SYSTEMATIC REVIEW AND META-ANALYSIS

Cytotoxicity and Bioactivity of Mineral Trioxide Aggregate and Bioactive Endodontic Type Cements: A Systematic Review

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Abstract

Background: Knowledge of the cytotoxicity and bioactivity of endodontic materials may assist in understanding their ability to promote dental pulp stem cell activity and pulp healing in primary teeth.

Materials and methods: This systematic review was carried out by searching the electronic databases such as PubMed, Google Scholar, and Cochrane reviews for the articles published between January 2000 and December 2018 using the appropriate MeSH keywords. An independent investigator evaluated the abstracts and titles for possible inclusion, as per the stipulated inclusion and exclusion criteria. The topics considered for extracting data from each study were: cell lineage, cytotoxicity assay used, and type of material tested.

Results: Seven eligible studies were selected for assessing the quality of evidence on the bioactivity of bioactive endodontic cements (BECs) (1 human cell line, 2 animal cell lines, and 4 *in vitro*, animal, and human studies) and 13 studies were selected for reviewing the quality of evidence on cytotoxicity (7 human cell lines, 4 animal cell lines, and 2 animal model studies). Very limited studies had been conducted on the bioactivity of materials other than mineral trioxide aggregate (MTA). With regards to cytotoxicity, the studies were diverse and most of the studies were based on MTT assay. Mineral trioxide aggregate is the most frequently used as well as studied root-end filling cement, and the literature evidence corroborated its reduced cytotoxicity and enhanced bioavailability.

Conclusion: There was a lack of sufficient evidence to arrive at a consensus on the ideal material with minimal cytotoxicity and optimal bioactivity. More focused human/cell line-based studies are needed on the available root filling materials.

Clinical significance: The present systematic review provides an update on the available literature evidence on the cytotoxicity and bioactivity of various BECs including MTAs and their influence on the different cells with respect to their composition and strength.

Keywords: Bioactive endodontic cements, Bioactivity, Cytotoxicity, Mineral trioxide aggregate.

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Introduction

Bioactive endodontic cements (BECs) are bioactive materials that form apatite in body fluids, including synthetic body fluids and they are mainly used for pulp capping, pulp therapy, pulpotomy, apexogenesis, apexification, perforation repair, root canal filling, and root canal sealing.[1,2] Despite the differences in chemical composition, the bioactivity of BECs is similar.[1] The commonly used BECs include calcium-based materials, mineral trioxide aggregate (MTA), Biodentine, root repair material (iRoot), calcium-enriched mixture (CEM), bioaggregate, endosequence root repair material, MTYA1-Ca filler, TheraCal, and bioactive glass.[3,4] Mineral trioxide aggregates are the most commonly used BECs owing to their high biocompatibility, sealing ability, and desirable outcomes.[5,6] Mineral trioxide aggregate consists of tricalcium silicate, dicalcium silicate, and some traces of tricalcium aluminate and calcium aluminoferrite.[7–9] The various MTAs available are ProRoot MTA (gray), tooth-colored ProRoot, Angelus MTA, Biodentine, MTA Bio, and MTA Plus (white and gray). The availability of a various range of bioactive materials needs a proper understanding and guidance for the appropriate use of material for different clinical conditions.[10–12] Due to some disadvantages of MTAs such as high cost, long setting time, and tooth discoloration; several newer BECs have been recently introduced to the market.[13]

Cytotoxicity assays are carried out to study the toxicity of the materials used in BECs, and the damage or irritation they cause when used for various endodontic procedures. Cytotoxicity is tested using *in vivo* and *in vitro* methods and the choice of test depends on the chemical composition of the test materials.[14,15] The *in vitro* cytotoxic assays are most relevant and suitable for evaluation due to their reproducibility, simplicity, and cost-effectiveness.[16] Cellular viability is influenced by the materials used in filling or treating.[17] It is tested by cytotoxicity tests, which measures the biocompatibility of the materials.[18]

Cell viability and bioactivity tests are significant to assess cellular damage and the biological effect of new biomaterials.[19,20] Bioactive endodontic cements materials should possess adequate

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biocompatibility and bioactivity to promote dental pulp stem cell activity and pulp healing in primary teeth.[21] Bioactivity index is the measure of hydroxyapatite formation when used for filling.[22,23] Bioactivity index is measured to know the activity, which further depends on the capacity of bone conduction and the material composition[22,24] but total cytocompatibility needs to be checked for complete characterization of bioactive materials. However, a critical evaluation and assessment are required to know the complete cytotoxicity and bioactivity of MTA and other BECs.[25]

The present systematic review is intended to provide an update on the available literature evidence on the cytotoxicity and bioactivity of various BECs including MTAs and their influence on the different cells with respect to their composition and strength.

