REVIEW

Mineral trioxide aggregate: a review of the constituents and biological properties of the material

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Abstract

Camilleri J, Pitt Ford TR. Mineral trioxide aggregate: a review of the constituents and biological properties of the material. *International Endodontic Journal*, **39**, 747–754, 2006.

This paper reviews the literature on the constituents and biocompatibility of mineral trioxide aggregate (MTA). A Medline search was conducted. The first publication on the material was in November 1993. The Medline search identified 206 papers published from November 1993 to August 2005. Specific searches on constituents and biocompatibility of mineral trioxide aggregate, however, yielded few publica-

Introduction

Mineral trioxide aggregate (MTA) was developed at Loma Linda University in the 1990s as a root-end filling material. It received acceptance by the US Federal Drug Administration and became commercially available as ProRoot MTA (Tulsa Dental Products, Tulsa, OK, USA). Until recently, two commercial forms of MTA have been available (ProRoot MTA) in either the grey or white forms. Recently MTA-Angelus (Angelus Soluções Odontológicas, Londrina, Brazil) has become available. The use of MTA as a root-end filling material was identified because the material is a hydraulic cement that sets in the presence of water. Much work has been published on the biocompatibility tions. Initially all abstracts were read to identify which fitted one of the two categories required for this review, constituents or biocompatibility. Based on this assessment and a review of the papers, 13 were included in the constituent category and 53 in the biocompatibility category. Relatively few articles addressed the constituents of MTA, whilst cytological evaluation was the most widely used biocompatibility test.

Keywords: biocompatibility, constituents, mineral trioxide aggregate.

Received 5 January 2006; accepted 20 February 2006

of this material, but relatively little on its constituents. A literature review was thus undertaken to scrutinize publications dealing with these two issues. The literature review was performed using a Medline electronic search. The cut-off date was the end of August 2005. The key words that were used and the results of this search are shown in Table 1.

Constituents

The number of papers reviewed was 13. A patent was taken out for MTA in 1995 (Torabinejad & White 1995). This states that MTA consists of 50–75% (wt) calcium oxide and 15–25% silicon dioxide. These two components together comprise 70–95% of the cement. When these raw materials are blended they produce tricalcium silicate, dicalcium silicate, tricalcium aluminate and tetracalcium aluminoferrite. On addition of water the cement hydrates to form silicate hydrate gel. The patent states that MTA is a Type 1 ordinary

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Keyword	Number of publications	Earliest paper	Latest paper
Mineral trioxide aggregate	206	November 1993	August 2005
Mineral trioxide aggregate composition	7	July 1995	February 2005
Mineral trioxide aggregate constitution	1	April 2005	-
Mineral trioxide aggregate biocompatibility	19	November 1995	August 2005
Mineral trioxide aggregate cells	37	October 1995	August 2005
Mineral trioxide aggregate tissue response	10	December 1995	June 2005
Mineral trioxide aggregate properties	28	July 1995	July 2005

Table 1 The keywords searched onMedline at the end of August 2005 andthe number of publications found

Portland cement (American Society for Testing Materials, http://www.astm.org) with a fineness (Blaine number) in the range of $4500-4600 \text{ cm}^2 \text{ g}^{-1}$. A radiopacifier (bismuth oxide) is added to the cement for dental radiological diagnosis (Torabinejad & White 1995). Although the patent reported that MTA is essentially ordinary Portland cement, few studies have been conducted on the comparative constituents of Portland cement and MTA.

