tissue and its necrosis. It is also possible to use this method if the dental element is to be involved in prosthetic rehabilitations, which due to the considerable reduction of the dental tissue, it would determine, with high probability, an irreversible pulp alteration. During endodontic treatment, blood contamination should be absolutely avoided, and the roots canal system needs to be dry, to obtain a successful root canal filling. During direct pulp capping or perforation sealing, it is fundamental to control the bleeding and obtain a dry field too. The mechanism of action of the MTA is related with the clinical features of the human oral cavity. MTA, when placed in direct contact with human tissues, is able to release calcium ions for cell proliferation. Moreover, it creates an antibacterial environment by its alkaline pH, regulating the cytokine production. Therefore, it favors the migration and differentiation of hard tissue producing cells forming hydroxyapatite on MTA surface and providing a biological seal. Finally, during a surgical endodontic procedure, the retrograde cavity should be completely dry. This cement differs from all other materials currently in existence, thanks to its biocompatibility, its antibacterial properties, its marginal adaptation, and its sealing capacities, and finally, thanks to its hydrophilic nature. It is important to understand the functioning of this biomaterial, its behavior with contact with other materials used in dentistry, and above all, over time or from a clinical and radiographic point of view.¹⁰⁻¹² Investigating these topics requires a research into the international literature, which also includes the use of cutting-edge technologies for examination.¹³⁻¹⁶

The purpose of this review is to evaluate all the recent scientific literature concerning this topic and to evaluate all its clinical features. The evaluation of different studies offers information about the facets of the material related to endodontics, conservative dentistry, and oral surgery.

Materials and Methods

Protocol and Registration

This article has been registered as review in a systemic review database called PROSPERO. It is an International Prospective Register of Systematic Reviews about health and social care. Obtained PROSPERO registration number is 156248 on October 27, 2019. The main question of this study has been elaborated following PICOT (Population/Intervention/Comparison/Outcome/Time) study design.

This review follows a protocol according to PROSPERO and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Transparent Reporting of Systematic Reviews and Meta-Analyses).

Eligibility Criteria

The results obtained from the literature search were filtered, through software and manual screening, according to the following inclusion and exclusion criteria:

- Inclusion criteria
 - Human studies
 - Information about MTA clinical use
 - Information about MTA and other biomaterials in endodontics
 - In vitro and in vivo studies about MTA
 - Last 10 years of studies
- Exclusion criteria
 - In silica studies
 - Not on human studies
 - Not in English
 - Not accessible title or abstract
 - Not enough information about main question

Information Sources

Results were obtained after a research and a screening on scientific international database as PubMed, Embase, and Web of Science. Automatic filter and platforms software have been used for results screening.

Search

Search has been conducted using this keyword on information sources: "Mineral Trioxide Aggregate." Search date is August 1, 2019.

The database search protocol details are: ("mineral trioxide aggregate" [Supplementary Concept] OR "mineral trioxide aggregate" [All Fields]) AND ("2009/10/30" [Pdat]: "2019/10/27" [Pdat] AND "humans" [MeSH Terms]).

Keywords have been chosen by authors after a discussion with the aim to include as large as possible number of results (► Fig. 1).

PICO questions are:

- In dental patients, what is the effect of MTA use on pulp vitality?
- How MTA features could improve clinical success on dental patients?

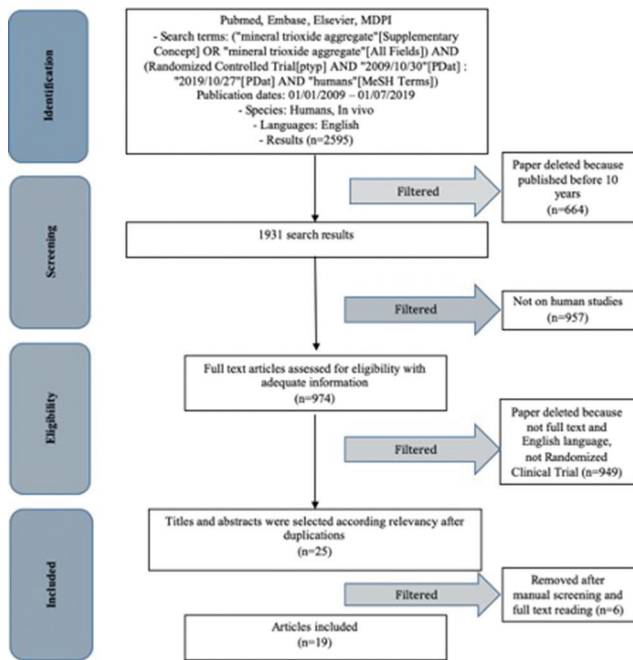


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow chart.