Materials and Methods

Search Strategy

The protocol for this systematic review has been registered with the PROSPERO International prospective register of systematic reviews, registry No. CRD42021227636 and this review followed PRISMA guidelines.

Electronic databases such as PubMed, Google Scholar, and Cochrane reviews were searched for eligible articles published from January 2000 to December 2018. This particular study period was selected for the following two reasons (1) several studies with a focus on bioactivity and cytotoxicity of BECs had been published during this study period; (2) several newer BECs had been introduced to the market during this period. The search was conducted using all the appropriate MeSH keywords including MTAs and the names of all the available BECs and MTAs for both cytotoxicity and bioactivity. The present review considered *in vitro* studies using animal and human cells, and those conducted in animal models and pulp tissues. References in the retrieved articles were also explored for potentially relevant studies. Complete versions of all the potentially relevant studies were obtained. The same investigator scrutinized and selected the studies for systematic review based on the inclusion and exclusion criteria.

Inclusion criteria were limited to articles written in English and published in a peer-reviewed journal. All eligible studies were included, regardless of the journal. An independent investigator evaluated the abstracts and titles for possible inclusion. The inclusion and exclusion criteria were as follows:

Inclusion Criteria

- Studies on cytotoxicity and bioactivity of BECs.
- Original article.
- Original data available (results).
- English language full-text publication.
- Description of methodology completion, which includes usage of multiple dilution and reporting of duration.

Exclusion Criteria

- Data not available or only abstract available.
- Case reports or letters.
- Duplicate studies.
- Systematic studies.
- Non-English studies.

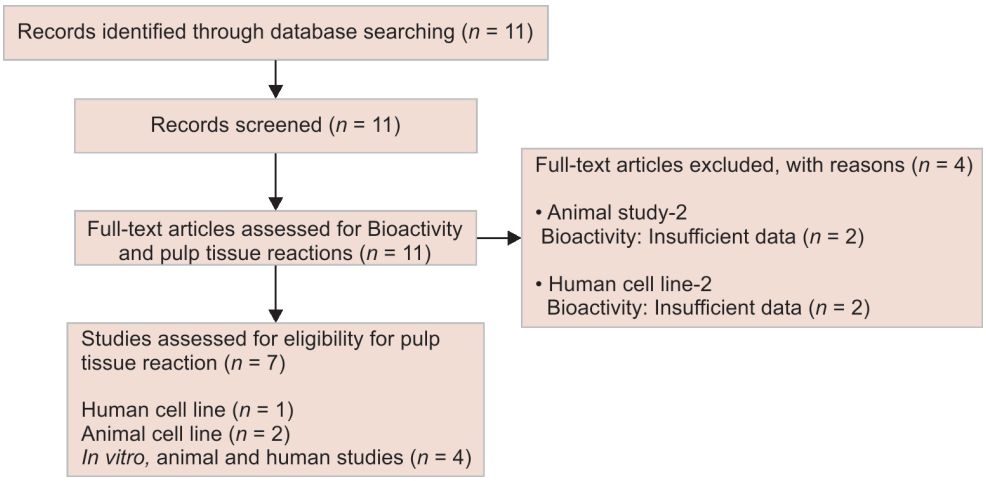
To extract data from each study, the investigator considered the following topics: cell lineage, cytotoxicity assay used, and type of material tested.

