Mineral Trioxide Aggregate: A Comprehensive Literature Review—Part II: Leakage and Biocompatibility Investigations

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Abstract

Introduction: Mineral trioxide aggregate (MTA) was developed because existing materials did not have the ideal characteristics for orthodox or retrograde root-end fillings. MTA has been recommended primarily as a root-end filling material, but it has also been used in pulp capping, pulpotomy, apical barrier formation in teeth with open apaxes, repair of root perforations, and root canal filling. Part I of this literature review presented a comprehensive list of articles regarding the chemical and physical properties as well as the antibacterial activity of MTA. The purpose of part II of this review is to present a comprehensive list of articles regarding the sealing ability and biocompatibility of this material. Methods: A review of the literature was performed by using electronic and hand-searching methods for the sealing ability and biocompatibility of MTA from November 1993–September 2009. Results: Numerous studies have investigated the sealing ability and biocompatibility of MTA. Conclusions: On the basis of available evidence it appears that MTA seals well and is a biocompatible material. (J Endod 2010;36:190–202)

Key Words
Apical plug, biocompatibility, cytokine production, marginal adaptation, mineral trioxide aggregate, MTA, root-end filling, sealing ability, signaling molecule

Most endodontic failures occur as a result of leakage of irritants from pathologically involved root canals into the periradicular tissues; therefore, a repair material should provide a good seal to an otherwise unobturated root canal or improve the seal of an existing filling material. An adequate apical seal is a major factor for improving endodontic success (1). One of the most important criteria for an ideal endodontic material is its sealing ability and marginal adaptation (2). The sealing ability of original mineral trioxide aggregate (MTA), other types of MTA, and its new compositions has been tested by leakage studies (dye, fluid filtration, bacteria and bacterial by-products) and scanning electron microscopy (SEM). Because materials used in endodontics are frequently placed in close contact with the periodontium, they also must be biocompatible with host tissues. The purpose of this literature review is to present a comprehensive list of articles from November 1993–September 2009 regarding the sealing ability and biocompatibility of MTA.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this literature review were identical to those used for Part I of the review (3).

Search Methodology

An electronic search was conducted in the PubMed and Cochrane databases with appropriate MeSH headings and key words related to the sealing ability and biocompatibility of MTA. The hand-searching methodology used in this literature review was identical to that used for Part I of the review (3).

Leakage Studies

Leakage investigations on MTA have evaluated the sealing ability of the material as a root-end filling material, perforation repair material, root canal filling, coronal and apical barrier material (4, 5–85).

Leakage of MTA as a Root-end Filling Material and Other Root-end Filling Materials to Materials Tested

The sealing ability of MTA and other root-end filling material has been tested by using dye, fluid filtration, protein leakage, and bacterial leakage methods. Dye Leakage. Numerous dye leakage studies have been performed on MTA when used as a root-end filling material (4–20). Various types of dyes have been used to evaluate MTA’s sealing ability, including methylene blue, fuchsin, rhodamine B, silver nitrate, India ink, and Pelikan ink.

Results from most of these investigations indicated that MTA exhibits significantly less dye leakage in comparison with Super EBA, amalgam (4–7, 9, 10), and intermediate restorative material (IRM) (5, 7, 11). An investigation compared dye penetration in roots filled with MTA as a root canal filling material (in an orthograde manner) with fresh MTA as a root-end filling material (in a retrograde manner). Results showed no significant difference between the 2 groups (8).

Gondim et al (17) investigated microleakage of three root-end filling materials with or without finishing. Their results revealed that Pro Root MTA displays significantly less mean dye microleakage as a root-end filling material than Super EBA and IRM.
Variation in the finishing techniques does not significantly affect dye leakage of the tested materials (17).

In contrast to these studies, 2 investigations showed the inferiority of MTA in terms of dye (India ink) penetration when compared with Super EBA and Geristore (15, 16). Tobón-Arroyave et al (16) attributed more leakage in MTA specimens to placing the white MTA (WMTA) samples in dye before complete setting.

Rahimi et al (85) compared dye leakage of different depths of MTA when used as a root-end filling material. They placed their samples in phosphate-buffered saline (PBS) for 48 hours before dye exposure. Dye penetration was not significantly different between 1-mm, 2-mm, or 3-mm thicknesses of MTA.

One investigation reported that the amounts of dye leakage of MTA without calcium phosphate cement (CPC) matrix samples was greater in acidic pH than in a neutral environment (19).

A dye leakage study testing different dental materials showed a decoloration effect of MTA with methylene blue (20). The formation of calcium hydroxide (CH) after the reaction of MTA with moisture (86, 87) might be the reason for methylene blue decoloration when the dye is used for leakage evaluation. The same finding was observed when the roots were filled with CH (20). A comparison of WMTA and a glass ionomer cement (GIC) by using rhodamine B (with varying pH values) showed that WMTA is affected less by changes in dye pH; however, more dye extension was observed through the material rather than at the tooth-to-material interface (21). Another dye leakage study with India ink showed penetration of dye through WMTA (16).

Storage of the teeth in formalin before a dye study might also affect leakage results. An investigation on various root-end filling materials revealed that storing the teeth in formalin for 4 weeks significantly decreases the amount of dye leakage in comparison to that observed with freshly extracted teeth (15). A recent investigation evaluated the effect of the presence of cracks on sealing ability and quality of filling with a GIC or WMTA as root-end filling materials. Both materials showed similar sealing ability, but WMTA had better obturation quality in comparison to Fuji IX (88).

On the basis of available information, it appears that MTA is one of the most resistant root-end filling materials to dye penetration. Different factors influence MTA leakage. They include thickness of the dentinal wall (18), the dye pH (19), the type of dye (12, 14, 20), pretreatment with chelating agents (13), the tooth storage environment before the experiment (15), and the setting status of MTA before its placement in the dye (16).

Fluid Filtration. Fluid filtration investigations showed the superior quality of MTA compared with amalgam (22–25) and Super EBA (24).

In an investigation with 2 different cavity preparation techniques (erbium:YAG laser and ultrasonic), IRM, Super EBA, and MTA were used as root-end filling materials. MTA showed significantly less leakage than the other test materials when a laser was used for cavity preparation (26). Another fluid filtration study evaluated the sealing ability of MTA when used as a root canal filling material followed by root-end resection. No significant leakage was observed when at least 3 mm of MTA remained after root-end resection. However, the authors reported significantly more leakage when 2 mm or less thickness of MTA remained after root-end resection (27).