Study Selection

Authors with the aim to include relevant studies for this review have conducted selection process. After applying the electronic eligibility criteria, the authors conducted a manual study selection independently.

Data Collection Process

Two independent authors from two different universities conducted the data collection process (D.R., University of Naples and L.F., University of Messina). After data screening completion, they clarified any doubt with other expert reviewers (M.D.T. and L.L.).

Data Items

The following data items were considered during data collection; summary measures and data items are shown in ►Tables 1 and 2:

- Investigated data items on articles (►Table 2)
 - Authors and year—article authors and year of publication (references have been added)w
 - Sample—sample size and groups size
 - Outcome—main results of the study
 - Type of study—type of article.

Table 1 All mineral trioxide aggregate use

Conservative dentistry	Indirect pulp capping
	Direct pulp capping
Endodontic dentistry	Root filling
	Root filling with postcore indication

Summary Measures

Summary measures are shown in ►Table 1.

Synthesis of Results

The authors performed the summary of the results manually, after reading the title, abstract, and full text of each article.

Risk of Bias

A risk of bias evaluation was performed according to Higgins et al. Risk of bias has been conducted to improve review quality according to PRISMA statement too.¹⁷⁻²⁰

Results

Study Selection

The results were obtained in relation to the “Materials and Methods” instructions. Using the set out in paragraph 2.4 keywords, 2,595 results were obtained. Subsequently, according to eligibility criteria, results have been screened. The authors decided to maintain only past 10 years results to underline the novelty and accuracy on diagnostics method as well as the quality of the new technologies results in the field of MTA application. A total of 1,931 results remained after this first screening. Only 25 studies on human have been considered, and the authors analyzed full text and English articles. The last step to complete the revision of the results was to compare only review articles type. Only 19 results, after a reading and a manual authors screening, were resulted eligible for this study (►Fig. 1).

Results of Individual Studies

Results of individual studies are listed in ►Table 2 and ►Fig. 2. The results are divided accordingly to PRISMA statement and organized into sample, items, outcomes, and type of study. Authors’ name and year have been restricted following the interval time range of 10 years.

Synthesis of Results

Çelik et al²⁰ analyzed differences between two groups of patients involved in pulpotomy treatment. The MTA groups had a 100% success rate at 24 months instead of 89.4% with Biodentine use. According to Erfanparast et al,²¹ there are no significant differences on resin-modified Portland cement-based materials versus MTA in direct pulp capping. After 12 months, the success rate for MTA and resin-modified one were 94.5 and 91.8%, respectively. Koc Vural et al²² evaluated differences between Ca(OH)₂ and MTA. The follow-up term for a total of 100 samples was of 24 months. Four Ca(OH)₂ capped teeth and two MTA capped received endodontic emergency treatments. But there are no significant differences between groups. Kang et al²³ studied clinical differences between three MTA groups (ProRoot MTA, Ortho MTA, and RetroMTA). The success rate at 1 year was high with no significant differences; the success rates were 96, 92.8, and 96%, respectively (as listed in parentheses). Bakhtiar et al²⁴ investigated differences on third molar pulpotomy between