Results

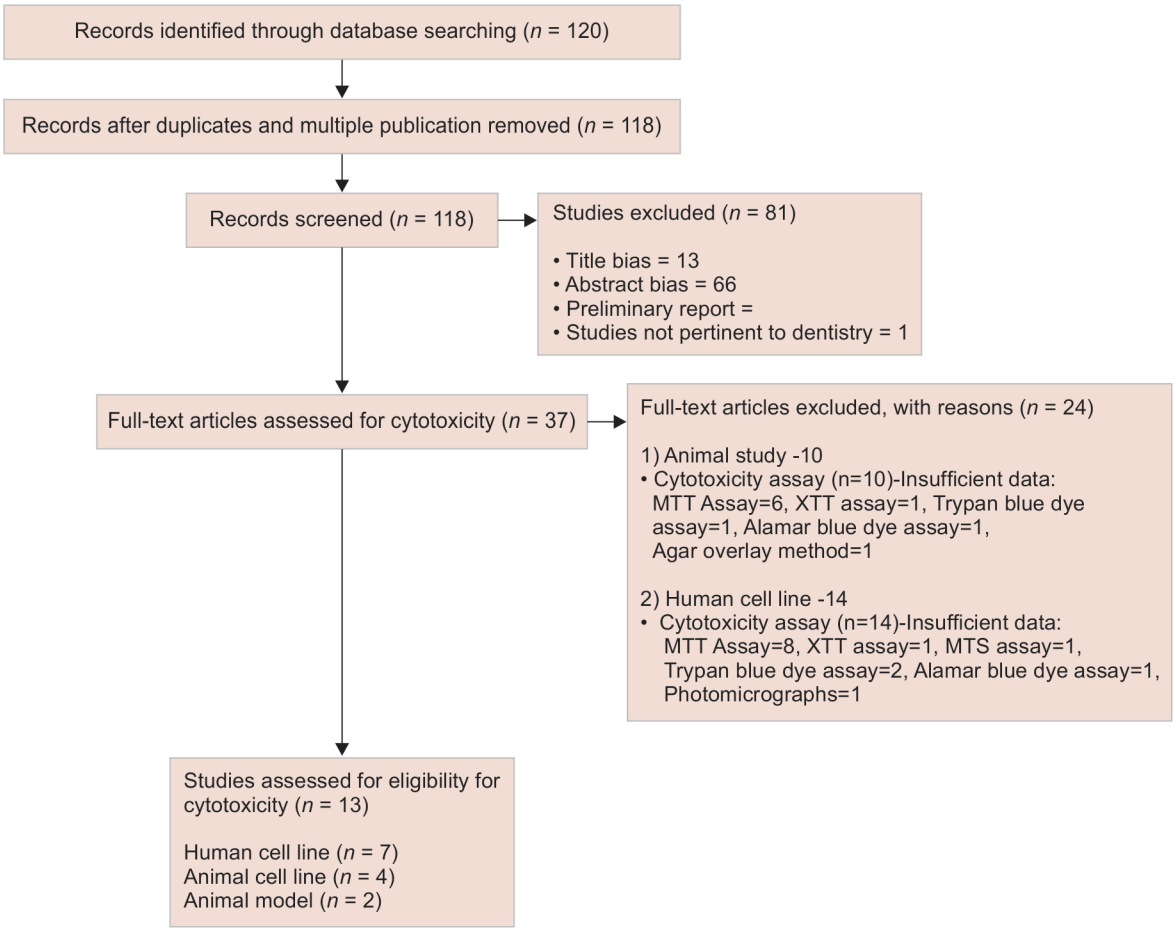
With regard to bioactivity, around 11 full-text articles were selected based on the literature search using the aforementioned keywords (Flowchart 1). Two animal studies and 2 cell line-based studies were excluded due to insufficient data based on the pre-defined inclusion and exclusion criteria. After the exclusion, seven eligible studies were selected for assessing the quality of evidence on the bioactivity of BECs (one human cell line, two animal cell lines, and four *in vitro*, animal, and human studies).

For evaluating the available literature on cytotoxicity, around 120 articles were identified on a literature search using the specific keywords (Flowchart 2). The total number of articles were 118 after the removal of duplicates and multiple publications. Studies not pertaining to dentistry (1) preliminary report (1) and those with the title (130) and abstract bias (66) were excluded. Out of the 37 full-text articles selected, 24 were excluded due to insufficient data based on the pre-defined inclusion and exclusion criteria. After the exclusion, 13 eligible studies were selected for reviewing the quality of evidence on cytotoxicity of BECs (7 human cell lines, 4 animal cell lines, and 2 animal model studies).

