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Biocompatibility of root-end filling materials: recent update

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The purpose of a root-end filling is to establish a seal between the root canal space and the periradicular tissues. As root-end filling materials come into contact with periradicular tissues, knowledge of the tissue response is crucial. Almost every available dental restorative material has been suggested as the root-end material of choice at a certain point in the past. This literature review on root-end filling materials will evaluate and comparatively analyse the biocompatibility and tissue response to these products, with primary focus on newly introduced materials. (*Restor Dent Endod* 2013;38(3):119-127)

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Introduction

Surgical root canal therapy is often the indicated treatment when nonsurgical retreatment has failed or cannot be performed. Surgical root canal therapy usually involves resecting a portion of the root apex and preparing and filling a cavity in the root-end. The purpose of the retrograde filling is to seal the canal in order to prevent passage of bacteria or their toxins from the canal space into periradicular tissues. Practically every restorative material used on the crowns of teeth has been tried as a root-end filling material.[1] Unlike orthograde root canal filling materials, root-end filling materials are placed in direct contact with vital periapical tissues. The tissue response to these materials, therefore, becomes important and may influence the outcome of surgical endodontic treatment.

The deposition of cementum on the cut root face is considered a desired healing response and a prerequisite for the reformation of a functional periodontal attachment.[2] Cementum deposition occurs from the circumference of the root-end and proceeds centrally toward the resected root canal. The cementum provides a 'biological seal,' in addition to the 'physical seal' of the root-end filling, thereby creating a 'double seal.'[3]

This paper deals with the comprehensive literature review about the biocompatibility of endodontic root-end filling materials. This toxic response may be investigated on several levels, i.e. using cells and tissue from animals, animal studies and observations from clinical investigations addressing suitability of the material.[4]

Review

Materials used for root-end filling

A plethora of restorative and endodontic materials have been suggested over the years for root-end filling, including amalgam, zinc oxide eugenol (ZOE) cement (plain or reinforced), ethoxy benzoic acid (EBA) and Super EBA cement, polycarboxylate cement, glass ionomer cement (GIC), gutta-percha (GP, burnished or injectable), composite resin, cyanoacrylate glue, Teflon, gold foil, titanium screws, Cavit, and a number of newly introduced materials.[5,6] Unfortunately, the ideal retrograde filling material is yet to be found.

1. Amalgam

Traditionally, amalgam was the material of choice for root-end fillings.[7-9] The biocompatibility of amalgam is cited as a current issue of concern in dentistry.[10] Many *in vivo* usage studies in animals have reported unfavorable tissue response to amalgam.[11-19] The use of amalgam as a root-end filling material can now be confined to history.

2. Gutta-percha (GP)

When GP is used as a root-end filling material, it absorbs moisture from periapical tissues because of its porous nature. It expands initially then contracts.[20] Pitt Ford *et al*. found that the tissue response to GP with zinc oxide root canal sealer was characterized by little or no inflammation.[21] In a comparative *in vivo* study on bone defect regeneration, most histological sections using GP as retrograde material showed signs of non-healing with lack of cortical bone and high level of inflammatory infiltration.[22]

3. Zinc oxide eugenol (ZOE) cement

The material was considered to have good handling properties and postoperative results. However, the original ZOE cements were weak and likely to be absorbed over a period of time.[23-25] Therefore, it was unsuitable for long-term use. Consequently, modified forms of ZOE cements were suggested.[26,27]

Two approaches were adopted to improve the physical properties of ZOE cements:

(i) The partial substitution of eugenol liquid with EBA and the addition of fused quartz or aluminum oxide to the powder to give an EBA cement, Super EBA cement (Staident International Ltd., Staines, UK)

(ii) The addition of polymeric substances to the powder,
   (a) polymethymethacrylate to the powder, Intermediate Restorative Material (IRM, DENTSPLY DeTrey GmbH, Konstanz, Germany)
   (b) polystyrene to the liquid, Kalzinol (DENTSPLY DeTrey GmbH)

