Biocompatibility of root-end filling materials: recent update

Payal Saxena¹*, Saurabh Kumar Gupta¹, Vilas Newaskar²

¹Department of Conservative Dentistry and Endodontics, Government College of Dentistry, Indore, Madhya Pradesh, India
²Department of Oral and Maxillofacial Surgery, Government College of Dentistry, Indore, Madhya Pradesh, India

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)

Key words: Biocompatibility; Comparative evaluation; Root-end filling; Toxicity

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

Received May 3, 2013;
Revised May 31, 2013;
Accepted June 24, 2013.

¹Saxena P; Gupta SK, Department of Conservative Dentistry and Endodontics, Government College of Dentistry, Indore, Madhya Pradesh, India
²Newaskar V, Department of Oral and Maxillofacial Surgery, Government College of Dentistry, Indore, Madhya Pradesh, India

*Correspondence to
Payal Saxena, MDS.
Assistant Professor, Department of Conservative Dentistry and Endodontics, Government College of Dentistry, Indore, Madhya Pradesh, India
TEL, +91-930-2793700; FAX, +91-731-2701608; E-mail, payalmds@yahoo.co.in

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

©Copyrights 2013. The Korean Academy of Conservative Dentistry.
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. Unfortunately, the ideal retrograde filling material is yet to be found.

1. Amalgam

Traditionally, amalgam was the material of choice for root-end fillings. The biocompatibility of amalgam is cited as a current issue of concern in dentistry. Many in vivo usage studies in animals have reported unfavorable tissue response to amalgam. 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. Pitt Ford et al. found that the tissue response to GP with zinc oxide root canal sealer was characterized by little or no inflammation. 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.

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. Therefore, it was unsuitable for long-term use. Consequently, modified forms of ZOE cements were suggested.

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, Intermediate Restorative Material (IRM, DENTSPLY DeTrey GmbH, Konstanz, Germany)

Eugenol is the major cytotoxic component in ZOE cements. Zinc released from these cements is considered to be partly responsible for the prolonged cytotoxic effect. Results of a comparative study showed no cell growth in the originally seeded cells in fresh IRM. Recent studies have shown IRM to be more toxic than comparative materials. 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.

4. Glass ionomer cement (GIC) and related materials

GIC have been suggested as an alternative root-end filling material. Biocompatibility studies exhibited evidence of initial cytotoxicity with freshly prepared samples. 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. The healing response of the periapical tissues to composite resins in general appears to be very diverse, ranging from poor to good depending on the type of material used. 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). Other in vitro interpretations indicate that Geristore is less cytotoxic to gingival fibroblasts in comparison to MTA, GIC and IRM. 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.

6. Diaket

Diaket (3M ESPE GmbH, Seefeld, Germany) a polyvinyl resin, has been advocated for use as a root-end filling material. 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. However, when mixed at the thicker consistency advocated for use as a root-end filling material, Diaket has shown good biocompatibility with osseous tissues.
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. 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. 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.

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. 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. 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. 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. 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 simulated mineralization.

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. Both ERRM putty and paste have shown similar *in vitro* biocompatibility to both gray and white MTA (WMTA).

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.

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. 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.

4) Novel root-end filling material

A novel resin based root-end filling material (termed New resin cement, NRC) has been introduced. NRC is a powder and liquid system. The liquid is composed of hydroxymethylacrylate, 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. 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.

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. 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 (Fe₂O₃), which is responsible for tooth darkening. Among recent materials, EndoBinder presented satisfactory tissue reaction, it was biocompatible when tested in subcutaneous tissue of rats.

(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. Generex A mixes to a dough-like consistency, making it easy to roll into a rope-like mass similar to intermediate restorative material.

(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. 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.

(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. 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.

(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. Biodentine shows apatite formation after immersion in phosphate solution, indicative of its bioactivity. The elemental (Ca and Si) uptake into root canal dentine was found to be more prominent for Biodentine than for MTA. In a comparative in vitro biocompatibility evaluation, Biodentine caused gingival fibroblast reaction similar to that by MTA. Both materials were less cytotoxic than GIC.