Flowchart 1: The screening and selection of studies on the bioactivity of various BECs



Flowchart 2: The screening and selection of studies on cytotoxicity of various BECs



Bioactivity

Cell Line-based Bioactivity Studies

Cell line-based studies were distinct with respect to the assay used for the assessment of bioactivity. Güven et al. compared MTA with iRoot SP using ALP and Von Kossa staining. After 14 days of exposure, the iRoot SP-treated group showed less ALP activity and the mineralization through Ca^{2+} deposits was found to be more for MTA through light microscopic examination.[26]

Haglund et al. noted that the MTA, IRM, amalgam, and Retroplast had inhibited the cell growth of mouse fibroblasts and macrophages. The cell morphology was examined under a phase-contrast microscope and individually detached cells were counted. The retroplast group showed fewer cell numbers when compared to MTA and amalgam. No cytokine production was detected for the four root filling materials, but this could be attributed to the difference in cell type used.[27]

Portland cement (PC) is commonly used in clinical practice due to its comparatively less price. It has a similar composition as that of MTA, except for increased calcium aluminate and calcium sulfate levels. Saidon et al. reported the greater tolerability of both MTA and PC and both did not show any cell reaction in, *in vivo* and *in vitro* tests conducted using L929 culture cells.[28]

Table 1 briefs about the bioactivity studies conducted using cell lines.

In Vitro Animal and Human Studies

Studies had validated the effectiveness of MTA and PC in pulp capping. Bidar et al. had performed a histopathological evaluation of direct pulp capping involving MTA and PC in dog premolars ($n = 64$). Although the researchers had confirmed the pulp protection benefits of these materials, they highlighted the need for conducting extensive research before using them in humans for a longer duration.[29]

Two studies had reported the superiority of MTA over calcium hydroxide due to the formation of a highly thicker calcified bridge. Leye Benoist et al. had compared the effectiveness of MTA and Dycal in forming dentin bridge using specialized software. The software collected data regarding digitized images and surface length for 3 and 6 months. The researchers observed a statistically significant higher success rate for MTA than Dycal for 3 months, but no difference in dentin thickness was noted after 6 months.[30] The randomized control trial by Eskandarizadeh et al. had recommended both white and gray type MTA as the materials of choice for direct pulp capping, in contrast to the hard setting calcium hydroxide cement (Dycal). The study involving 90 intact first and second premolars showed the formation of a significantly thicker calcified bridge with gray MTA when compared to Dycal at 30 and 60 days ($p = 0.015$ and $p = 0.002$, respectively), and the same was noted at 90 days for white MTA ($p = 0.02$).[31]

Shokouhinejad et al. had evaluated the bioactivity of bioaggregate (BA), endosequence root repair material (ERRM), and

Table 1: Characteristics of bioactivity studies conducted using cell lines

Author and year	*Assay*	*Materials evaluated*	*Results*
Güven et al. (2013)[26]	Type of assay (TA): Real-time polymerase chain reaction expression analysis (RT-PCR) and Von Kossa staining Cell lineage (CL): Teflon rings cultured with hTGSCs Type of contact (TC): Indirect	MTA and iRoot SP	MTA was found to be more efficient to mineralize than iRoot SP
Haglund et al. (2003)[27]	TA: ELISA testing. CL: L929 mouse fibroblasts and mouse macrophage cell line RAW 264.7 TC: Direct	MTA, amalgam, IRM, and Retroplast	All the materials showed cell growth inhibition
Saidon et al. (2003)[28]	TA: *In Vitro*: Cell morphology under a phase-contrast microscope *In Vivo*: Light microscope evaluation CL: L929 mouse fibroblasts TC: Direct and indirect	MTA and Portland cement	MTA and PC did not show any cell reaction differentiation and had great tolerability