Table 2 Main results and item investigated on reviews

Authors (y)	Sample	Items	Outcomes	Type of study
Çelik et al (2019) ²⁰	24 + 20	MTA vs. Biodentine	Differences on success, $p = 0.646$	RCT
Erfanparast et al (2018) ²¹	46 × 2 (split mouth)	Resin modified Portland cement vs. MTA	Differences are not significant, $p > 0.05$	RCT
Koc Vural et al (2017) ²²	49 + 51	MTA vs. calcium hydroxide	There are no differences between used materials, $p = 0.238$ (or higher)	RCT
Kang et al (2017) ²³	33 + 36 + 35	ProRoot MTA vs. Ortho MTA vs. RetroMTA	No significant differences between groups	RCT
Bakhtiar et al (2017) ²⁴	9 + 9 + 9	TheraCal vs. Biodentine vs. ProRoot MTA	Normal pulp organization ($p = 0.06$); dentinal bridge formation ($p = 0.001$)	RCT
Asl Aminabadi et al (2016) ²⁵	40 + 40 + 40 + 40	Simvastatin vs. 3Mix vs. 3Mixtatin vs. MTA	No differences between MTA and 3Mixtatin ($p > 0.05$)	RCT
Aminabadi et al (2016) ²⁶	40 + 40	3Mixtatin vs. MTA	Clinical differences between groups	RCT
Nowicka et al (2015) ²⁷	11 + 11 + 11 + 11	Calcium hydroxide, MTA, Biodentine, Single Bond Universal	Reparative formed dentin was less in Single Bond Universal group; the mean density of dentin bridges was the highest in the MTA group and the lowest in the Single Bond Universal group	RCT
Kang et al (2015) ²⁸	49 + 47 + 47	RetroMTA vs. Ortho MTA vs. ProRoot MTA	Clinical success rate is similar and not statistically significant	RCT
Bonte et al (2015) ²⁹	15 + 15	MTA vs. calcium hydroxide	Success rate demonstrated a difference between groups, $p < 0.7$	RCT
Petrou et al (2014) ³⁰	31 + 26 + 29	Calcium hydroxide vs. medical Portland cement vs. white MTA	Difference between groups are not significant ($p = 0.72$)	RCT
Hilton et al (2013) ³¹	181 + 195	Calcium hydroxide vs. MTA	Failure rate at 24 mo was 31.5% for calcium hydroxide and 19.7% for MTA	RCT
Gandolfi et al (2013) ³²	8 + 8	AH Plus vs. MTA Flow	MTA flow sealer created a dense apatite layer after 7 d	RCT
Bernabé et al (2013) ³³	34	ProRoot MTA	Sonic vibration could be considered an efficient aid to improve MTA sealing ability	RCT
Sönmez et al (2012) ³⁴	15 + 15 + 15 + 6	AH Plus vs. MTA Fillapex vs. ProRoot MTA vs. control	MTA Fillapex had higher microleakage values, $p < 0.05$	RCT
Leye Benoist et al (2012) ³⁵	60	MTA vs. calcium hydroxide	Success rates are different between groups at 3 mo, $p = 0.02$	RCT
Ghoddusi et al (2012) ³⁶		MTA vs. ZOE)	MTA and ZOE showed both clinical success	RCT
Hansen et al (2011) ³⁷	12 + 12	ProRoot MTA vs. EndoSequence Root Repair Material	pH level was higher for MTA and EndoSequence $p < 0.05$	RCT
Yildirim et al (2009) ³⁸	15 + 15 + 15 + 6	Gutta-percha vs. Gutta-percha prepared with gates vs. MTA vs. control	MTA showed less microleakage, $p < 0.005$	RCT

Abbreviations: MTA, mineral trioxide aggregate; RCT, randomized controlled trial; ZOE, zinc oxide eugenol.

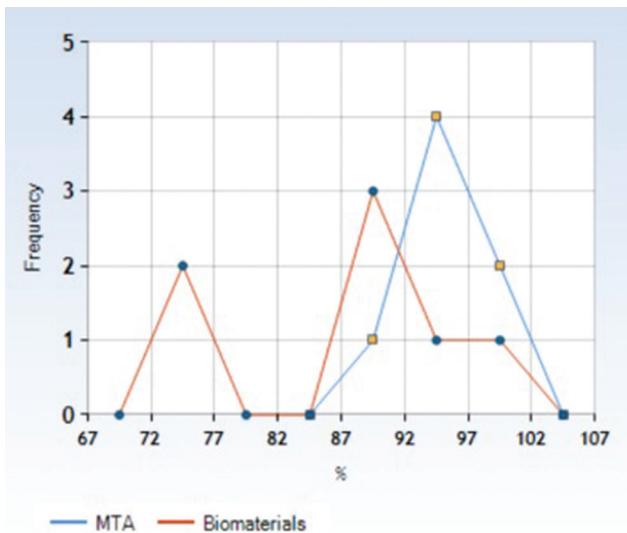


Fig. 2 Success rate frequency polygon chart of MTA (blue) versus other biomaterials. MTA, mineral trioxide aggregate.