Eugenol is the major cytotoxic component in ZOE cements.[28] Zinc released from these cements is considered to be partly responsible for the prolonged cytotoxic effect.[29] Results of a comparative study showed no cell growth in the originally seeded cells in fresh IRM.[30] Recent studies have shown IRM to be more toxic than comparative materials.[22,31] In a research that investigated cellular attachment to root-end filling materials as a measure of the biocompatibility of the materials, both IRM and Super EBA rendered poor attachment.[32]

4. Glass ionomer cement (GIC) and related materials

GIC have been suggested as an alternative root-end filling material.[33-35] Biocompatibility studies exhibited evidence of initial cytotoxicity with freshly prepared samples.[36,37] Toxicity decreases as the setting occurs.

5. Composite resins and resin-ionomer hybrids

The biocompatibility of composite resin is influenced by the amount and nature of its leachable components.[38] The healing response of the periradicular tissues to composite resins in general appears to be very diverse, ranging from poor to good depending on the type of material used.[39,40] Two composite resin-based materials, Retroplast (Retroplast Trading, Rørvig, Denmark) and Geristore (Den-Mat, Santa Maria, CA, USA) have been advocated for use as root-end filling materials. Results of the observational studies examining various root-end filling materials on gingival fibroblast cells showed greater cell attachment to Geristore in comparison to mineral trioxide aggregate (MTA).[41,42] Other *in vitro* interpretations indicate that Geristore is less cytotoxic to gingival fibroblasts in comparison to MTA, GIC and IRM.[31,42] Considering cellular attachment, a more sensitive indicator of cytotoxicity, a recent study concluded that the best cellular attachment was present in MTA and Geristore while IRM, Super EBA, Ketac Fil and Retroplast showed poor cellular attachment among the materials investigated.[32]

6. Diaket

Diaket (3M ESPE GmbH, Seefeld, Germany) a polyvinyl resin, has been advocated for use as a root-end filling material.[43] When Diaket was used as a root canal sealer, biocompatibility studies showed that it was cytotoxic in cell culture and generated long-term chronic inflammation in osseous and subcutaneous tissues.[44-46] However, when mixed at the thicker consistency advocated for use as a root-end filling material, Diaket has shown good biocompatibility with osseous tissues.[47]

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7. Mineral trioxide aggregate (MTA)

MTA was developed as a new root-end filling material at Loma Linda University, California, USA. Unlike a number of dental materials that are not moisture-tolerant, MTA actually requires moisture to set.[6] In a review article regarding concepts in endodontic surgery, Kim and Kratchman stated that MTA is the most biocompatible root-end filling material and can be used with predictable outcomes in endodontic surgery.[48] A comprehensive literature review affirmed that the main drawbacks of MTA include a discoloration potential, presence of toxic elements in the material composition, difficult handling characteristics, long setting time, high material cost, an absence of a known solvent for this material, and the difficulty of its removal after setting.[49]

Cytotoxicity and cell attachment investigations with various cell cultures showed better results with MTA in comparison to amalgam, Super EBA, IRM, various types of glass ionomers, GP and Diaket.[50-58] In an *in vitro* study with murine cerebral cortical cells, neurotoxic effects of MTA, Diaket, amalgam, and Super EBA were compared on both glial and neuronal cultures.[59] Results showed that all of the materials except MTA are toxic in either freshly mixed or set conditions.

8. Other MTA formulations

An experimental light-cure MTA has been developed to have similar properties to MTA and also better working properties. Although this experimental material apparently presents positive characteristics, there are very few studies regarding its biocompatibility.[60-62] Other MTA formulations aiming to improve its physical properties have been proposed. Recently, a new MTA formulation (Cimento Endodôntico Rápido or Fast Endodontic Cement) composed of Portland cement in a gel with water, barium sulphate, and an emulsifier, whose function is to improve handling properties, has been also tried.[63] One research evaluated the rat subcutaneous tissue response to Fast Endodontic cement (CER, Cimento Endodôntico Rápido) and Angelus MTA. Results showed that both materials were biocompatible and stimulated mineralization.[63]