De Bruyne et al (28) used fluid filtration and capillary flow porometry for comparing leakage of WMTA with Fuji IX and IRM. After 6 months, Fuji IX leaked significantly less than IRM and MTA. The same investigators repeated the study with capillary flow porometry and reported that IRM and WMTA leak significantly less than Fuji IX (29). The authors attributed the conflicting results to the size of the root-end cavity preparations and the use of human teeth in the first study in contrast with bovine teeth in their second study (29). Nakamichi et al (30) compared the adhesive strength of 5 dental materials to bovine and human teeth. They found no statistically significant difference between human and bovine teeth, although the mean values were always slightly lower for bovine teeth.

Most fluid filtration investigations have shown the superiority of MTA as a root-end filling material in comparison to other currently used root-end filling materials.

Protein Leakage. Valois and Costa (31) used bovine albumin for evaluating the influence of the thickness of MTA on the sealing ability of this material as a root-end filling material. A 4-mm thickness of MTA leaks significantly less than lesser thicknesses of the material. Another study evaluated the effect of pH on protein leakage of WMTA (32). Teeth that were stored in acidic environments had significantly lower resistance to leakage than teeth that were stored under high pH conditions.

On the basis of limited available data and using protein as a tracer, it appears that a thin layer of MTA and acidic conditions adversely influence the leakage of MTA to protein leakage.

Bacterial Penetration. A large number of bacterial penetration investigations have been performed on MTA, comparing it with other currently used root-end filling materials (33–40). These studies have used different species of microorganisms to test bacterial penetration. The majority of the studies have compared amalgam and MTA (33–35, 40); most of them showed that MTA is more resistant to bacterial penetration than amalgam (33, 34, 40). In contrast, one investigation reported no significant difference in bacterial penetration between the 2 materials (35). Many bacterial penetration studies demonstrated the superiority of MTA to Super EBA (33, 34, 38). Conversely, others have shown no significant difference between the 2 materials (36, 37).

In an endotoxin leakage study, MTA was more resistant to leakage than amalgam, Super EBA, and IRM in most time intervals tested (41). Two investigations compared the bacterial penetration of IRM with MTA, showing the superiority of MTA (33, 34). Other studies showed no significant difference between MTA and Geristore (36), hydroxyapatite (HA) (37), a composite, amalgam with Pro-Bond dentin bonding agent (35), and Resilon (38).

In an investigation of WMTA as a root-end filling material, the material was contaminated with blood, saline, and saliva. The saliva-contaminated samples showed significantly more bacterial leakage in comparison with uncontaminated WMTA (39).

In an investigation simulating an environment similar to that of the human body, researchers immersed teeth with MTA as a root-end filling either in PBS or in normal saline for 1 month and showed formation of HA over MTA in all teeth placed in PBS and significantly higher resistance to Enterococcus faecalis penetration in this group in comparison to teeth placed in normal saline (43).

Available data showed that the type of microorganism and the length of leakage evaluation directly influence the results of bacterial leakage investigations. A meta-analysis of the results of current studies showed that MTA prevents bacterial and dye penetration better than Super EBA, amalgam, or IRM (44).

Leakage of MTA as a Perforation Repair Material

Many restorative materials have been used for repairing furcation perforations (45). Various in vitro methods have been used to compare MTA with these materials (46–55).

Dye Leakage Investigations. The superiority of MTA over IRM and amalgam was initially established in a study that used MTA as an endodontic filling material for repairing lateral root perforations (46). Gray MTA (GMTA) has superior sealing ability as a perforation...
repair material compared with Vitrebond (a modified GIC) (48), Cavit-W, and tricalcium phosphate in conjunction with AH26 (50).

Hamad et al (55) used a dye extract method (using a spectrophotometer) and compared WMTA and GMTA as furcation perforation repair materials; no significant difference was found between the two materials. Greater dye penetration was observed in an orthograde direction (from coronal to apical) than in a retrograde direction (from furcation to coronal portion).

One of the drawbacks of MTA is its long setting time. For this reason, many investigations are searching for permanent filling materials that can be placed over MTA without interfering with its setting properties for 1-visit furcal perforation repair. Nandini et al (89) reported that placement of GIC 45 minutes after placing WMTA does not interfere with MTA setting, and calcium salt can be formed in the interface of both materials.

In another dye extraction investigation, an internal matrix was used before placing various furcation repair materials (55). The presence or absence of an internal matrix has no significant effect on the leakage of GMTA, whereas it does reduce leakage of IRM. MTA samples leak significantly less than IRM, regardless of the use of an internal matrix. Hamad et al (53) have shown that using a collagen matrix does not prevent MTA overextension as a perforation repair material.

Most studies showed that MTA is resistant to dye penetration when used as a perforation repair material. In addition, the presence of a matrix beneath the material has no significant effect on its resistance to dye penetration. Fluid Filtration. An investigation compared Super EBA, MTA, and a combination of both to repair furcation perforation (49). All test materials sealed the perforations well. The Super EBA group showed significantly less leakage than the other groups only at the 24-hour observation period. Another investigation compared sealing saucer-shaped furcation perforations by using MTA, One-Up Bond, and MTA with a secondary seal of One-Up Bond or Super EBA (50). Fluid filtration was used for leakage evaluation. After 24 hours, MTA demonstrated significantly more leakage than the other groups. However, after 1 month there was no significant difference between the test materials.

These investigations showed that when MTA is used as a perforation repair material, it has no superiority over other materials when tested with the fluid filtration technique.

A recent fluid filtration investigation examined the effect of different irrigation regimens on the sealing ability of WMTA and showed that using sodium hypochlorite with a mixture of tetracycline, an acid, and a detergent (MTAD) or ethylenediaminetetraacetic acid (EDTA) significantly increases leakage in comparison to using only NaOCl or no irrigation before placing WMTA for perforation repair (90). Another study showed that WMTA partially dissolves when it remains in contact with BioPure MTAD for 5 minutes (91).

Bacterial Leakage Studies. MTA has been shown to be superior to amalgam when challenged by a bacterial leakage model using Pseudobacterium nucleatum (47). Another investigation showed no significant difference between GMTA and WMTA after 60 days when they were used as furcation repair materials (51). De-Deus et al (54) compared MTA and PC as perforation repair materials and found no significant difference between the two.