Table 2: Characteristics of *in vitro* human and animal studies

Author and year	*Assay*	*Materials evaluated*	*Results*
Bidar et al. (2017)[29]	TA: Light microscope evaluation Animal: 64 dog premolars TC: Direct	MTA and PC	Chronic inflammation in WMTA, GMTA, white, and gray PC were 45.5, 27.3, 57.1, and 34.1%, respectively
Leye et al. (2012)[30]	TA: Mesurim Pro(®) software Human: 60 teeth TC: Indirect	MTA and Dycal	MTA and Dycal success rate 3 months: 93 and 73% 6 months: 89.6 and 73% Dentine thickness increased in both materials with time
Eskandarizadeh et al. (2011)[31]	TA: Mesurim Pro(®) software Human: 90 intact first and second premolars of human maxillary and mandibular teeth TC: Indirect	White MTA, Gray MTA, and Dycal	Calcified bridge of GMTA > Dycal at 30 and 60 days WMTA > Dycal at 90 days
Shokouhinejad et al. (2012)[32]	TA: Scanning electron microscopy (SEM) observation and energy dispersive X-ray (EDX) instrument for elemental analysis Human: 60 horizontal root sections TC: Indirect	BA, EndoSequence Root Repair Material (ERRM), and white ProRoot Mineral trioxide aggregate (MTA)	MTA, BA, and ERRM showed increased precipitation with time

white ProRoot MTA. This study conducted on 60 horizontal root sections noted the formation of a substantially greater amount of apatite aggregate after 2 months on the surfaces of all the materials.[32] The characteristics of *in vitro* human and animal studies are summarized in Table 2.

Cytotoxicity

Studies on Human Cell Lines

The selected literature on cytotoxicity assessment conducted in human cell lines demonstrated that the studies were diverse, especially with respect to the BECs compared. Whereas, most of the studies had evaluated the cytotoxicity using MTT assay (Table 3). A 2012 study by Hirschman et al. had reported a statistically significant cytotoxic effect with Dycal (Dentsply).[33]

Two studies had highlighted the increased cytotoxicity of MTA Fillapex. The cytotoxicity evaluation conducted by Yoshino et al. on human cultured periodontal ligament fibroblasts had noted that MTA Fillapex conferred the highest cytotoxic effect followed by white MTA and Portland cement.[34] Similarly, Zhou et al. had reported increased toxicity of MTA Fillapex at ≥2 weeks when compared to fresh/1-week-old cement, but the toxicity was not seen at a concentration of ≥1:32. The study also ruled out the incidence of toxicity of AH plus after setting.[35] An earlier study by Zhou et al. had concluded that the toxicity of Biodentine and MTA was less than the ionomer cement.[36] The researchers used flow

Table 3: Characteristics of cytotoxic studies conducted in human cell lines

Study	*Assay*	*Materials evaluated*	*Result*
Hirschman et al. (2012)[33]	TA: MTT-based colorimetric assay CL: Human dermal fibroblasts Type of contact (TC): Indirect	White mineral trioxide aggregate cement (AMTA, MTA-Angelus), Brasseler ERRM putty, Dycal, and Ultra-blend Plus (UBP)	AMTA, ERRM, and UBP had statistically similar cytotoxicity levels. However, Dycal demonstrated a statistically significant cytotoxic effect
Ma et al. (2011)[37]	TA: MTT assay CL: Gingival fibroblast	ERRM Putty and Paste with gray MTA	(ERRM Putty) and Paste (ERRM Paste) showed similar *in vitro* biocompatibility as that of gray MTA
Yoshino et al. (2013)[34]	TA: MTT assay CL: Periodontal ligament fibroblasts TC: Indirect	White MTA, MTA Fillapex® and Portland cement (PC)	MTA Fillapex demonstrated the highest cytotoxic effect on periodontal ligament fibroblasts followed by white MTA and PC
Zhou et al. (2015)[35]	TA: Flow cytometry and electron microscopy CL: Human gingival fibroblasts TC: Indirect	EndoSequence BC, MTA Fillapex, and AH Plus (control sealer)	The 2 calcium silicate-containing endodontic sealers demonstrated different cytotoxicities. MTA Fillapex of ≥2 weeks demonstrated more toxicity than fresh/1-week-old cement. MTA Fillapex did not show toxicity at concentration ≥ 1:32. AH plus was not toxic after setting
Mukhtar-Fayyad (2011)[38]	TA: MTT assay CL: Human fibroblast MRC-5 cells TC: Indirect	BioAggregate and iRoot SP	Both the materials had acceptable biocompatibility and their cytotoxic effects were concentration-dependent
Zhou et al. (2013)[36]	TA: Flow cytometry and electron microscopy CL: Human gingival fibroblasts TC: Indirect	Biodentine, White ProRoot MTA, and glass ionomer cement	No significant difference in cell viability was noted between Biodentine and MTA, and they had a less cytotoxic effect than glass ionomer cement

cytometry and electron microscopy-based assays for the evaluation of cytotoxicity in both studies.