9. New materials under research

1) Endosequence root repair material (ERRM), putty and paste

Recently, ERRM putty and paste (Brasseler USA, Savannah, GA, USA) have been developed as ready-to-use, premixed bioceramic materials recommended for perforation repair, apical surgery, apical plug, and pulp capping.[64] Both ERRM putty and paste have shown similar *in vitro* biocompatibility to both gray and white MTA (WMTA).[65-67]

2) Bioaggregate

Bioaggregate appears to be a modified or synthetic version of original MTA. According to the manufacturer, this material contains biocompatible pure white powder composed of ceramic nano-particles and deionized water. Bioaggregate appeared to be biocompatible compared with WMTA on human pulp cells, PDL cells and MG63 cells.[68,69]

3) iRoot BP Plus bioceramic putty

iRoot BP Plus (Innovative BioCeramix Inc., Vancouver, Canada) is a fully laboratory-synthesized, water-based bioceramic cement. It claims to be a more convenient reparative material, because it is a ready to-use white hydraulic premixed formula.[70] A current study to verify *in vitro* cytocompatibility of iRoot BP Plus bioceramic putty concluded that iRoot and MTA were biocompatible and did not induce critical cytotoxic effects.[71]

4) Novel root-end filling material

A novel resin based root-end filling material (termed New resin cement, NRC) has been introduced.[72] NRC is a powder and liquid system. The liquid is composed of hydroxyethylmethacrylate, benzoyl peroxide, toluidine, and toluenesulfinate. And the powder is made of calcium oxide, calcium silicate, and triphenylbismuth carbonate. One study determined the cytotoxicity of NRC and concluded that the initial biocompatibility results of NRC are favorable for a root-end filling material.[72] A recent *in vivo* study concluded that NRC shows moderately higher inflammatory reaction than MTA however, the calcium reservoir capability of NRC may contribute to mineralization of the tissues.[73]

5) Experimental calcium aluminosilicate based materials

(1) EndoBinder

A new calcium aluminate-based endodontic cement, called EndoBinder (Binderware, São Carlos, SP, Brazil), has been developed with the intention of preserving the properties and clinical applications of MTA eliminating its negative characteristics.[74] EndoBinder is produced with high levels of purity, eliminating traces of free magnesium oxide (MgO) and calcium oxide (CaO), which are responsible for the undesired expansion of the material, and ferric oxide (Fe_2O_3), which is responsible for tooth darkening.[75,76] Among recent materials, EndoBinder presented satisfactory tissue reaction, it was biocompatible when tested in subcutaneous tissue of rats.[75]

(2) Generex A

Generex A (Dentsply Tulsa Dental Specialties, Tulsa, OK, USA) is a calcium-silicate-based material that has some

similarities to ProRoot MTA but is mixed with unique gels instead of water used for MTA. Generex A material has very different handling properties in comparison to MTA.[77] Generex A mixes to a dough-like consistency, making it easy to roll into a rope-like mass similar to intermediate restorative material.[78]

(3) Capasio

Capasio (Primus Consulting, Bradenton, FL, USA) is composed primarily of bismuth oxide, dental glass, and calcium alumino-silicate with a silica and polyvinyl acetate-based gel. A recent study found that Capasio and MTA promote apatite deposition when exposed to synthetic tissue fluid thus had the mineralization capacity.[79] The same researchers also concluded that when used as a root-end filling material, Capasio is more likely to penetrate dentinal tubules. Another study compared Generex A, Generex B, Capasio along with Ceramicrete-D (magnesium phosphate based) using primary osteoblasts. Generex A was the only new generation endodontic material that supported primary osteoblast growth. No material besides MTA facilitated nodule formation. Only Generex A and MTA allowed cell growth and proliferation throughout the experiment.[80]

(4) Quick-Set

Recently, Capasio powder has been refined and renamed as Quick-Set (Primus Consulting), and the cationic surfactant was removed from the liquid gel component, which was thought to interfere with cytocompatibility.[74,81] In a contemporary research using odontoblast-like cells, Quick-Set and MTA exhibited similar cytotoxicity profiles. They possess negligible *in vitro* toxicologic risks after time-dependent elution of toxic components.[74]