three different materials (TheraCal, Biodentine, and ProRoot). They showed how there were no clinical signs on ProRoot MTA and Biodentine groups as two patients reported significant pain in TheraCal group. Pulp reorganization was seen in 33.33% of ProRoot MTA, 11.11% of TheraCal, and 66.67% of Biodentine groups. Moreover, dentinal bridge formation was seen on 11% of TheraCal and 56% of ProRoot MTA. Asl Aminabadi et al²⁵ tested clinical differences between four groups for direct pulp capping. Noncarious pulpal exposures were treated with simvastatin, 3Mix, 3Mixtatin, or MTA. At the end of a 12-month follow-up period, the overall success rates were 93.8% (MTA), 91.9% (3Mixtatin), 62.5% (3Mix), and 57.1% (simvastatin). According to the authors, there were no significant differences ($p = 0.05$) between MTA and 3Mixtatin groups. 3Mixtatin groups had a statistical difference on simvastatin and 3Mix groups ($p < 0.01$). Another study of Aminabadi et al²⁶ confirmed 3Mixtatin efficiency on pulp capping. The authors inspected MTA versus 3Mixtatin on direct pulp capping with a 96.8% of success rate against MTA with 48.6% of referred pain. Nowicka et al²⁷ evaluated differences on direct pulp capping between four groups: Ca (OH)₂, MTA, Biodentine, and Single Bond Universal. The reparative dentin formed in the Ca (OH)₂, MTA, and Biodentine was superior to the Single Bond Universal group. Moreover, the dentin bridges density was the highest in the MTA group and the lowest in the Single Bond Universal group. Kang et al²⁸ published a report about differences on three MTA materials. At 12 months, the radiographic success rates in these groups were 100% (RetroMTA), 97.4% (Ortho MTA), and 100% (ProRoot MTA). The Kaplan–Meier's survival function relative to clinical and radiographic rates did not differ between groups. According to Bonte et al,²⁹ MTA at 12 months produced mineralized barrier in 82.4% of cases instead of Ca (OH)₂ (50%). Pain and tenderness to percussion had disappeared in both groups. In a Petrou et al³⁰ randomized controlled trial, it was demonstrated at ~6.3 months of time on 86 patients how Ca (OH)₂ versus medical Portland cement

versus white MTA did not show any statistical difference. The total success rate was 90.3%. Hilton et al³¹ recently published a study about the clinical and radiographic differences on two direct capping materials groups, Ca (OH)₂ versus MTA. MTA showed a less failure rate ($p = 0.046$). Gandolfi et al³² analyzed, through a three-dimensional microcomputed tomography (3D micro-CT) analysis, differences between AH Plus and MTA flow on their microstructure. Bernabé et al³³ tested the MTA sealing ability for apicectomy. They filled with MTA plus sonic, ultrasonic, or no vibration. The sonic vibration could improve sealing level. Sönmez et al³⁴ showed differences on the apical microleakage between AH Plus, MTA Fillapex, and ProRoot MTA. Fillapex had better results about microleakage and there are no statistical differences between AH Plus and MTA. Leye Benoist et al³⁵ highlighted differences between Ca (OH)₂ and MTA for indirect pulp capping. At 3 months, the success rate of MTA was 93% instead of 73% for Ca (OH)₂. At 6 months, the success rate was 89.6% for MTA instead of 73%. The mean initial residual dentine thickness was 0.23 mm, this value has been increased to 0.121 mm with MTA and 0.136 with Ca (OH)₂ at 3-month time. According to Ghoddsi et al,³⁶ there are no statistical differences between MTA or zinc oxide eugenol (ZOE) in pulpotomy after a carious or traumatic pulp exposure. Hansen et al³⁷ considered the pH level with the use of different biomaterials for pulp capping. The authors studied MTA, Endodontic Sealing(ES); control pairs were filled with Ca (OH)₂ (positive group) and saline (negative). The pH was measured at 20 minutes, 3 hours, 24 hours, and 1–2 to 3–4 weeks. The MTA pH was significantly higher during the time than ES (at 1 week, $p < 0.0001$). Yildirim et al³⁸ discovered differences on filling between gutta-percha with two methods and MTA. Cervino et al obtained better results with MTA, then showed less microleakage (► Fig. 3).⁷

Discussion

All the conclusions of the selected articles for this present review have been summarized in this section as follows: Çelik et al²⁰ evaluated clinical success differences between MTA and Biodentine. The authors showed how both MTA and Biodentine are appropriate options for pulpotomy. According to this study, it seems how the etiology of pulp exposure is the crucial on pulpal response (mechanical or carious) whether or not the kind of material applied. Erfanparast et al²¹ concluded that resin-based Portland cement results are comparable to MTA for primary molars after 12 months of follow-up and no significant differences can be underlined between the two biomaterials investigated. Koc Vural et al performed a similar study, about the comparison of two endodontic materials.²² The authors reported that Ca (OH)₂ and MTA are both accepting pulp-capping materials at a 24-month follow-up term.