Ma et al. had demonstrated that *in vitro* biocompatibility of ERRM putty and ERRM paste were comparable to that of gray MTA.[37] Hirschman et al. had also reported the statistically comparable cytotoxicity levels of AMTA, ERRM putty, and UBP.

One study had identified the acceptable biocompatibility of BioAggregate and iRoot SP, the calcium silicate-phosphate-based ceramic with nano-composition. The study on human fibroblast showed cytotoxicity of BioAggregate was more when compared to iRoot SP and their cytotoxicity was independent of extract concentration.[38]

Cytotoxicity Studies on Animal Cell Lines

Most of the cytotoxicity studies on animal cell lines were based on MTT assay (Table 4). The genotoxic and cytotoxic study conducted on L929 mouse fibroblast cells by Naghavi et al. had suggested a calcium-enriched mixture (CEM) with comparable biocompatibility as an alternative to MTA. Another major finding was the increased damage of cells by MTA at higher concentrations than CEM (1,000 µg/mL). The researchers speculated high level of arsenic in the medium containing MTA as the reason for increased toxicity at higher concentrations.[39]

Alanezi et al. had concluded that the cytotoxicity of ERRM was comparable to that of gray and white MTAs at both set and fresh conditions.[40] The study also underscored the need for further investigating the solubility, sealing ability, and *in vivo* endodontic usage of ERRM.[41]

Ma et al. had noted elevated cytotoxicity of MTA Fillapex at 1:1, 1:2, 1:4, and 1:8 dilutions, and that of AH plus at 1:1, 1:2, and 1:4 dilutions. In addition, both these sealers showed reduced cell viability rates and increased formation of micronuclei when compared to control. The study had concluded white MTA as a less cytotoxic material with cell viability >70%.[42]

Ribeiro et al. had shown that both MTA and Portland cement do not induce DNA damage and cellular death, which are important events in carcinogenesis. The study conducted on Chinese hamster ovary (CHO) cells using trypan blue staining further corroborated the use of MTA and Portland cement in dentistry.[43]

Cytotoxic Studies Conducted in Animal Models

Saidon et al. had evaluated the *in vitro* and *in vivo* biocompatibility of MTA and PCs using L929 cell lines and guinea pig models. *In vitro* study did not show any difference in cell reaction between ProRoot MTA and PC. The *in vitro* study and insertion of materials into the bone cavities of animal models showed bone healing and minimal inflammatory response adjacent to both the material implants. Though the study had suggested PC as a less expensive root-end filling material, the researchers highlighted the need for more human-based studies before the recommendation for unlimited clinical use (Table 5).[28]

Table 4: Cytotoxicity studies on animal cell lines

Author and year	*Assay*	*Material evaluated*	*Results*
Naghavi et al. (2014)[39]	Type of assay (TA): MTT assay Cell lineage (CL): L929 mouse fibroblast Type of contact (TC): Indirect	Calcium enriched mixture (CEM) and MTA	Statistically no difference was found between the materials at concentration 0–500 µg/mL, except at concentration 1,000 µg/mL
Alanezi et al. (2010)[40]	TA: MTT assay CL: L929 mouse fibroblast TC: Indirect	ERRM with gray MTA (GMTA), white MTA (WMTA), and AH26	The cell viability of ERRM was comparable to GMTA and WMTA in both set and fresh conditions
Bin et al. (2012) [42]	TA: MTT assay CL: Chinese hamster fibroblasts (V79) TC: Indirect	WMTA (Branco, Angelus), MTA Fillapex (Angelus), and AH Plus (Dentsply)	WMTA cell viability rates were above 70% at all concentrations but MTA Fillapex and AH Plus were cytotoxic at higher concentrations
Ribeiro et al. (2006)[43]	TA: Comet assay using trypan blue staining CL: Chinese hamster ovary (CHO) cells TC: Indirect	MTA Angelus, Portland cement, and white Portland cement	MTA and Portland did not produce or induce any strand breaks in DNA at all concentration

The cytotoxicity of ProRoot MTA and DiaRoot BA, a bioceramic nanoparticulate cement, were compared in a study involving 50 Sprague-Dawley rats. The histopathologic evaluation carried out after implanting the materials into a dorsal connective tissue of rats for 7, 15, 30, 60, and 90 days showed that BA is more biocompatible than MTA.[44] However, the results were more favorable for MTA in the presence of dystrophic calcification (Table 5).