(5) Biodentine

Biodentine (Septodont, Saint Maur des Fossés, France) powder is mainly composed of tricalcium silicate, calcium carbonate and zirconium oxide as the radio-pacifier, whilst Biodentine liquid contains calcium chloride as the setting accelerator and water as reducing agent.[81] Biodentine shows apatite formation after immersion in phosphate solution, indicative of its bioactivity.[82] The elemental (Ca and Si) uptake into root canal dentine was found to be more prominent for Biodentine than for MTA.[83] In a comparative *in vitro* biocompatibility evaluation, Biodentine caused gingival fibroblast reaction similar to that by MTA. Both materials were less cytotoxic than GIC.[84]

6) Polymer nanocomposite (PNC) resin

Nanocomposites are a new class of composites that have shown great potential. A PNC is a generalized term for polymeric materials that are loaded with minimal amounts of nanoparticles such as clays, carbon nanotubes, etc. dispersed at a nanoscale.[85] PNC resins such as C-18 Amine montmorillonate (MMT) and vinylbenzyl octadecyldimethyl ammonium chloride (VODAC) MMT, both containing 2% chlorhexidine diacetate salt hydrate, have been tried for their potential as root-end filling material.[86] Cytotoxicity study evaluating these two forms PNC resins found no significant difference between MTA, Geristore and PNC resin C-18 Amine MMT on 24 hours, 1, 2 and 3 weeks samples. Sample elutes of PNC resin VODAC MMT, however, revealed cytotoxic activity during most of these experiments.[86]

7) Novel root-end filling material using epoxy resin and Portland cement (EPC)

EPC, a novel composite made from a mixture of epoxy resin and Portland cement, was found to be a useful material for root-end filling, with favorable radio-opacity, short setting time, low microleakage, and clinically acceptable low cytotoxicity.[87]

8) Iron-free partially stabilized cement

Partial stabilized cement (PSC) is an innovative material prepared to address some of the drawbacks of MTA. Portland cement-based PSC with Zn was synthesized by replacing iron nitrate using one-step sol-gel process. The physical properties and biocompatibility of PSCZn were found to be favourable as an ideal root-end filling material.[88]

Comparative studies evaluating toxicity of various root-end filling materials

1. *In vitro* studies and *in vivo* experimental studies

Comparative results of recent *in vitro* and *in vivo* experimental studies have been summarized in tables 1 and 2 respectively.

2. Clinical studies

In a recent prospective randomized controlled study, Song *et al.* found no significant difference in the clinical outcomes of endodontic microsurgery when Super EBA and MTA were used as root-end filling materials.[91] In two separate prospective clinical investigations, Chong *et al.* and Lindeboom *et al.* compared IRM with MTA as root-end filling materials in single-rooted teeth and the mesiobuccal roots of maxillary molars.[92,93] The results of both studies showed more favorable results with MTA, although they found no significant statistical difference between the two materials. When IRM and Super EBA were compared, researchers found 91% success rate for the IRM group and 82% for the Super EBA group after 12 months. There was no statistical significance in the healing outcome between the 2 groups.[94]

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Table 1. Recent comparative studies evaluating *in vitro* toxicity of various root end filling materials