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. 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. 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.

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.

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.

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. 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. 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.
| Author (year of research) | Comparative materials used in study | Cell line used | Study inferences |
|---------------------------|------------------------------------|----------------|------------------|
| Haglund R et al. (2003)   | MTA, IRM, Amalgam, Retroplast      | Mouse fibroblasts and macrophages | All root-end filling materials inhibited cell growth |
| Thomson TS et al. (2003)  | MTA, IRM, Amalgam                  | Cementoblasts   | MTA can be considered cementoconductive and was most biocompatible |
| Camp MA et al. (2003)     | 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) | 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)    | MTA, Amalgam, Super EBA, Diaket, MTA, gutta-percha | Murine cerebral cortical cell | All materials except for MTA are toxic in either freshly mixed or set conditions. |
| Pelliccioni GI et al. (2004) | ProRoot MTA, Super EBA, Amalgam | Osteoblast-like cell | ProRoot MTA showed a good interaction with bone-forming cells |
| Huang TH et al. (2005)    | 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)  | Geristore, IRM, GIC               | GF              | Geristore is less cytotoxic to gingival fibroblasts than IRM and GIC |
| Souza NJ et al. (2006)    | 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) | 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) | GIC and MTA | PDL cells | Although GIC has the advantage of adhering to dentine, it is more cytotoxic to the PDL cells than MTA |
| Coon D et al. (2007)      | 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) | 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 |
| Gordiysus M et al. (2007) | 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. (2008)  | EndoSequence Root Repair Material (ERRM), gray MTA, white MTA | Cultured cells | ERRM have similar biocompatibility to GMA and WMTA in both set and fresh conditions |
| Chung CR et al. (2010)    | Bioaggregate, MTA                 | Human pulp and PDL cells | Bioaggregate appeared to be biocompatible compared with white MTA |
| Lee et al. (2010)         | 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) | 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 |
| Dumas BA et al. (2011)    | ERRM Putty, ERRM Paste, ProRoot MTA, MTA-Angelus | Human dermal fibroblasts | MTA demonstrated cellular responses similar to those of ProRoot MTA and MTA-Angelus |
| Ma J et al. (2011)        | ERRM Putty, ERRM Paste, Gray MTA  | Human GF        | ERRM Putty and ERRM Paste displayed similar cytotoxicity levels to those of ProRoot MTA and MTA-Angelus |
| Al-Hiyasat AS et al. (2012) | 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)   | iRoot BP Plus, MTA                | Primary human osteoblast | iRoot and MTA are biocompatible and do not induce critical cytotoxic effects. |
| Wei W et al. (2012)       | Experimental calcium aluminosilicate cement (QuickSet), MTA | Odontoblast-like cells | Quick-Set and MTA exhibited similar cytotoxicity profiles |
| Bird DC et al. (2012)     | 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)       | 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.
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. 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. 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. 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.

Conflict of Interest: No potential conflict of interest relevant to this article was reported.

**References**

1. Gatewood RS. Endodontic materials. Dent Clin North Am 2007;51:695-712.
2. Andreasen JO. Cementum repair after apicoectomy in humans. Acta Odontol Scand 1973;31:211-221.
3. Regan JD, Gutmann JL, Witherspoon DE. Comparison of Diaket and MTA when used as root-end filling materials to support regeneration of the periradicular tissues. Int Endod J 2002;35:840-847.
4. Dahl JE. Toxicity of endodontic filling materials. Endod Topics 2005;12:39-43.
5. Glickman GN, Hartwell GR. Chapter 33. Endodontic surgery. In: Ingle JI, Bakland LK, Baumgartner JC, ed. Ingle’s Endodontics. 6th ed. Hamilton: BC Decker Inc; 2008. p1261-1294.
6. Chong BS, Pitt Ford TR. Root-end filling materials: rationale and tissue response. Endod Topics 2005;11:114-130.
7. Gutmann JL, Harrison JW. Posterior endodontic surgery: anatomical considerations and clinical techniques. Int Endod J 1985;18:8-34.
8. Friedman S. Retrograde approaches in endodontic therapy. Endod Dent Traumatol 1991;7:97-107.
9. Pitt Ford TR, ed. Harty’s Endodontics in Clinical Practice. 5th ed. Edinburgh: Wright; 2004. Chapter 9, Surgical endodontics; p143-181.
10. Anusavice KJ, ed. Phillip’s Science of Dental Materials.