On the basis of limited available data, it can be concluded that MTA is superior to amalgam as a perforation repair material, and that there is no significant difference between MTA and Portland cement (PC). Other Leakage Methods. Zou et al (56) used a glucose leakage test for evaluating GMTA as a perforation repair material. Calcium sulfate and CollaPlug were used as a barrier (matrix) beneath GMTA. Neither of the barrier materials simultaneously improved the seal and prevented overextension of GMTA. The reliability of this method is questionable because MTA produces CH after hydration, which can react with glucose.

The results of a recent study confirmed that the glucose model should not be used for evaluating leakage of MTA, PC, and CH (57).

Leakage of MTA as a Coronal Plug Material

Two bacterial leakage investigations compared WMTA and GMTA with Fuji II and Fuji Triage glass ionomer as a coronal plug and reported no significant difference among the tested materials (58, 59). However, a dye comparison of GIC and GMTA as an orifice plug showed that GMTA is more resistant to dye penetration than GIC (60).

In a dye leakage study using India ink, Jenkins et al (61) compared various depths of Cavist, MTA, and Tetric composite as orifice plugs. The results of this study showed that Tetric composite is significantly more resistant to dye penetration, irrespective of orifice depth. In a saliva leakage penetration study comparing MTA, Geristore, Fuji Plus, and amalgam as orifice plugs, all test materials exhibited leakage in some specimens at 90 days (62).

Data regarding the effectiveness of MTA as a coronal plug are limited, and more studies are needed.

Leakage of MTA as an Apical Plug Material

Traditionally, apexification with CH has been the treatment of choice for teeth with necrotic pulps and open apexes (92). Generally, it is accepted that treatment time is too long, takes more visits, costs more, and increases the susceptibility of the tooth to fracture (92–94). In addition, the patient might experience periradicular necrosis after CH therapy (95). Shahabang and Torabinejad (96) described the use of MTA as an apical barrier in teeth with open apexes. Dye Leakage. The results of dye leakage studies with MTA as an apical barrier are in favor of GMTA (63, 97). In a dye leakage investigation comparing WMTA and GMTA as an apical barrier, the latter material showed significantly less leakage (97). Gutta-percha obturation after MTA has set showed less dye leakage in comparison with 1-step MTA insertion and immediate gutta-percha obturation. The drawback of this study (97) is the fact that MTA decolors methylene blue dye (20).

Another experiment comparing WMTA and GMTA as an apical barrier used CH medication before MTA placement (63). Results showed that pretreatment with CH adversely affects the seal of WMTA. A recent investigation reported unfavorable effect of a high alkaline environment on the MTA surface (98). In contrast to this finding, the results of a bacterial leakage study showed that pretreatment with CH has no significant effect on sealing ability of MTA as an apical barrier (99).

Available data suggested that inserting GMTA as an apical barrier and obturating the rest of the canal space later with gutta-percha improve resistance to dye penetration.

Fluid Filtration. Martin et al (64) compared leakage resistance of various thicknesses of WMTA by using a fluid filtration technique. Teeth whose root canals were filled completely with WMTA leaked significantly less after 48 hours. However, no significant difference was observed among the groups after 4 weeks. Immersion of the teeth in PBS during the study time (4 weeks) might have contributed to decreased leakage over time, along with the formation of HA crystals over the MTA samples (100, 101).

Bacterial Penetration. Hachmeister et al (99) investigated CH pretreatment in advance of MTA plug insertion and reported that most of the teeth with or without CH pretreatment showed bacterial penetration during the first 10 days of the study. By day 70, all MTA barriers showed bacterial penetration. In contrast, only 20% of control samples that had been filled in a retrograde manner revealed bacterial leakage at the same time. On the basis of these findings, the authors
concluded that the method of insertion might play an important role in bacterial penetration when MTA is used as an apical barrier.

The use of ultrasonic to increase the sealing ability of MTA is a matter of debate among investigators. An investigation compared using ultrasonic and non-ultrasonic placement of MTA as an apical barrier (102). Ultrasonic placement resulted in a significant reduction of bacterial penetration after 45 days. However, after 90 days no significant difference was observed between the groups (102). In contrast, a recent bacterial leakage investigation showed significantly lower E. faecalis penetration after use of MTA as an apical barrier with ultrasonic activation (105).

de Leimburg et al (65) used a polymerase chain reaction (PCR) for bacterial leakage detection. They showed no significant difference between 1-mm, 2-mm, and 3-mm thicknesses of MTA as an apical barrier in teeth with open apices. In contrast, one investigation demonstrated that only a 5-mm thickness of MTA adequately prevents bacterial penetration when used as an apical barrier (66).

Many factors influence bacterial penetration of MTA when it is used as an apical barrier in teeth with open apices (42, 65, 66, 101, 102), including the type of bacteria, methods of MTA insertion and compaction, the bacterial leakage evaluation method, thickness of the MTA, and length of study time.

Leakage of MTA as a Root Canal Filling Material

Vizgirda et al (67) compared lateral condensation, thermoplasticized gutta-percha, and MTA as root canal filling materials in bovine teeth. Both gutta-percha obturation techniques showed less methylene blue penetration than MTA. In contrast, another experiment comparing GMTA, WMTA, and gutta-percha with sealer as root canal filling materials by using a salivla leakage model on human teeth showed significantly less leakage in GMTA samples than in those filled with gutta-percha and sealer (68).

There are 3 important differences between the methods of these studies. First, Vizgirda et al (67) used a lentulo spiral for MTA placement, which has not been previously recommended for MTA placement (69, 101, 104). Second, there are many investigations that have questioned the similarity of human and bovine teeth in terms of dye leakage (70), dentin tubule size (71), and diffusion of cations and liquids (76, 77). Third, these studies used different methods (dye, bacteria, saliva) for leakage evaluation (67, 68).

A fluid filtration study reported significantly less leakage after 48 hours when WMTA was used as a root canal filling material compared with an apical plug and gutta-percha insertion. However, no significant difference was reported after 4 weeks (64).

Chogle et al (105) evaluated the sealing ability of WMTA as a root canal filling material. After a 3-mm root-end resection, the apical 9 mm of each root was filled with WMTA. The samples that were incubated for 2 and 7 days demonstrated significantly less bacterial leakage than those incubated for 4 hours.

MTA can be used as a root canal filling material, although clinicians should be aware of some of its limitations such as difficulty in controlling the length of the filling, the chance of producing voids, and the absence of a known solvent for MTA removal.