Kang et al²³ in a 1-year follow-up study investigated three different materials applied to pulpotomy technique. The procedure was classified as safe and predictable with ProRoot MTA, Ortho MTA, or RetroMTA documented through clinical and radiographical data. Bakhtiar et al²⁴ published an *in*

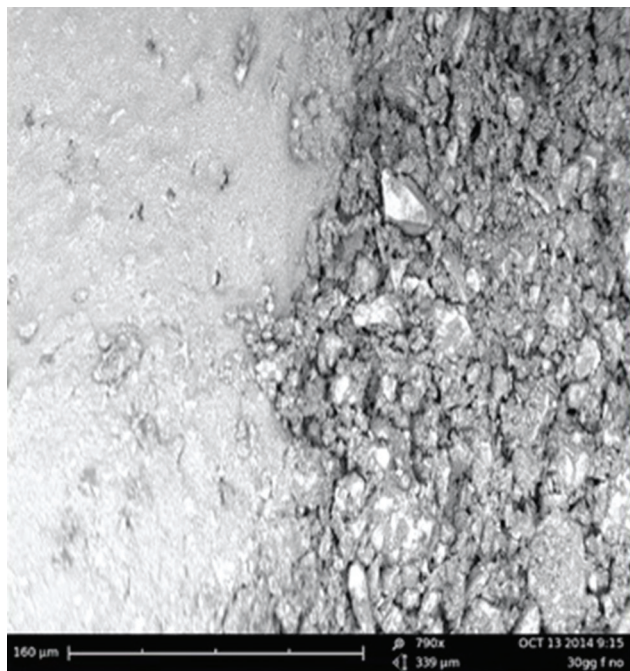


Fig. 3 SEM microleakage between MTA and bonding agents. The MTA use could, in some cases, make the definitive reconstruction complex due to the physical–chemical properties of itself and difficulty of use with hydrophobic substances. MTA, mineral trioxide aggregate; SEM, scanning electron microscope.

in vitro study about how some endodontic biomaterials could be efficient than others for the pulp capping procedures. The authors performed histology to evaluate dentinal bridge formation and organization after teeth extraction (disodontiasis third molar). Data demonstrated how Biodentine and ProRoot MTA work better than TheraCal.

According to Asl Aminabadi et al,²⁵ there are no radiographic and clinical differences between MTA and 3Mixtatin, and it could represent a valid alternative in direct pulp capping. Aminabadi et al²⁶ evaluated at 24 months the efficiency of 3Mixtatin, showing how this biomaterial could have better clinical result than MTA from a clinical and radiographic point of view. According to the authors, it could represent the future pulp capping material.

Several published articles underlined the clinical features of the MTA just evaluating clinical and radiological data. Nowicka et al²⁷ demonstrated how the reparative dentin bridges are dependent on the material used. Biodentine and MTA resulted in the highest volumes after the cone beam radiography. According to Kang et al,²⁸ RetroMTA, Ortho MTA, and ProRoot MTA success rates did not differ and are indistinguishable, and these results indicate that pulpotomy could be performed with a high success rate with all the evaluated biomaterials. Bonte et al²⁹ showed how there is no statistical difference between $\text{Ca}(\text{OH})_2$ and MTA, but MTA produced a better dentin healing, apexification using MTA could give better results than $\text{Ca}(\text{OH})_2$.

Petrou et al³⁰ concluded that MTA or medical Portland cements are preferable to $\text{Ca}(\text{OH})_2$ for indirect pulp capping because those materials are nonresorbable materials. Hilton et al³¹ showed how MTA is superior for direct pulp capping

to $\text{Ca}(\text{OH})_2$. Gandolfi et al³² concluded in their study, after a 3D micro-CT analysis, that MTA flow created an apatite layer after 7 days, and AH Plus even after 28 days. Bernabé et al³³ showed how MTA could be useful item for root canal filling after apicectomy; moreover, a sonic vibration could improve sealing ability. Sönmez et al³⁴ concluded that the sealing ability of AH Plus and ProRoot is similar, but MTA Fillapex showed microleakage compared with the other two materials.