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) | 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) | 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) | 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) | 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) | EndoBinder (EB) and Grey MTA | Subcutaneous tissue of rats | EndoBinder presented satisfactory tissue reaction; it was biocompatible |
| Wälivaara DA et al. (2012) | 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 Endodontico Rápido; MTA, mineral trioxide aggregate; EBA, ethoxy benzoic acid.
11. Pitt Ford TR, Andreasen JO, Dorn SO, Kariyawasam SP. Effect of IRM root end fillings on healing after replantation. J Endod 1995;20:102-114.

12. Pitt Ford TR, Andreasen JO, Dorn SO, Kariyawasam SP. Effect of various zinc oxide materials as root-end fillings on healing after replantation. J Endod 1995;20:283-278.

13. Chong BS, Ford TR, Kariyawasam SP. Tissue response to potential root-end filling materials in infected root canals. Int Endod J 1997;30:239-249.

14. Chong BS, Pitt Ford TR, Kariyawasam SP. Short-term tissue response to potential root-end filling materials in infected root canals. Int Endod J 1997;30:240-249.

15. Kimura JT. A comparative analysis of zinc and non-zinc alloys used in retrograde endodontic surgery. Part 1: apical seal and tissue reaction. J Endod 1982;8:359-363.

16. Kimura JT. A comparative analysis of zinc and non-zinc alloys used in retrograde endodontic surgery. Part 2: optical emission spectrographic analysis for zinc precipitation. J Endod 1982;8:407-409.

17. Pitt Ford TR, Andreasen JO, Dorn SO, Kariyawasam SP. Effect of super-EBA as a root end filling on healing after replantation. J Endod 1995;20:13-15.

18. Torabinejad M, Pitt Ford TR, McKendry DJ, Abedi HR. A study of root-end filling in the ferret canine: a comparison of a glass ionomer cement and gutta-percha with sealer. Oral Surg Oral Med Oral Pathol 1996;81:221-228.

19. Baek SH, Plenk H Jr, Kim S. Periapical tissue responses and cementum regeneration with amalgam, SuperEBA, and MTA as root-end filling materials. J Endod 2005;31:444-449.

20. Kaplan SD, Tanzilli JP, Raphael D, Moodnik RM. A comparison of the marginal leakage of retrograde techniques. Oral Surg Oral Med Oral Pathol 1982;54:583-585.

21. Pitt Ford TR, Andreasen JO, Dorn SO, Kariyawasam SP. Effect of various sealers with gutta-percha as root-end fillings on healing after replantation. Endod Dent Traumatol 1996;12:33-37.

22. Wålivaara DA, Abrahamsson P, Isaksson S, Salata LA, Sennerby L, Dahlin C. Periapical tissue response after use of intermediate restorative material, gutta-percha, reinforced zinc oxide cement, and mineral trioxide aggregate as retrograde root-end filling materials: a histologic study in dogs. J Oral Maxillofac Surg 2012;70:2041-2047.

23. Phillips RW, Love DR. The effect of certain additive agents on the physical properties of zinc oxide-eugenol mixtures. J Dent Res 1961;40:294-303.

24. Weine FS. Endodontic Therapy. 4th ed. St Louis: Mosby; 1982. p498-502.

25. Torabinejad M, Walton RE. Principles and Practice of Endodontics. 3rd ed. Philadelphia: Saunders; 2002. p275-278.

26. Hendra LP. EBA cement. A practical system for all cementation. J Br Endod Soc 1970;4:28-32.

27. Oynick J, Oynick T. A study of a new material for retrograde fillings. J Endod 1978;4:203-206.

28. Jeng JH, Hahn LJ, Lu FJ, Wang YJ, Kuo MY. Eugenol triggers different pathobiological effects on human oral mucosal fibroblasts. J Dent Res 1994;73:1050-1055.