Marginal Adaptation of MTA

In several investigations, MTA has shown better marginal adaptation than IRM, Super EBA (74, 75), amalgam (74, 76), and GIC (21). In one investigation comparing marginal adaptation of MTA and Super EBA as root-end filling materials (77), samples were subjected to in vitro chewing cycles in a computer-controlled chewing simulator. Marginal adaptation was controlled before and after testing. Both materials showed no significant change after occlusal loading, although margin continuity was slightly decreased, particularly for Super EBA. Although bur-finishing techniques do not significantly improve MTA marginal adaptation after root-end filling (75), MTA has better marginal adaptation than amalgam when observed under both high- and low-vacuum SEM (76).

Gandolfi et al (78) compared 2 new cements with WMTA by using SEM. Their evaluation of WMTA samples showed limited marginal gaps. Another recent study compared the marginal adaptation of WMTA, GMTA, and PC (106). Results showed no significant difference between the tested materials, although GMTA showed better marginal adaptation. In contrast to these findings, another investigation compared marginal adaptation of WMTA, IRM, and Super EBA (16) and reported that IRM has the best marginal adaptation, whereas WMTA is prone to washing out and exhibits a higher number of underfilled specimens.

The type of SEM used for evaluation of marginal adaptation and methods for preparation of the samples are very important in SEM studies. In an SEM study, Shipper et al (76) compared MTA with amalgam by using high- and low-vacuum conditions. The results of this study demonstrated that the size of the gap between the root-end filling material and the margin of the root-end cavity is smaller under the low-vacuum microscope. They attributed this finding to examination of the samples without standardized preparations and in moist conditions.

A number of investigations have shown that MTA has better adaptation to tooth structure than Super EBA, IRM, and amalgam. Test conditions can influence the results of these investigations.

Leakage Studies and Marginal Adaptation of Other Types of MTA

A dye leakage study compared Angelus MTA (AMTA), zinc-free amalgam, Vitremer (a resin-modified GIC), and Super EBA (10). The results showed that AMTA presented the best seal among all of the tested materials. Use of 1% methylene blue was a shortcoming of this study because of the decoloration effect of MTA on the dye (20). Another dye and marginal adaptation investigation compared AMTA, Vitremer, and Super EBA as root-end filling materials (79). The authors also prepared 3 transverse slices from each sample and assessed the amount of dye leakage in each slice separately. Super EBA showed significantly less leakage than AMTA and Vitremer in most apical sections. However, in other sections, no significant difference was found between AMTA and Super EBA. AMTA showed significantly smaller gaps between the material and the root-end cavity than Vitremer and Super EBA when examined under SEM. Statistical analysis revealed no correlation between the dye penetration and the marginal adaptation (79). An SEM investigation has reported similar marginal adaptation when white Portland cement (WPC) was compared with white MTA (AWMTA) as root-end filling materials (107). Another investigation showed no significant difference between AMTA and a GIC as root-end filling materials in a dye leakage model (108).

Another investigation compared AWMTA and WMTA as apical barrier for open apex teeth. Results showed no significant difference in dye penetration (109). However, the major drawback for this study was use of methylene blue dye for assessing leakage of the materials (20, 82).

Another study evaluated the effect of calcium chloride (CC) on the sealing ability of WMTA, AWMTA, and a modified WPC as root-end filling materials. Results showed that the addition of 10% CC improves the sealing ability of all 3 tested materials (110). Two experiments evaluated the effect of a laser on AMTA as a root-end filling material (80, 81). The first study showed that diode laser irradiation does not improve the apical seal of AMTA (80). A dye
leakage study compared a combination of using Er,Cr:YSGG laser and an AMTA root-end filling with laser and cyanoacrylate (81). The results of this study revealed that using the laser adversely affects leakage of AMTA as a root-end filling material.

Hashem and Hassanien (55) recently compared AMTA with IRM and GMTA as perforation repair materials. GMTA samples showed the least amount of dye leakage. In addition, their results showed that the presence of an internal matrix had no influence on the amount of dye leakage of GMTA. However, a gray AMTA (AGMTA) demonstrated a better seal when an internal matrix was used for this material.

A fluid filtration investigation compared PC, AWMTA, and MTA-Bio as a perforation repair material (111). The results of this study showed no significant difference between the tested materials, and none of them could develop a fluid-tight seal. A dye extraction study testing perforation repair materials demonstrated that AMTA without an internal barrier matrix absorbs significantly more dye than GMTA with or without an internal matrix (55). The methods and materials of this study have been questioned because they used 2% methylene blue, which interacts with MTA during the experiment (20, 82).

Compared with MTA, there are a limited number of studies related to the sealing ability of AMTA as a root-end filling or perforation repair material.

A recent investigation reported that various types of MTA and WPC, with or without CC, form an interfacial layer between the material and dentin, which might affect their sealing ability (112).

Leakage Studies and Marginal Adaptation of New Compositions of MTA

Pellicioni et al (83) compared WMTA mixed with sterile water as recommended or dry MTA for filling root-end preparations. They used the fluid filtration method for measuring microleakage and reported no significant difference between the 2 groups, except for the 1-week samples. Nonetheless, it has been shown that when MTA is placed under dry conditions, a complete set can be delayed (113), compromising the samples. Nonetheless, it has been shown that when MTA is placed under dry conditions, a complete set can be delayed (113), compromising the biocompatibility and bioactive properties of MTA, including the release of the calcium ions, production of CH, and a delayed increase in pH value.

Two separate dye and fluid filtration investigations evaluated the sealing ability of MTA mixed with 10% CC when used either as an apical barrier or as a root-end filling material (110, 114). Both investigations reported significantly better results when MTA is mixed with 10% CC rather than with sterile water.

A dye leakage investigation compared chlorhexidine (CHX) mixed with water as a vehicle for WMTA and GMTA (84). Results revealed no significant difference between the 2 groups. However, MTA’s compressive strength decreased after mixture with CHX (115). Peters and Peters (77) used SEM and showed that the marginal adaptation of MTA used as a root-end filling material might be slightly affected after occlusal loading.

There are limited data available regarding leakage and marginal adaptation of the new versions of MTA.

MTA as Root Filling Material and Root Canal Sealer

A recent form of MTA was introduced as ProRoot Endo Sealer (Dentsply Tulsa Dental Specialties), which is a calcium silicate–based endodontic sealer. The liquid component consists of a viscous aqueous solution of a water-soluble polymer (116). An investigation comparing ProRoot Endo sealer with AH Plus and pulp canal sealer either stored in tissue synthetic fluid or without storing reported higher push-out strength for the former material (117).