The first research paper on the chemistry of Portland cement that had potential for dental use demonstrating the similarity of grey MTA (Loma Linda University, Loma Linda, CA, USA) to Portland cement was published in 2000 (Estrela et al. 2000). A study comparing white MTA (White MTA, Dentsply; Tulsa Dental Products) to white Portland cement showed the cements to have similar constituent elements except for the bismuth oxide in the MTA (Asgary et al. 2004). No difference was found in the presence of 14 elements between MTA (ProRoot MTA) and Portland cement except for the bismuth which was present in MTA (Funteas et al. 2003). Investigations of the chemical and physical, surface and bulk material properties of Portland cement CEM I (Teutonia Portlandzement, EN 197-1-CEM I 32,5 R; Teutonia Zementwerk. Hannover. Germany). CEM II (Felsenfest Portlandkalksandsteinzement, CEM II/A-LL 32,5 R EN 197-1; Spenner Zement, Erwitte, Germany) and MTA Dentsply DeTrey (Konstanz, Germany; batch: 02093081) have shown that MTA had less gypsum. Decreased gypsum causes a reduction in setting time of the cement (Lea 1998). Other findings included a higher level of toxic heavy metals and aluminium in Portland cement CEM I (Teutonia Portlandzement, EN 197-1-CEM I 32,5 R; Teutonia Zementwerk), CEM II (Felsenfest Portlandkalksandsteinzement, CEM II/A-LL 32,5 R EN 197-1; Spenner Zement) and a difference in the particle size distribution. Portland cement exhibited a wide range of sizes whereas MTA Dentsply DeTrey (batch: 02093081) showed a uniform and smaller particle size. Thus, MTA cannot be substituted by a cheaper Portland cement (Dammaschke et al. 2005). Both MTA (Pro-Root) and Portland cement (Quikrete, Columbus, OH, USA) had similar physical, chemical and biological properties, and the biocompatibility of both materials was due to the similarity in constituents (Saidon et al. 2003). The production of calcium hydroxide as a byproduct of the hydration reaction of MTA (ProRoot, White MTA) has been published (Camilleri et al. 2005a). The biological response to MTA (ProRoot MTA), had been likened to that of calcium hydroxide (Holland et al. 1999a) and it was postulated that the mechanisms of action were similar (Holland et al. 2001a). It has been reported that MTA (MTA Angelus), released calcium ions and promoted an alkaline pH (Duarte et al. 2003, Santos et al. 2005). The physicochemical basis for the biological properties of MTA (ProRoot), had recently been attributed to the production of hydroxyapatite when the calcium ions released by the MTA came into contact with tissue fluid (Sarkar et al. 2005). Although the release of calcium ions had been reported (Duarte et al. 2003, Lee et al. 2004, Santos et al. 2005, Sarkar et al. 2005), none of the publications demonstrated the origin of the calcium ions. Camilleri et al. (2005a) showed that MTA (ProRoot, White MTA) and Portland cement (Italcementi spa, Bergamo, Italy) had the same constituent elements, except for the bismuth oxide present in MTA. Thus, on hydration both MTA and Portland cement would produce calcium silicate hydrate gel and calcium hydroxide. This would explain the similar mode of tissue reaction to MTA and calcium hydroxide reported previously (Holland *et al.* 1999a, 2001a).

The first research paper on the constituents of MTA (Loma Linda University) in 1995 reported the presence of calcium phosphate (Torabinejad *et al.* 1995a). However, Asgary *et al.* (2005) using energy dispersive analysis with X-ray (EDAX) could not detect the presence of phosphorus. Camilleri *et al.* (2005a) also showed MTA (ProRoot) did not contain phosphorus. The samples used by Torabinejad *et al.* (1995a) were contaminated by prior immersion in phosphate solution. The powder of MTA was composed mainly of tricalcium and dicalcium silicates with bismuth oxide also present for radiopacity (Camilleri *et al.* 2005a). X-ray diffraction (XRD) analysis of the cement showed that the material was completely crystalline, with definite peaks attributable to specific phases (Fig. 1).

Two forms of MTA (Dentsply) are available on the market, grey and white. The difference between them has been reported to be in the concentrations of aluminium, magnesium and iron compounds (Asgary *et al.* 2005). The white MTA lacks the aluminoferrite phase that imparts the grey colour to grey MTA (Camilleri *et al.* 2005a).

Biocompatibility

The biocompatibility of MTA has been investigated in a number of ways, using cell expression and growth,

subcutaneous and intra-osseous implantation and direct contact with dental tissues *in vivo*.

Cytological investigation of biocompatibility

The number of papers reviewed was 27. The cell type, contact time and method of assessment of the various studies are shown in Table 2. Seven studies used more than one cell type to study the behaviour of MTA. Most of the cell studies showed good cell growth over MTA with the formation of a cell monolayer over the material. In comparison Haglund *et al.* (2003) showed that MTA (ProRoot) was cytotoxic to both macrophages and fibroblasts. Cell studies test the cytotoxicity *in vitro* but cannot examine the complex interactions between materials and host. Contact time was generally less than 7 days. Only one study evaluated biocompatibility of MTA 28 days following its setting (Camilleri *et al.* 2004).