Discussion

In dentistry, the bioactivity of a material signifies its ability to hydrolyze and produce calcium hydroxide, which in turn contributes to the formation of an interfacial layer and development of an apatite layer.[45–49] The activity or bioactivity index is a measure of dental bone regeneration rate and apatite formation level. The dentin bridge is formed by the increased activity of pyrophosphates, which is augmented by the calcium ion release.[50–52] The bioactivity assays are intended to evaluate the ability of different materials to form apatite and mineralization based on their composition and strength.[53] Alkaline phosphatase (ALP)[54,55] and simulating body fluid (SBF) medium are the most commonly used quantitative indicators of mineralization.[56,57]

Literature search shows that there are very limited studies with sufficient data on the bioactivity of BECs. Such studies have been conducted mainly on cell lines such as human dental pulp cells (HDPCs), human tooth germ stem cells (hTGSCs), MG-63, etc.[32,58] The available bioactivity studies are mainly on the comparison of MTAs with other popular sealing materials to characterize their effects and bioactivity. The literature evidence shows that MTA is more efficient with regard to mineralization and improved tolerability;[59,60] however, it should be noted that very limited studies have been conducted on the bioactivity of materials other than MTAs.

The study conducted by Guven et al. had concluded that MTA is superior and more bioactive compared to iRoot SP using hTGSCs cell line. Comparison of the same materials by Yuan et al. using RAW 264.7 had provided insights on the mechanism involving the use of MTA as a potential endodontic material for the treatment of persistent apical periodontitis. The researchers reported that both iRoot SP and MTA, induced by lipopolysaccharide, can augment the expression of IL-1β, TNF-α, and IL-6.[61]

The present review could identify the cell lines (Saidon et al.) and animal studies (Bidar et al.) suggesting comparable bioactivity of Portland cement and MTA. In concurrence with these findings, Bhagat et al. had concluded that the favorable biological response of PC to pulpotomy treatment was comparable to that ProRoot MTA.[62] Shahi et al. had also advocated the use of PC as an alternative to MTA. The study reported no statistically significant difference between white MTA, gray MTA, white PC, and gray PC.[63]

The present review has quoted two human studies comparing the bioactivity of MTA and Dycal (Leye Benoist et al., Eskandarizadeh et al.). Both the studies had highlighted the superiority of MTA over Dycal; but activities such as solubility, dentin bridge formation, and biointeractivity varied between the studies. Similar to these findings, Gandolfi et al. had recommended MTA Plus as a substitute for conventional calcium silicate MTA-like cements owing to its enhanced reactivity, and prolonged potential to release calcium and increase the local pH.[64] In contrast, a review by Al-Sabri had concluded calcium hydroxide as the first choice in clinical practice due to the high cost of MTA and the challenges associated with its mixing and handling.[65]

ProRoot MTA and MTA Angelus were found to be inert and viable.[15] ProRoot MTA had demonstrated greater biological properties over OrthoMTA and Endocem MTA in root repair and excellent bioactivity over the traditional cements.[66,67]

Collado-González et al. reported better cytocompatibility and bioactivity of Biodentine than MTA Angelus, TheraCal LC, and IRM when tested on stem cells from human exfoliated primary teeth.[68] Biodentine has been reported to be more advantageous than MTA owing to its consistency, better mechanical properties, and improved handling.[3,69]

Though *in vitro* and *in vivo* studies corroborated the biocompatibility of MTAs, further human studies involving genotoxicity tissue implantation tests and sensitization tests are required to establish a more general outlook on the safety profile of these materials.[70]

Table 5: Characteristics of cytotoxic studies conducted in animal models

Author and year	*Assay*	*Materials evaluated*	*Results*
Saidon et al. (2003)[28]	TA: *In vitro* and *in vivo* assay *In vitro*: Millipore culture plate inserts with freshly mixed or set material placed on already attached L929 cell plates *In vivo*: Freshly mixed materials were inserted into the bone cavities of adult male guinea pigs and histologically evaluated using a light microscope	ProRoot MTA and Portland cement	Both *in vitro* and *in vivo* studies demonstrated that MTA and PC have comparative biocompatibility
Batur et al. (2013)[44]	TA: *In vivo* assay The materials were implanted into a dorsal connective tissue of rats for 7, 15, 30, 60, and 90 days	ProRoot MTA and DiaRoot BA	DiaRoot BioA was found to be more biocompatible than MTA