A fluid filtration investigation on sealing ability of a new form of MTA, namely ProRoot Endo Sealer, as root canal sealer showed significantly less leakage in ProRoot Endo Sealer samples in comparison to pulp canal sealer but no significant difference between the pulp canal sealer and AH Plus root canal sealer (116).

Removing smear layer always is a matter of debate among endodontists. Results of a meta-analysis based on in vitro investigations showed superior apical seal after removal of smear layer before root canal obturation (118). However, a recent long-term fluid filtration investigation on MTA as root canal filling material showed significantly higher leakage when smear layer was removed before placing the material (119). An investigation has reported EDTA might influence MTA setting (120). The higher leakage in smear removed group might be because of reaction between MTA and residual EDTA inside the root canal (119).

A coronal bacterial leakage investigation reported no E. faecalis penetration in teeth that had AWMTA as a root canal filling material. A major drawback of this particular study, however, was the duration of the investigation, which was too short (30 days) (121).

A recent dye leakage investigation used AGMTA and CPM™ sealer (Egeo S.R.L., Buenos Aires, Argentina) and MBPc sealer (School of Dentistry, University of São Paulo, São Paulo, Brazil) as an apical plug and reported no significant difference between these materials (122). The major drawback for this study was using EDTA for removing the smear layer before MTA placement (119, 120).

Biocompatibility

Materials used in endodontics are frequently placed in intimate contact with the periodontium and thus must be nontoxic and biocompatible with host tissues. There are several in vitro and in vivo tests to evaluate the biocompatibility of dental materials. They include testing the general toxicity profile of potential materials in a cell culture, implantation tests, and usage tests in experimental animals according to accepted clinical protocols. A number of biocompatibility and mutagenicity studies have shown that MTA is a biocompatible material (123–164). In fact, the results of a meta-analysis on MTA biocompatibility showed that MTA is more biocompatible than Super EBA, IRM, and silver amalgam (44).

Mutagenicity

The Ames mutagenicity test was used to assess the mutagenicity of MTA (129). This test uses strains of Salmonella typhimurium LT-2, which are sensitive to various classes of mutagens. Results of this study determined that MTA is not mutagenic.

Neurotoxicity and Neurologic Effects

With murine cerebral cortical cells (130), neurotoxic effects of MTA, Diaket, amalgam, and Super EBA were compared on both glial and neuronal cultures. Results showed that all of the materials except MTA are toxic in either freshly mixed or set conditions.

Nociceptive and anti-nociceptive effects of WMTA were evaluated in a rat animal model. WMTA did not irritate nerve tissues and was more effective in relieving orofacial nociceptive pain of formalin injection in comparison to eugenol (131).

Vascular Effect

Two different models have evaluated the effect of MTA on vascular tissues (132, 133). One investigation on rabbit ear chambers evaluated the effect of MTA on microcirculation (132). The results of this investigation showed that 4 weeks after MTA placement, microcirculation was completely restored, and new vessels were formed. Another experiment used a rat aortic ring model to simulate the pulpal vessels’ smooth muscle contraction (133). The results of this investigation showed that MTA induces vessel contraction in a dose-dependent manner.
On the basis of current information, it can be concluded that MTA is nonmutagenic and non-neurotoxic and does not produce a side effect on microcirculation, despite the fact that it can influence a vessel’s contraction.

**Cell Cultures**

Cell culture studies evaluate cytotoxicity through morphologic observation of the cultured cells in the vicinity of the test materials or their extracts, recording the number of detached cells, alkaline phosphatase activity, SEM observation, fluorescent measurements, and cell viability (123–127, 134–166).

By using various cell culture systems, a number of investigations have shown that MTA is one of the least cytotoxic dental materials (123–164). Torabinejad et al (134) have shown that freshly mixed and set MTA and amalgam are less cytotoxic than Super EBA or IRM. Another study on human periodontal ligament (PDL) cell cultures compared MTA with amalgam and Super EBA (136). Results indicated that freshly mixed MTA exhibits lower cytotoxicity than Super EBA or amalgam. Twenty-four hours after mixing at a higher extract concentration, MTA showed the least amount of cytotoxicity of all the tested materials; at a lower extract concentration, Super EBA showed higher cytotoxicity than amalgam or MTA.

Cytotoxicity and cell attachment investigations with various cell cultures showed better results with MTA in comparison to amalgam (135, 137, 138, 140, 144), gallium GF2 (135), Super EBA (135, 144, 147, 151, 155), IRM (137, 138, 156, 161), various types of glass ionomers (135, 149, 155, 157), gutta-percha (155), N-Rickerts (155), Dialet (157), a cyanoacrylate-based adhesive dental cement (157), Life (147, 151, 162), and Dyocal (165).

In contrast to these studies, an experiment with mouse fibroblast and macrophage cells on freshly mixed and set MTA, IRM, amalgam and Retroplast (166) found no significant difference between amalgam and MTA. The total cell number in freshly mixed or set Retroplast was significantly less than both MTA and amalgam. The cytotoxicity of MTA is similar to chemically inert titanium alloy (140). In another study on murine pre-osteoblastic clone cell cultures, MTA and Super Bond resin showed no significant difference in cell adhesion and proliferation (156). Results of an observational study examining various root-end filling materials on gingival fibroblast cells showed greater cell attachment to Geristore in comparison to MTA (165). In a study on rat bone marrow cells, MTA did not inhibit cell growth but suppressed osteoblast-like cell proliferation (146).

Because of differences in the chemical composition of WMTA and GMTA (167, 168), several investigations have been performed on the cytotoxicity of both types of MTA (124, 139, 150, 154). There is disagreement among investigators regarding the cytotoxicity of WMTA and GMTA (124, 139, 150, 154). One study using osteoblast and MG-63 osteosarcoma cells determined that after initial cell attachment to the WMTA surface after 13 days, the former cell type could not survive over WMTA, whereas they did grow over GMTA during the same period of time (139). In contrast, an investigation comparing the incubation of WMTA and GMTA with oral keratinocyte and cementoblast cell cultures showed greater proliferation of both cell types on the WMTA surface in comparison with GMTA (154).

Another investigation on osteoblast cell cultures compared 1-day and 28-day cured samples of WMTA and GMTA (124). Overall, 1-day cured samples of both GMTA and WMTA showed more biocompatibility than the 28-day cured samples. In contrast to these results, another experiment found that 12-day cured GMTA significantly increases cell proliferation in comparison with 1-day cured GMTA (154). Two other studies with human alveolar bone, fibroblast, and macrophage cell cultures showed no difference between GMTA and WMTA in terms of cytotoxicity and cell proliferation (123, 150).