The most commonly used method for evaluation of cell proliferation was scanning electron microscopy (SEM) followed by enzyme assay. The main issue with the use of SEM in cell culture studies involving MTA was the material reaction with the preparation media. Calcium hydroxide which is a by-product of calcium silicate hydration reacted with phosphate-buffered solutions producing calcium phosphate crystals over the material surface (Camilleri *et al.* 2005a). In addition, critical point drying, which is an essential step for material preparation prior to viewing under SEM



Figure 1 X-ray diffraction analysis of mineral trioxide aggregate (MTA) powder showing the main constituent elements of the material (Camilleri *et al.* 2005a).

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		Contact		
Author and date	Cell type	time	Method of	
		(days)	assessment	Biocompatibility
Torabinejad <i>et al.</i> (1995)	Mouse L929	1	Agar overlay	Biocompatible
Torabinejad <i>et al.</i> (1995)	Mouse L929	1	Radiochromium	Biocompatible
			release	
Koh <i>et al.</i> (1997)	MG 63	6	SEM	Biocompatible
Koh <i>et al.</i> (1998)	MG 63	1–7	SEM	Biocompatible
Osorio <i>et al.</i> (1998)	Gingival fibroblasts, L929	-	Enzyme assay	Biocompatible
Mitchell <i>et al.</i> (1999)	MG 63	2, 4, 7	SEM	Biocompatible
Keiser <i>et al.</i> (2000)	Periodontal ligament	1	Enzyme assay	Biocompatible
	fibroblasts			
Zhu <i>et al.</i> (2000)	HOBs	1	SEM	Biocompatible
Abdullah <i>et al.</i> (2002)	SaOS-2	1, 2, 3	SEM	Biocompatible
Saidon <i>et al.</i> (2003)	Mouse L929	3	SEM	Biocompatible
Haglund <i>et al.</i> (2003)	Mouse L929,macrophages	3	SEM	Not biocompatible
Huang <i>et al.</i> (2003)	U2OS	-	Enzyme assay	Biocompatible
Perez et al. (2003)	Osteoblasts, MG 63	6, 9, 13	SEM	Not biocompatible
Pistorius <i>et al.</i> (2003)	Periodontal ligament,	4	Enzyme assay	Biocompatible
	Gingival fibroblasts			
Camp <i>et al.</i> (2003)	Gingival fibroblasts	1, 2, 3	Fluorescence	Biocompatible
Asrari and Lobner (2003)	Neurons	12–14	Enzyme assay	Biocompatible
Balto (2004)	Periodontal ligament	1	SEM	Not biocompatible
	fibroblasts			
Bonson <i>et al.</i> (2004)	Periodontal ligament,	15	Fluorescence	Biocompatible
	gingival fibroblasts			
Pelliccioni et al. (2004)	SaOS	1, 3	Enzyme assay	Biocompatible
Camilleri <i>et al.</i> (2004)	SaOS	1, 5, 7	SEM	Biocompatible
Camilleri <i>et al.</i> (2005b)	HOS	1–7, 1–21	Enzyme assay	Not biocompatible ^a
Huang <i>et al.</i> (2005)	U2OS	1, 2	Enzyme assay	Biocompatible
Koulaouzidou <i>et al.</i> (2005)	L929, BHK21/C13 fibroblasts	1, 2	Enzyme assay	Biocompatible
Hernandez <i>et al.</i> (2005)	Mouse fibroblasts, macrophages	1	Flow cytometry	Biocompatible
Nakayama <i>et al.</i> (2005)	Rat bone marrow cells	3	SEM, TEM	Biocompatible ^b
Moghaddame-Jafari et al. (2005)	Mouse odontoblastic cells	1	Flow cytometry	Biocompatible
Ribeiro <i>et al.</i> (2005)	Mouse lymphoma cells	-	Trypan blue exclusion test	Biocompatible

Table 2 Cell type, contact time ar	d method of assessment	used in cell culture	studies conducted on MTA
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SEM: Scanning electron microscopy; TEM: transmission electron microscopy.