The viability of periradicular cells following retrograde filling, pulp capping, and perforation repair may depend on the cytotoxicity of the root filling material used and they may induce apoptosis or necrosis .[71,72] Hence, the use of materials that are toxic to pulpal and periapical tissues may impair the prognosis and clinical outcome.[73]

The present review has identified literature evidence from both human and animal cell lines suggesting increased cytotoxicity of Fillapex. A comparative study of odontoblast-like cells showed that MTA Fillapex possess more cytotoxicity than AH Plus.[74–76] The cellular responses in human dental pulp stem cells noted by Victoria-Escandell et al. had identified MTA-Fillapex as the most cytotoxic oxidative stress inductor in preincubated cell culture medium. The ability of endodontic materials to produce oxidative stress correlates with their cytotoxicity and genotoxicity.[77–79]

One study had reported a statistically significant cytotoxic effect of Dycal to adult human dermal fibroblasts.[33] In concurrence with this finding, a comparative study involving 7 pulp-capping materials had demonstrated the highest cytotoxic effect with Dycal (10% cell viability).[80] The study compared the following pulp-capping materials *in vitro*: TheraCal LC, Dycal, Calcicur, Calcimol LC, ProRoot MTA, MTA-Angelus, and Biodentine. This study also reported the comparable cytotoxic effect of Biodentine with that of MTA, thereby suggesting it as an alternative pulp-capping material.[81–83]

Biodentine was introduced to the market in 2010 to overcome the limitations of the MTA such as increased cost, slow setting time, and difficulty in manipulation.[24] Biodentine and MTA have been reported to be less toxic and more viable than glass isomers at all concentrations.[84] Calcium-enriched mixture cement, Biodentine, and MTA exhibited similar cytotoxicity and can be considered equally for root-end surgery procedures.[19,85–87] The cytotoxicity is dependent on the chemical composition and varies with the incubation period or setting time. ProRoot MTA and Biodentine with a greater incubation period of 48 hours showed less cytotoxicity than CEM and Biosealer.[21,44] In the current review, the 2013 and 2015 studies by Zhou et al. have corroborated the reduced cytotoxicity of MTA-based products. The researchers used flow cytometry and electron microscopy-based assays for the evaluation of cytotoxicity.

The present review has quoted the studies by Hirschman et al. and Jingzhi et al. suggesting the comparable cytotoxicity of ERRM putty with MTA. Contrary to these findings, a rat-model study by Khalil and Abunasef had reported that the implantation of both ERRM and MTA produced injurious effects on subcutaneous tissues.[44]

The present systematic review holds considerable significance, as to the best of our knowledge, there is no review evaluating the cytotoxicity and bioactivity of available BECs and MTAs. Moreover, following a more rigorous and prospectively defined objective process for the data collection, extraction, and compilation helped in critically scrutinizing the study methodologies and excluding those with vague study designs and unclear protocols. Another area of research is cytotoxicity of the freshly mixed material and its reduction with time. The present review showed that there is very limited data on the cytotoxicity of the freshly mixed materials.

The current study could not perform a meta-analysis of the available literature due to the diversity of the studies including the type of cell lines used and assays conducted. Since a meta-analysis could not be carried out, generalization of the study findings was not possible. Another limitation was the availability of a few studies on all the available BECs in the market, especially pertaining the bioactivity. Moreover, the majority of the studies have used MTA for comparison. Hence, the present literature evidence was inadequate to conduct a more credible review to arrive at a consensus on the ideal material with minimal cytotoxicity and optimal bioactivity.[47,88–90] However, the present review confirmed that MTA is the most frequently used as well as studied root-end filling cement, and substantiates its reduced cytotoxicity and enhanced bioavailability.

Conclusion

The current review serves as an update on the available evidence on the cytotoxicity and bioactivity of available BECs and MTAs. It may assist researchers to conduct more focused human-based studies, thereby developing a general agreement on the available root filling materials. The available literature indicates MTA as the most frequently used endodontic filling material with reduced cytotoxicity and improved bioavailability.

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