A recent investigation has shown that the survival rate and morphologic appearance of cementoblasts are not affected by low concentration of WMTA (169). However, a high concentration of the material (20 mg/mL) decreased cell viability and inhibited mineralization as well as bone sialoprotein production by cementoblasts.

MTA releases significantly more calcium ions than Dyocal (152). In the absence of MTA, when 0.3 mmol/L of CC is added to the cell culture, the same pattern of cell proliferation is observed. On the basis of these results, the authors concluded that the continuous release of ions from MTA provides an optimum amount of calcium for cell proliferation.

A recent investigation examined the effect of MTA and CH on ST3 fibroblast cells and showed that MTA has a significantly shorter duration of cytotoxicity in comparison to CH (170).

In a human PDL cell culture study on root ends that were filled with MTA or gutta-percha and treated with a CO2 laser, SEM observation indicated no cell attachment to either the laser-irradiated area or gutta-percha (141). In contrast, cell attachment to MTA and the root surface area without laser irradiation was observed.

PDL fibroblasts show enhanced proliferation on MTA and survival on amalgam when compared with gingival fibroblasts (142). The authors also reported that MTA induces an osteogenic phenotype, which reflects up-regulation of the expression of alkaline phosphatase, osteonidogen, osteoectin, and osteopontin. Twenty-four–hour cured MTA shows a more favorable response to PDL fibroblast cell types than freshly mixed MTA (142). On the other hand, WMTA induces proliferation of murine odontoblast-like and undifferentiated pulp cells, with no noticeable difference between fresh and premixed WMTA (146). Investigators reported that WMTA induces more DNA synthesis in both cell types.

In an experiment on the antiproliferative effects of dental materials, Koulaouzidou et al (145) compared MTA, zinc oxide–eugenol (ZOE) cement, and glass ionomer on fibroblast cell lines (L929, BHK21/C13, and RPC-C2A). They determined that MTA exhibits the lowest antiproliferative activity, whereas ZOE has the highest antiproliferative activity.

A study comparing WMTA, Resilon, and gutta-percha on primary osteoblast and osteoclast cultures showed that none of the materials led to any significant osteostel formation (160). Another investigation compared WMTA, Sealapex, and Roth 801 on macrophages and gingival fibroblasts (153). Only WMTA showed no adverse effect on the viability of either cell line, and none of the materials tested increased the release of prostaglandin E2 (PGE2). A recent experiment comparing the cytotoxicity of CH and GMTA (161) demonstrated that CH produces more cytotoxicity and decreases cell metabolic activity approximately 3 times more than GMTA.

By using rat dental pulp cell cultures, Yasuda et al (163) compared MTA, Dyocal, and an adhesive resin cement. Their data indicated that MTA has no cytotoxicity after 72 hours, and it not only significantly increases mineralization by stimulating dental pulp cells but also increases the amount of bone morphogenetic protein-2 (BMP-2) production. In contrast, Dyocal decreases BMP-2 production and increases cell death, whereas dentin adhesive cement has no effect on cytotoxicity and BMP-2 production.

Several cell culture studies have shown production of type I collagen and osteocalcin expression in the presence of MTA (144, 158, 163, 171).

Two recent studies have confirmed cementoconductivity, cementoinductivity, and osteoconductivity of WMTA (169, 171).

Cell culture studies on MTA showed that the cell response to the material depends on many factors such as the cell types and the choice of study duration (139, 142, 154, 155), use of a fresh or cured material (124), frequency of changing the medium (123), the use of direct...
contact or extract of MTA (123, 162), and the concentration of the material in the cell culture media (169).

**Cell Culture and Genotoxicity Studies of Other Types of MTA**

Results of 3 cell culture studies determined that both AGMATA and AWMTA exhibit no cytotoxicity and genotoxicity on various cell lines (172–174). Two other studies confirmed these results and showed that PC and WPC, as well as AMTA, have no cytotoxicity and genotoxicity in concentrations of 1 to 1000 μg/ml for 1-hour exposure at 37°C (175, 176).

De Deus et al (177) showed that both GMA and AMTA significantly inhibit endothelial cell viability during the first 24 hours. However, at 48 and 72 hours, no significant difference was found between control cell cultures and the 2 experimental materials. Two separate investigations indicated that both ProRoot MTA and AMTA have cytotoxic effects on the cell viability of V79 fibroblast (155) and human gingival fibroblasts (159).

A recent cell culture investigation showed that both AWMTA and WMTA are relatively inert and superior in cell viability in comparison to Vitrebond and Super EBA (178). Another study compared GMA with AWMTA in a L929 cell culture and reported that both types of MTA were superior in cytotoxicity to a CH base cement. The major drawback of the study was mixing both types of MTA in a 1:1 ratio of powder to liquid (179). Another cell culture investigation has shown that AMTA had the least cytotoxicity compared with some current pulpotomy agents such as Buckey’s formocresol, CH, and ferric sulfate solution (180).

An investigation that compared AGMATA with AWMTA and castor oil reported no significant difference among these materials; none showed a cytotoxic effect on transfected human pulp cells (181).

On the basis of these studies, it appears that both AMTA and MTA have similar effects on cell cultures.

**Cell Culture Studies of New Compositions of MTA**

Many investigations have tried to change the MTA powder composition or substitute distilled water with other liquids in the MTA mixture (89, 110, 115, 182–188). The rationale for these various combinations includes a possible increase in antimicrobial activity, a decrease in setting time, or improved ease of handling of this material. A number of investigations have been performed to evaluate the cytotoxicity of the new compositions of MTA (189–193).

Mixing WMTA with 0.12% CHX significantly increases mouse fibroblast and macrophage apoptosis in comparison with a mixture of WMTA and sterile water (192). Karijme et al (193) mixed K-Y jelly (Johnson & Johnson) with WMTA powder and examined its cytotoxicity on human PDL cells. Their results showed no significant difference between WMTA mixed with water and WMTA mixed with K-Y jelly. A mixture of 15% Na2HPO4 solution and WMTA cultured on L929 cells showed no significant difference in cell viability after 1 and 7 days (189).

An L929 cell culture investigation tested the effect of various additives such as water, saline, 2% lidocaine, 5% CaCl2, 3% NaOCl gel, and K-Y liquid on set and freshly mixed WMTA and GMA cytotoxicity. Except for 3% NaOCl gel, the rest of these additives had no significant effect on WMTA cytotoxicity for time intervals up to 48 hours (190).