^agood cell growth observed on material extracts but not on the material itself.

^bmaterial does not inhibit cell growth but suppresses differentiation of osteoblast-like cells.

caused cement carbonation (Camilleri *et al.* 2004). Enzyme assay, which is the next most common method, would seem to be more reliable as it avoids material preparation. Enzyme assay measures the metabolic activity of cells grown over the materials under study.

Few studies have been published on the material extracts of MTA and this may reflect an incomplete understanding of the chemical constitution of the material. As MTA is calcium silicate cement, its biocompatibility may be questioned. The observed biocompatibility of MTA could arise from reaction by-products. Good cell growth was demonstrated on material extracts when tested using methyltetrazo-lium (MTT) assay (Keiser *et al.* 2000, Huang *et al.*

2003, Camilleri *et al.* 2005b). The agar overlay method and radiochromium release methods have only been reported in one study (Torabinejad *et al.* 1995b).

In other experiments cytokine expression, primarily interleukin (IL), has been used as a marker for cell differentiation. MTA induced expression of inflammatory cytokines from bone cells and exhibited good cell attachment. MTA (ProRoot) caused an increase in IL-4 and IL-10 expression (Huang *et al.* 2005). Increase in IL-6 and IL-8, with no increase in levels of IL-1 α and IL-1 β was demonstrated in the presence of MTA (Loma Linda University; Mitchell *et al.* 1999). Conversely, Koh *et al.* (1997, 1998) showed a rise of both IL-1 α and IL-1 β together with IL-6 after the cells were in contact

750

with the material for 6 days. Osteocalcin levels were also increased in the presence of MTA (ProRoot; Thomson *et al.* 2003). There was a negligible increase in levels of cytokines with the other materials used as controls. MTA (ProRoot) also preferentially induced alkaline phosphatase expression and activity in both periodontal ligament and gingival fibroblasts (Bonson *et al.* 2004). In general, MTA elicited an inflammatory cytokine response. In contrast, no cytokine production was observed in one study. The lack of cytokines was accompanied by cell lysis and protein denaturing around the MTA (Haglund *et al.* 2003). Cell culture experiments are easier, quicker and cheaper than other methods used to test biocompatibility.

Subcutaneous and intra-osseous implantation

The number of papers reviewed was 11. Histological evaluation of tissue reaction to MTA has been evaluated by subcutaneous and intra-osseous implantation of the materials in test animals. Subcutaneous implantation in rats showed that MTA (ProRoot) initially elicited severe reactions with coagulation necrosis and dystrophic calcification (Moretton et al. 2000, Yaltirik et al. 2004). The reactions, however, subsided with time. Osteogenesis was not observed with MTA (Loma Linda University) upon subcutaneous implantation indicating that the material was not osteo-inductive in this tissue. Implantation of MTA in rat connective tissue (Holland et al. 2001a, 2002) and dog (Holland et al. 1999b, 2001b) produced granulations that were birefringent to polarized light and an irregular structure like a bridge was observed next to the material. Reactions to intraosseous implants of MTA (ProRoot) were less intense than with subcutaneous implantation. Osteogenesis occurred in association with these implants (Moretton et al. 2000). With intra-osseous implantation the tissue reactions to the material subsided with time over a period of 12 weeks (Sousa et al. 2004). MTA (ProRoot) implantation in the mandible of guinea pigs resulted in bone healing and minimal inflammatory reactions (Saidon et al. 2003). The tissue reaction to MTA (Loma Linda University) implantation was the most favourable reaction observed in both tibia and mandible of test animals, as in every specimen, it was free of inflammation. In the tibia, MTA (Loma Linda University) was the material most often observed with direct bone apposition (Torabinejad et al. 1995c, 1998). In another study MTA (ProRoot,) was shown to be biocompatible and did not produce any adverse effect on microcirculation of the connective tissue (Masuda et al. 2005).