29. Meryon SD, Jakeman KJ. The effects in vitro of zinc released from dental restorative materials. Int Endod J 1985;18:191-198.

30. Haglund R, He J, Jarvis J, Safavi KE, Spångberg LS, Zhu Q. Effects of root-end filling materials on fibroblasts and macrophages in vitro. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:739-745.

31. Al-Sabek F, Shostad S, Kirkwood KL. Preferential attachment of human gingival fibroblasts to the resin ionomer Geristore. J Endod 2005;31:205-208.

32. Al-Hyasat AS, Al-Sa’eed OR, Darmani H. Quality of cellular attachment to various root-end filling materials. J Appl Oral Sci 2012;20:82-88.

33. BarkhorDar RA, Pelzner RB, Stark MM. Use of glass ionomers as retrofilling materials. Oral Surg Oral Med Oral Pathol 1989;67:734-739.

34. Pissiotis E, Sapounas G, Spångberg LS. Silver glass ionomer cement as a retrograde filling material: a study in vitro. J Endod 1991;17:225-229.

35. Pissiotis E, Spångberg L. Reaction of bony tissue to implanted silver glass ionomer and a reinforced zinc oxide-eugenol cement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89:623-629.

36. Brook IM, Hatton PV. Glass-ionomers: bioactive implant materials. Biomaterials 1998;19:565-571.

37. Callis P, Santini A. Tissue response to retrograde root filling in the ferret canine: a comparison of a glass ionomer cement and gutta-percha with sealer. Oral Surg Oral Med Oral Pathol 1987;64:475-479.

38. Geurtsen W. Biocompatibility of resin-modified filling materials. Crit Rev Oral Biol Med 2000;11:333-355.

39. Andreasen JO, Rud J, Munksgaard EC. Retrograde root obturations using resin and a dentin bonding agent: a preliminary histologic study of tissue reactions in monkeys. Tandlaegebladet 1989;93:195-197.

40. Trope M, Lost C, Schmitz HJ, Friedman S. Healing of apical periodontitis in dogs after apicoectomy and retrofilling with various filling materials. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81:221-228.

41. Camp MA, Jeansonne BG, Lallier T. Adhesion of human oral fibroblasts to potential root-end filling materials in infected root canals. J Endod 1995;20:273-278.

42. Gupta SK, Saxena P, Pant VA, Pant AB. Adhesion and biologic behavior of human periodontal fibroblast cells to resin ionomer Geristore: a comparative analysis. Dent Traumatol 2012; Nov 6 [Epub ahead of print]. DOI: 10.1111/edt.12016.
58. Gorduysus M, Avcu N, Gorduysus O, Pekel A, Baran Y, Avcu F, Ural AU. Cytotoxic effects of four different endodontic materials in human periodontal ligament fibroblasts. J Endod 2007;33:1450–1454.

59. Asrari M, Lobner D. In vitro neurotoxic evaluation of root-end filling materials. J Endod 2003;29:743–746.

60. Gomes-Filho JE, de Faria MD, Bernabé PF, Nery MJ, Otoboni-Filho JA, Dezan-Júnior E, de Moraes Costa MM, Cannon M. Mineral trioxide aggregate but not light-cure mineral trioxide aggregate stimulated mineralization. J Endod 2008;34:62–65.

61. Gomes-Filho JE, de Moraes Costa MM, Cintra LT, Duarte PC, Takamiya AS, Lodi CS, Bernabé PF. Evaluation of rat alveolar bone response to Angelus MTA or experimental light-cured mineral trioxide aggregate using fluorochromes. J Endod 2011;37:250–254.