A recent investigation reported that a combination of enamel matrix derivative with MTA improves human dental pulp cell differentiation, alkaline phosphatase activity, dentin sialophosphoprotein, bone sialoprotein, and mineralization (191). The investigators suggested this combination as a pulp capping agent (191).

From the results of these studies, it can be concluded that improving antibacterial properties of MTA when mixed with CH adversely affects the material’s biocompatibility. Comprehensive evaluations should be performed before recommending new compositions for clinical applications. Because responses of various cell types are different to MTA in various cell culture environments, investigators should carefully select cell types that would be in contact with MTA for clinical applications of this material (139, 142, 154, 155).

**Production of Cytokine and Signaling Molecules**

**Cell Culture Studies**. Cell response to the presence of MTA or MTA extracts has been extensively investigated (138, 140, 158, 159, 162, 164–166, 194–202). Up-regulation of various types of cytokines and biologic markers has been reported in the presence of MTA in several cell culture studies when compared with control or other tested materials. These cytokines and biologic markers include interleukin (IL)-1α (164, 195), IL-1β (164, 194, 195), IL-2 (198), IL-4 (198), IL-6 (164, 194–196, 205), IL-8 (196), IL-10 (198), IL-18 (194), osteocalcin (138, 158, 171, 194, 195), alkaline phosphatase (138, 171, 191), bone sialoprotein (171), osteopontin (142, 171), and BMP-2 (159).

In an investigation on cytokine up-regulation, 3 variants of MTA were compared with Dycal, dental plaster, HA, and Biogran. In contrast to the findings of Koh et al (164, 195), there was no evidence of IL-1α expression in the cell culture (196, 205).

Huang et al (198) compared the effect of a CH-based material (Life), Super EBA, and MTA on inflammatory cytokines. Their results determined that the amount of IL-4 and IL-10 is significantly greater in the presence of MTA than in the presence of the other 2 materials.

Separate studies have shown that macrophage colony-stimulating factor up-regulation is not specific to MTA, and its production occurs in the presence of other dental materials (164, 196). Guven et al (159) found no significant difference between the control and GMA group when they compared the up-regulation of transforming growth factor—β1 (TGF-β1) derived from human gingival fibroblasts.

Tomson et al (200) investigated the effect of soluble components of set and setting WMTA and GMA on the release of signaling molecules. Their results showed that both types of MTA liberate glycosaminoglycans and noncollagenous proteins, adrenomedullin (ADM), and TGF-β1. GMA liberates more ADM, whereas WMTA liberates more TGF-β1.

In contrast to the above-mentioned experiments, 2 investigations revealed that MTA does not influence cytokine production when mouse fibroblasts and macrophages are used (166, 199). Another experiment reported that MTA has no influence on M1 and M2 macrophage phagocytosis (201).

Pistorius et al (140) used gingival fibroblasts and compared MTA with amalgam and an inert titanium alloy to measure the amount of cellular PGE2 synthesis. Their results showed that amalgam down-regulates PGE2 synthesis, whereas titanium alloy and MTA up-regulate PGE2.

In a cell culture investigation, MTA up-regulated PGE2 production and increased cyclooxygenase-2 and nitric oxide synthase mRNA expression via activation of the nuclear factor kappa B signaling pathway (204). The mitogen-activated protein kinase (MAPK) pathway in part regulates cellular growth, division, differentiation, and death. By using human osteosarcoma cell line U2OS, Huang et al (197) determined that in the presence of MTA, extracellular regulated kinases (ERKs) are increased in cell culture. Suppression of the ERK pathway by the addition of an ERK inhibitor suggests that MTA’s effect on osteosarcoma cells is induced by a cascade of ERK MAPK.

Tomson et al (200) compared the release of dentin components when in contact with solubilized components of GMA, WMTA, and CH. The results of this study indicated that CH and GMA release more ADM than WMTA, whereas TGF-β1 is up-regulated in WMTA samples in comparison to GMA and CH samples.
Recently, Simon et al (202) reported the strong expression of type I collagen and dentin sialoprotein (DSP) when media containing extracts of MTA were added to pulp-derived cell cultures. Meanwhile, Laurent et al (162) observed nestin expression and formation of a mineralized matrix after adding a medium containing MTA extracts to cell cultures. The presence of DSP in dentin bridges after pulp capping has also been confirmed (205).

Another cell culture study on human alveolar osteoblasts reported the expression of Runx-related transcription factor 2 (essential for osteoblast differentiation and bone formation) in the presence of both types of MTA and WMTA mixed with either sterile water or anesthetic solution (206).

An investigation using rat pulp cells and immunohistochemical method compared the effect of WMTA with Dycal (207). Most of the cells cultured with WMTA revealed heat-shock protein 25 as a marker for odontoblast differentiation during pulp healing and higher mRNA expression for both DSP and heat-shock protein 25.

Another investigation on mouse preosteoblasts exhibited production of IL-6 in the presence of both types of MTA and WMTA (203).

Conflicting results among the studies in regards to the effect of MTA on cytokine production can be attributed to the type of cell culture, the type of MTA and the cytokines investigated (140, 164–166, 194–202). Most in vitro investigations have confirmed MTA as a cytokine and signaling molecule productive material.

Animal Studies. Andelin et al (205) investigated the presence of DSP after pulp capping with either MTA or BMP-7. Their results revealed more staining for DSP in the calcified bridge of teeth that were capped with MTA than with BMP-7. On the basis of the DSP-positive staining of MTA-capped pulps, the authors concluded that hard tissue produced by MTA has a closer similarity to dentin.

Ham et al (208) compared CH and MTA for expression of BMP-2 after apericition of immature teeth in monkeys. Both materials produced similar BMP-2 expression. Kurata et al (209) showed up-regulation of osteopontin, nestin, and 5-bromo-2-deoxyuridine assay (BrdU) immunopositive cells after pulp capping with WMTA in rats.

Studies showed that an increased concentration of some cytokines and signaling molecules can cause adverse effects that include cell apoptosis (209–213). It is therefore important that the release of bioactive signaling molecules from the dentin matrix occur at an appropriate amount, rate, and ratio (200). Investigations showed that HA forms over MTA after the contact of this material with a simulated tissue fluid (100, 101). HA formation should be encouraged HA formation (214, 215).

Human Study

Min et al (216) capped human third molar pulps with MTA or Dycal and examined dentin bridge formation, expression of DSP, and heme oxygenase-1 in the dental pulp. Results indicated the presence of significantly more positive immunostaining in the MTA group than in the Dycal group for DSP and heme oxygenase-1.