Author (year of research)	Comparative materials used in study	Cell line used	Study inferences
Haglund R *et al.* (2003)[30]	MTA, IRM, Amalgam, Retroplast	Mouse fibroblasts and macrophages	All root-end filling materials inhibited cell growth
Thomson TS *et al.* (2003)[50]	MTA, IRM, Amalgam	Cementoblasts	MTA can be considered cementoconductive and was most biocompatible
Camp MA *et al.* (2003)[41]	Geristore, ProRoot, Tytin amalgam, Super EBA	Human periodontal ligament (PDL) fibroblasts and gingival fibroblasts (GF)	Gingival fibroblasts attach to Geristore which can be considered as indicator of biocompatibility
Pistorius A *et al.* (2003)[51]	MTA, Amalgam,Titanium	GF	MTA demonstrated cellular responses similar to those of titanium. Amalgam showed an irritation rate higher than that of MTA and titanium.
Asrari M *et al.* (2003)[59]	MTA, Amalgam, Super EBA, Diaket.	Murine cerebral cortical cell	All materials except for MTA are toxic in either freshly mixed or set conditions.
Pelliccioni GA *et al.* (2004)[52]	Proroot MTA, Super EBA, Amalgam	Osteoblast-like cell	Proroot MTA showed a good interaction with bone-forming cells
Huang TH *et al.* (2005)[53]	MTA, calcium hydroxide-based cement, eugenol-based cement,	Human osteogenic sarcoma cells	MTA is more biocompatible than other two materials used
Al-Sabek F *et al.* (2005)[31]	Geristore, IRM, GIC	GF	Geristore is less cytotoxic to gingival fibroblasts than IRM and GIC
Souza NJ *et al.* (2006)[55]	Amalgam, GIC, Super EBA, N-Rickert, MTA, gutta-percha	V79 fibroblasts and murine granulocyte-macrophage progenitor cells	MTA was ranked as the least cytotoxic cement in both cell systems
Al-Rabeah E *et al.* (2006)[54]	ProRoot Gray MTA, tooth-colored (white) MTA	Human alveolar bone cells	ProRoot and tooth-colored MTA support cell attachment, proliferation, and matrix formation showing the biocompatible nature
Vajrabhaya LO *et al.* (2006)[57]	GIC and MTA	PDL cells	AlthoughGI has the advantage of adhering to dentine, it is more cytotoxic to the PDL cells than MTA
Coon D *et al.* (2007)[89]	Gutta-percha, Resilon, MTA	Primary osteoblast and osteoclast cultures	Exposure to materials did not lead to any significant osteoclast formation.
Yoshimine Y *et al.* (2007)[56]	MTA, 4-META/MMA-TBB resin (Super-bond), IRM	Osteoblast	MTA and Super-bond have good biocompatibility and allow hard-tissue forming cells to create a matrix layer
Gorduysus M *et al.* (2007)[58]	White MTA, Diaket Endion, CYMED 8410	PDL cells	MTA is a very biocompatible material in comparison to other materials used in study
Alanezi AZ *et al.* (2010)[65]	EndoSequence Root Repair Material (ERRM), gray MTA, white MTA	Cultured cells	ERRM have similar biocompatibility to GMTA and WMTA in both set and fresh conditions
Chung CR *et al.* (2010)[68]	Bioaggregate, MTA	Human pulp and PDL cells	Bioaggregate appeared to be biocompatible compared with white MTA
Lee *et al.* (2010)[69]	Bioaggregate, MTA	MG63 cells	There was no difference in the number of attached cells, which show biocompatibility of the material, to be comparable to MTA
Modareszadeh MR *et al.* (2011)[86]	Polymer nanocomposite (PNC) resins [C-18 Amine montmorillonate (MMT) and VODAC MMT], MTA, Geristore	Mouse fibroblasts L-929	No significant difference between MTA, Geristore and PNC resin C-18 Amine MMT. PNC resin VODAC MMT, however, revealed significantly more cytotoxicity compared to the other tested materials
Damas BA *et al.* (2011)[67]	ERRM Putty, ERRM Paste, ProRoot MTA, MTA-Angelus	Human dermal fibroblasts	ERRM Putty and ERRM Paste displayed similar cytotoxicity levels to those of ProRoot MTA and MTA-Angelus.
Ma J *et al.* (2011)[66]	ERRM Putty, ERRM Paste, Gray MTA	Human GF	ERRM Putty and ERRM Paste displayed similar *in vitro* biocompatibility to MTA
Al-Hiyasat AS *et al.* (2012)[32]	MTA, Geristore, IRM, Super EBA, GIC, Retroplast	Balb/C 3T3 fibroblasts	Best cellular attachment was seen on the surfaces of MTA and Geristore
De-Deus G *et al.* (2012)[71]	iRoot BP Plus, MTA	Primary human osteoblast	iRoot and MTA are biocompatible and do not induce critical cytotoxic effects.
Wei W *et al.* (2012)[74]	Experimental calcium aluminosilicate cement (Quick-Set), MTA	Odontoblast-like cells	Quick-Set and MTA exhibited similar cytotoxicity profiles
Bird DC *et al.* (2012)[79]	Generex A, Generex B, Capasio, Ceramicrete-D	Synthetic tissue fluid (STF)	Both Capasio and MTA promote apatite deposition when exposed to STF
Ndong *et al.* (2012)[88]	Partially stabilized cement (PSC) with zinc (Zn)	Primary osteoblasts cell	Partially stabilized cement (PSC) with zinc (Zn) was biocompatible