62. Gomes-Filho JE, de Moraes Costa MT, Cintra LT, Lodi CS, Duarte PC, Okamoto R, Bernabé PF, Nery MJ, Cannon M. Evaluation of alveolar socket response to Angelus MTA and experimental light-cure MTA. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:e93–97.

63. Gomes-Filho JE, Rodrigues G, Watanabe S, Estrada Bernabé PF, Lodi CS, Gomes AC, Faria MD, Domingos Dos Santos A, Silos Moraes JC. Evaluation of the tissue reaction to fast endodontic cement (CER) and Angelus MTA. J Endod 2009;35:1377–1380.

64. Brasseler USA Co.: EndoSequence root repair material paste, Information. Available from: http://www.brasselerusa.com/display.cfm?pid=newproducts (updated 2010 Dec).

65. Alanezi AZ, Jiang J, Safavi KE, Spangberg LS, Zhu Q. Cytotoxicity evaluation of endosequence root repair material. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:e122–125.

66. Ma J, Shen Y, Stojicic S, Haapasalo M. Biocompatibility of two novel root repair materials. J Endod 2011;37:793–798.

67. Damas BA, Wheater MA, Bringas JS, Hoen MM. Cytotoxicity comparison of mineral trioxide aggregates and EndoSequence bioceramic root repair materials. J Endod 2011;37:372–375.

68. Chung CR, Kim E, Shin SJ. Biocompatibility of biogoggregate cement on human pulp and periodontal ligament (PDL) derived cells. J Korean Acad Conserv Dent 2010;35:473–478.

69. Lee JH, Shon WJ, Lee W, Baek SH. The effect of several root-end filling materials on MG63 osteoblast-like cells. J Korean Acad Conserv Dent 2010;35:222–228.

70. Innovative BioCeramix, Inc Co.: Information. Available from: http://www.ibioceramix.com/Publications.html (updated 2012 Jan).