Both animal and human investigations have confirmed the encouraging role of MTA on the production of signaling molecules.

Production of Cytokines and Signaling Molecules by Other Types of MTA

Macrophages produce different types of cytokines and inflammatory products. A cell culture study evaluated the response of 2 mouse macrophage cell lines to GMTA and AMTA (199). Results indicated the absence of cytokine up-regulation by both cell lines.

Gomes et al (217) investigated the effect of AMTA on polymorphonuclear (PMN) migration by injection of AMTA suspension into the peri-tissue of mice. Their results determined that in the presence of MTA, mast cells and macrophages produce many cytokines such as IL-1, IL-4, macrophage inflammatory protein-2 (MIP-2), and LT-B4 that mediate PMN migration in a time-dependent and dose-dependent manner.

Several substances have been known as vaccine adjuvants. Immune adjuvants induce antibody response against protein antigens (218). Aluminum hydroxide is the only adjuvant approved for human use by the U.S. Food and Drug Administration. Because aluminum is one of the elements that is released from MTA in direct contact with tissue synthetic fluid (100), an animal study evaluated the effect of MTA on immunoglobulin G production against F. nucleatum and Pepto-streptococcus anaerobius (219). Because the activation of T-helper cells is necessary for induction of specific responses against protein antigens, the investigators assessed cytokines released from memory T cells after a primary challenge with F. nucleatum or P. anaerobius.

They reported that AMTA had little or no effect on anti-inflammatory or bone-destructive cytokines such as receptor activator for nuclear factor kappa B ligand (RANKL), IL-10, and tumor necrosis factor–α, whereas the material exhibited an adjuvant effect against F. nucleatum.

Guven et al (159) compared the effects of GMTA and AMTA on TGF-β1 and BMP-2 production by human gingival cells; they showed that both types of MTA stimulate cell growth. The amount of TGF-β1 at 24 and 72 hours was higher in the AMTA group than in the GMTA group. In contrast, BMP-2 levels were higher in the GMTA group at 24 hours compared with AMTA. As previously indicated, higher levels of TGF-β1 might have a down-regulatory effect on the proliferation of some cell types (212).

Silva et al (220) evaluated remaining pulp tissue after partial pulpotomy in murine teeth for mRNA expression in the presence of various inflammatory cytokines. Their results indicated that AGMTA down-regulates mRNA expression for CCL5, IL-1α, and interferon-γ. On the basis of these results, it appears that AGMTA has anti-inflammatory effects.

Subcutaneous Reaction

Many studies have compared the subcutaneous reaction of experimental animals to MTA and other materials such as amalgam, CH, Super EBA, various root canal sealers, IRM, ZOE, cold ceramic and ethoxybenzoic acid (EBA) (132, 151, 221–229). Some studies reported a calcific tissue response to MTA specimens (221–226). Most of these studies have used the Von Kossa technique to detect the presence of calcified structures (221, 223–225). Their results showed the presence of Von Kossa-positive structures around MTA after 1 week. Larger calcified structures were present in MTA specimens at longer time intervals (221, 224). Both GMTA (221–226) and WMTA (225) show calcified structures around the implanted tubes. A similar subcutaneous response is reported for PC, CH, and MTA (223). Holland et al (225) suggested that all tested materials produce calcified tissue through the same phenomenon, which is mediated by calcium released from the materials when carbon dioxide is present in tissues. There are some studies that have not reported the formation of calcified structures around implanted MTA (151, 228–230) despite using the Von Kossa technique (231). Moreton et al (222) determined that GMTA produces significantly more inflammation in comparison to EBA. One study revealed no significant difference between MTA and amalgam at early intervals (228), in contrast with another study that showed less inflammation around GMTA samples in comparison to amalgam specimens at early time intervals (229). Conflicting reports are available regarding subcutaneous reactions to WMTA and GMTA (229, 230). In one study, after 3 days, WMTA caused significantly less inflammation in comparison with GMTA; in contrast, after 1 week, GMTA samples showed less...
inflammation than WMTA (229). In another study, a group of investigators from the same institution found no difference between the inflammatory response to GFTA and WMTA (230). The authors of these studies attributed the conflicting results to using different criteria for histologic evaluation.

A recent investigation showed similar mild to moderate tissue reaction when PC and WMTA were implanted in the subcutaneous tissue of rats (232). Another study reported more tissue necrosis and giant cell formation around MTA at 7 and 14 days after implantation in comparison to CPM, which showed more eosinophils over the same time periods (233). Another recent investigation added 2.5 wt% Na₂HPO₄ to WMTA and reported a significantly lower inflammatory reaction in comparison to WMTA when the materials were implanted subcutaneously (234).

Another investigation compared subcutaneous reaction to AMTA, Sealapex, and Endo CPM sealer (MTA sealer by an Argentine manufacturer). Results showed that except for early interval (7 days), no significant difference was seen between both types of MTA, which were more biocompatible than Sealapex. Calcified precipitations were observed around all implanted MTA samples (235).

These studies showed that subcutaneous responses to MTA range from necrosis to dystrophic calcification. In addition, at first, MTA produces a moderate to severe subcutaneous response, which subsides at longer time intervals.

Intraosseous Implantation

In a preliminary investigation, Torabinejad et al (236) examined the tissue reaction to implanted Super EBA and MTA in guinea pig mandibles and reported that bone reaction to MTA is slightly milder than to Super EBA. In another study, these researchers investigated the reaction of guinea pig tibias to amalgam, Super EBA, IRM, and MTA and reported that MTA had the most favorable response among the tested materials (237).

Sousa et al (238) compared the osseous reaction of guinea pigs to ZOE, light-cured composite, and MTA. Four weeks after implantation, whereas the MTA response was rated as none to slight, ZOE showed moderate chronic inflammatory infiltrate near the implanted material. After 12 weeks, all tested materials exhibited biocompatible characteristics.

Moreton et al (222) examined subcutaneous and intraosseous reaction to implantation of MTA and EBA. Although the pattern of osteogenesis was similar at early time intervals, at the 60-day interval, they observed greater osteogenesis around EBA. This study reported that both materials are osteoconductive. Cintra et al (239) analyzed the alveolar bone response of rats to MTA and a new CH-containing sealer and found no significant difference between the 2 test materials.

Osseous reaction investigations have shown that the bone response to MTA is relatively mild with minor inflammation.

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