MTA, mineral trioxide aggregate; IRM, intermediate restorative material; EBA, ethoxy benzoic acid; GIC, glass ionomer cement; VODAC, vinylbenzyl octadecyldimethyl ammonium chloride.

Table 2. Recent comparative studies evaluating *in vivo* toxicity of various root end filling materials

Author (year of research)	Comparative materials used in study	Animal model used	Study inferences
Gomes-Filho JE *et al.* (2009)[63]	Fast Endodontic cement (CER) and Angelus MTA	Connective tissue of Wistar rats	Both materials were biocompatible and stimulated mineralization.
Gomes-Filho JE *et al.* (2010)[62]	Experimental light-cured MTA or Angelus MTA	Rat alveolar bone	Both materials were well accepted by the alveolar tissue of rats, with the formation of mineralized tissue close to the materials
Gomes-Filho JE *et al.* (2011)[61]	Experimental light-cured MTA or Angelus MTA	Rat alveolar bone	The light-cured MTA presented a similar response when compared with Angelus MTA
Hammad HM *et al.* (2011)[90]	Gray MTA, Retroplast and Geristore	Wistar albino rats	Retroplast was the least biocompatible of the three tested materials at 2 mon, followed by Geristore then GMTA
Aguilar FG *et al.* (2012)[75]	EndoBinder (EB) and Grey MTA	Subcutaneous tissue of rats	EndoBinder presented satisfactory tissue reaction; it was biocompatible
Wälivaara DA *et al.* (2012)[21]	IRM, thermoplasticized gutta-percha, Super EBA, MTA	Mongrel dogs	MTA has the most favorable periapical tissue response when comparing the biocompatibility of the materials tested.

CER, Cimento Endodôntico Rápido; MTA, mineral trioxide aggregate; EBA, ethoxy benzoic acid.

Another clinical study compared MTA with Retroplast and concluded that MTA-treated teeth demonstrated a significantly higher rate of healed cases (91.3%) compared with Retroplast-treated teeth (79.5%). In a case series study on 276 teeth with WMTA as a root-end filling material, Saunders reported 88.8% clinical and radiographic success after 4 - 72 months.[95] The investigator concluded that using careful microsurgical techniques combined with MTA as root-end filling material result in high success rates for endodontic surgery. A recent clinical trial compared smoothing orthograde GP with placing WMTA as root-end filling material. Results showed significantly higher healing in the WMTA group after 1 year.[96] Presently, smoothing GP is not acceptable for treating teeth with periapical lesions during endodontic surgery.[97] On the other hand, a prospective randomized clinical study compared IRM or thermoplasticized GP with AH Plus sealer. According to the results of the healing outcome after 12 months follow-up (85% success rate for the IRM group and 90% for GP group), researchers concluded that both materials are suitable as retrograde root-end filling materials in conjunction with ultrasonic root-end preparation.[98] Further clinical studies are required in order to reveal the wound healing capabilities of newly introduced root-end filling materials and to comparatively assess their clinical performance with the commercially available materials.

Conclusions

On basis of numerous *in vitro, in vivo* investigations and clinical trials, MTA can be suggested as a biocompatible root-end filling material. Newly introduced materials have also shown comparable biocompatibility with potential to provide favorable environment for cell, showing cell proliferation and osteogenic capability but further researches and clinical trials are required.

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