Some studies reported how the results could be modified if the evaluation is reported at 3, 6 months, or 1 year after the treatment. This clinical condition demonstrated how the patient response could be individual and not related to the materials or technique applied. According to Leye Benoist et al,³⁵ a higher success rate was observed in the MTA group instead of $\text{Ca}(\text{OH})_2$. Differences were significant at 3 months but not at 6 months, with no dentine thickness differences, showing time of evaluation importance. Ghoddsi et al³⁶ concluded that there are no statistical differences between ZOE or MTA treatments, but MTA was successful, expensive, and because of dentin bridges could complicate future root canal therapy. Data reported by Hansen et al³⁷ demonstrated how the MTA produce an intracanal higher pH than ES. The same result was demonstrated by Yildirim et al.³⁸ MTA can be used in the root canals as apical filling materials, in particular, in teeth with postcore indication.

All these results extrapolated by the selected articles provide us documented clinical information and the MTA seems to be as having excellent abilities from the point of view of biocompatibility, as could be seen from the studies, but also of stability over time.^{39–41} The nanocharacteristic of the MTA could be related about its interactions with the human tissue during the endodontic treatment. Remineralizing potential intercepting early lesion progression as nanosized calcium phosphate, carbonate hydroxyapatite nanocrystals, nanoamorphous calcium phosphate, and nanoparticulate bioactive glass particularly with provision of self-assembles protein that furnish essential role in biomimetic repair even in the dental field. The unique size of nanomaterials makes them fascinating carriers for dental products.^{42–50} Thus, it is recently claimed that fortifying the adhesives with nanomaterials that possess biological merits does not only enhance the mechanical and physical properties of the adhesives but also help attain and maintain a durable adhesive joint and enhanced longevity. It is also necessary to report how these conservative therapies often do not expose patients to invasive surgical or not risks, practices that in patients with unfavorable systemic conditions would be complex to apply. Accordingly, this review will focus on the current status and the future implications of nanotechnology in preventive and adhesive dentistry. In dental materials, the main applications of nanotechnology have been to achieve better mechanical properties, higher abrasion resistance, less shrinkage, improved optical, and esthetic properties, and to provide antimicrobial properties. Antimicrobial activity is an important property for nanomaterials used in dentistry because of the lack of this property in resin-based materials. MTA is a biomaterial that has numerous

possibilities for endodontic therapy, as animal studies and clinical results are highly encouraging. It can also be used in deciduous dentition, with deep carious lesion or exposure to the traumatic pulp intended for endodontic therapy.⁵¹⁻⁶¹ The MTA could not be used to save all teeth with pulp involvement; however, with a meticulous technique, it could serve as a pulp drug in advance to add to a clinical use. Modern nanotechnology is used in the production of a variety of dental materials such as light-cured composite resins, adhesive systems, impression materials, ceramics, dental implant coatings, and bioceramics, among others. In pediatric age, a whole series of dental malocclusions could occur. There could be different types of dental malocclusions: some are genetic, and others are caused by external factors; the big difference in the treatment of these malocclusions in pediatric and in adulthood is that in children, treatment tends to be much less invasive as the bones have yet to fully develop and it is easier to intervene to correct their shape. Therefore, it should be understood how the absence of a dental element, extracted rather than saved, thanks to an endodontic treatment, even in borderline conditions, thanks to the use of these cements, could have repercussions on the whole stomatognathic system.^{62,63} Moreover, the material is versatile, guaranteeing different uses, and having excellent characteristics in being in contact with the materials for reconstruction.⁶⁴⁻⁷⁷

Conclusion

The results of this review would be certainly useful to fully understand the characteristics and advantages of this biomaterial from a clinical point of view; our structural analysis of the material explains its clinical behavior; and the studies examined are the proof. The numerous clinical, histological, and radiographic tests make this material a safe and predictable material in the endodontic and conservative dentistry fields. Some studies have shown better characteristics than the MTA, above all, from an antibiotic point of view. This could act as a starting point for the improvement of this material and the creation of even better materials.

Authors' Contributions

Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, original draft preparation, and review and editing of the manuscript were done by G.C., M.D.T., and L.F.; visualization was performed by D.R., L.N., and C.D.A.; data were curated by G.A., M.T., F.G., and A.T.; L.L. supervised the entire work and L.F. performed project administration.

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Conflict of Interest

None declared.

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