71. De-Deus G, Canabarros A, Alves GG, Marins JR, Linhares AB, Granjeiro JM. Cytocompatibility of the ready-to-use bioceramic putty repair cement iRoot BP Plus with primary
human osteoblasts. *Int Endod J* 2012;45:508-513.
72. Kim M, Ko H, Yang W, Lee Y, Kim S, Mante FK. A new resin-bonded retrograde filling material. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:e111-116.
73. Yang WK, Ko HJ, Kim MR. Evaluation of the rat tissue reaction to experimental new resin cement and mineral trioxide aggregate cement. *Restor Dent Endod* 2012;37:194-200.
74. Wei W, Qi YP, Nikonov SY, Niu LN, Messer RL, Mao J, Primus CM, Pashley DH, Tay FR. Effects of an experimental calcium aluminosilicate cement on the viability of murine odontoblast-like cells. *J Endod* 2012;38:936-942.
75. Aguilar FG, Roberti Garcia LF, Panzeri Pires-de-Souza FC. Biocompatibility of new calcium aluminosilicate cement (*EndoBinder*). *J Endod* 2012;38:367-371.
76. Torabinejad M, Chivian N. Clinical applications of mineral trioxide aggregate. *J Endod* 1999;25:197-205.
77. Ørstavik D, Nordahl I, Tibballs JE. Dimensional change evaluation of dentinal tubule penetration. *In Vitro* 2002;38:1093-1096.
78. Washington JT, Schneiderman E, Spears R, Fernandez CR, He J, Opperman LA. Biocompatibility and osteogenic potential of new generation endodontic materials established by using primary osteoblasts. *J Endod* 2011;37:1166-1170.
79. Bird DC, Komabayashi T, Guo L, Opperman LA, Spears R. *In Vitro* evaluation of dentinal tubule penetration and biomineralization ability of a new root-end filling material. *J Endod* 2012;38:1093-1096.
80. Washington JT, Schneiderman E, Spears R, Fernandez CR, He J, Opperman LA. Biocompatibility and osteogenic potential of new generation endodontic materials established by using primary osteoblasts. *J Endod* 2011;37:1166-1170.
81. Laurent P, Camps J, De Méo M, Déjou J, About I. Induction of specific cell responses to a Ca$_3$SiO$_5$-based posterior restorative material. *Dent Mater* 2008;24:1486-1494.
82. Goldberg M, Pradelle-Plasse N, Tran X, Colon P, Laurent P, Aubut V, About I, Boukpessi T, Septier D. Emerging trends in (bio)material researches. In: Goldberg M, ed. Biocompatibility or cytotoxic effects of dental composites. Oxford: Coxmoor Publishing; 2009. p.181-203.
83. Han L, Okiji T. Uptake of calcium and silicon released from calcium silicate-based endodontic materials into root canal dentine. *Int Endod J* 2011;44:1081-1087.
84. Zhou HM, Shen Y, Wang ZJ, Li L, Zheng YF, Häkkinen L, Haapasalo M. *In Vitro* cytotoxicity evaluation of a novel root repair material. *J Endod* 2013;39:478-483.
85. Krishnan PS, Joshi M, Bhargava P, Valiyaveettil S, He C. Effect of heterocyclic based organoclay on the properties of polyimide-clay nanocomposites. *J Nanosci Nanotechnol* 2005;5:1148-1157.
86. Modareszadeh MR, Chogle SA, Mickel AK, Jin G, Kowsar H, Salamat N, Shaikh S, Qutbudin S. Cytotoxicity of set polymer nanocomposite resin root-end filling materials. *J Endod* 2011;37:154-156.
87. Lee SJ, Chung J, Na HS, Park EJ, Jeon HJ, Kim HC. Characteristics of novel root-end filling material using epoxy resin and Portland cement. *Clin Oral Investig* 2013;17:1009-1015.
88. Ndong F, Sadhasivam S, Lin FH, Savitha S, Wen-Hsi W, Lin CP. The development of iron-free partially stabilized cement for use as dental root-end filling material. *Int Endod J* 2012;45:557-564.
89. Coon D, Gulati A, Cowan C, He J. The role of cyclooxygenase-2 (COX-2) in inflammatory bone resorption. *J Endod* 2007;33:432-436.
90. Hammad HM, Hamadah MA, Al-Omari WM. Histological evaluation of rat tissue response to GMTA, Retroplast, and Geristore retrograde filling materials. *Aust Endod J* 2011;37:18-25.
91. Song M, Kim E. A prospective randomized controlled study of mineral trioxide aggregate and super ethoxybenzoic acid as root-end filling materials in endodontic microsurgery. *J Endod* 2012;38:875-879.
92. Chong BS, Pitt Ford TR, Hudson MB. A prospective clinical study of mineral trioxide aggregate and IRM when used as root-end filling materials in endodontic surgery. *Int Endod J* 2003;36:520-526.
93. Lindeboom JA, Frenken JW, Kroon FH, van den Akker HP. A comparative prospective randomized clinical study of MTA and IRM as root-end filling materials in single-rooted teeth in endodontic surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;100:495-500.
94. Wälivaara DÅ, Abrahamsson P, Fogelin M, Isaksson S. Super-EBA and IRM as root-end fillings in periapical surgery with ultrasonic preparation: a prospective randomized clinical study of 206 consecutive teeth. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011;102:258-263.
95. Saunders WP. A prospective clinical study of periradicular surgery using mineral trioxide aggregate as a root-end filling. *J Endod* 2008;34:660-665.
96. Christiansen R, Kirkevang LL, Hørsted-Bindslev P, Wenzel A. Randomized clinical trial of root-end resection followed by root-end filling with mineral trioxide aggregate or smoothing of the orthograde gutta-percha root filling - 1-year follow-up. *Int Endod J* 2009;42:105-114.
97. Evidence-based review of clinical studies on the root apex. *J Endod* 2009;35:1158-1159.
98. Wälivaara DA, Abrahamsson P, Sämfors KA, Isaksson S. Periapical surgery using ultrasonic preparation and thermoplasticized gutta-percha with AH Plus sealer or IRM as retrograde root-end fillings in 160 consecutive teeth: a prospective randomized clinical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:784-789.