Periradicular tissue reactions

The number of papers reviewed was eight. When MTA (Loma Linda University) has been used for root-end filling in vivo, less periradicular inflammation was reported compared with amalgam (Torabinejad et al. 1995d). In addition, the presence of cementum on the surface of MTA (Loma Linda University) was a frequent finding (Torabinejad et al. 1997). It induced apical hard tissue formation with significantly greater consistency, but not quantity, in a study of three materials, although the degree of inflammation was not significantly different between the groups (Shabahang et al. 1999). Again, MTA (ProRoot) supported almost complete regeneration of the periradicular periodontium when used as a rootend filling material on noninfected teeth (Regan et al. 2002). The most characteristic tissue reaction to MTA was the presence of organizing connective tissue with occasional signs of inflammation after the first postoperative week (Economides et al. 2003). Early tissue healing events after MTA root-end filling were characterized by hard tissue formation, activated progressively from the peripheral root walls along the MTA-soft tissue interface (Economides et al. 2003). Both fresh and set MTA (ProRoot) caused cementum deposition when used after apical surgery (Apaydin et al. 2004). In addition, MTA (ProRoot) showed the most favourable periapical tissue response of three materials tested, with formation of cemental coverage over MTA (Baek et al. 2005). Use of MTA (ProRoot) in combination with calcium hydroxide in one study has shown that the periodontium may regenerate more quickly than either material used on its own in apexification procedures (Ham et al. 2005). All these studies in vivo have shown a favourable tissue response to MTA.

Pulpal reactions

The number of papers reviewed was seven. MTA used for pulp capping or partial pulpotomy stimulates reparative dentine formation. MTA-capped pulps showed complete bridge formation with no signs of inflammation (Pitt Ford *et al.* 1996, Tziafas *et al.* 2002, Andelin *et al.* 2003, Faraco & Holland 2004). The same results were obtained when MTA (Loma Linda University) was placed over pulp stumps following pulpotomy (Holland *et al.* 2001b). This hard tissue bridge formed over the pulp was documented after using ProRoot MTA and MTA Angelus and both grey and white Portland cement (grey: Votorantim-Cimentos, Saõ Paulo, Brazil and white: Irajazinho; Votorantim-Cimentos; Menezes *et al.* 2004). The incidence of dentine bridge formation was higher with MTA (Loma Linda University) than with calcium hydroxide (Faraco & Holland 2001).

Comparison of MTA and Portland cement

Both MTA and Portland cement have been shown to be biocompatible. The biocompatibility of Portland cement was tested using a cell culture study and the material allowed complete cell confluence (Abdullah *et al.* 2002). Implantation of Portland cement and MTA (Loma Linda University and ProRoot respectively) in rat connective tissue and mandibles of guinea pigs showed that both materials were biocompatible (Holland *et al.* 2001a, Saidon *et al.* 2003). Histological evaluation of pulpotomies in dogs using both MTA (ProRoot and MTA) and Portland cement (Irajazinho; Votorantim-Cimentos) showed that both types of material were equally effective as pulp protection materials (Menezes *et al.* 2004).

Comparison of grey and white materials

Most studies have been performed with grey MTA, as white MTA was introduced more recently. There has been some conflicting data on the biocompatibility of grey and white MTA. Holland et al. (1999a,b, 2001a,b,c, 2002) showed that both types (Loma Linda University) were biocompatible when implanted in rat connective tissue; however, the materials were not tested in the same experiment. In contrast, Perez et al. (2003) using a different type of cell showed that white MTA (White MTA) was not as biocompatible as the grey version (ProRoot) and postulated that the difference might be due to surface morphology of the materials. Camilleri et al. (2004) showed no difference between the two variants (Dentsply), however, both materials exhibited reduced cell growth when allowed to set for 28 days. Thus, aged material may not be as biocompatible as freshly mixed material. This could indicate that biocompatibility might be related to the amount of calcium hydroxide produced during the hydration reaction.

Conclusions

In the past 10 years, 13 studies have been published on the constituents, while 53 studies have been published on the biocompatibility of MTA: 27 studying the material to host interactions at a cellular level and 26 using histological methods to study host tissue reactions. Collectively, these studies have shown that MTA is biocompatible. There has, however, been a lack of knowledge and understanding about the constituents of the material and its interaction with the surrounding tissues. Recent studies on the material constituents have clarified that MTA is a silicate cement rather than an oxide mixture.

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754

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