How does the pulpal response to Biodentine and ProRoot mineral trioxide aggregate compare in the laboratory and clinic?

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Key points

- Represents a timely evidence-based analysis of whether Biodentine is more suitable for pulpal applications than the current 'gold-standard' ProRoot mineral trioxide aggregate (MTA).
- Highlights that although there is a lack of clinical studies comparing the materials, Biodentine appears to perform well compared with ProRoot MTA.
- Suggests that biologically the materials stimulate similar pulpal responses, however, ProRoot MTA has a better radioapacity, but longer setting time than Biodentine.
- Suggests that Biodentine discolours teeth less than ProRoot MTA.

Introduction Vital-pulp-treatment (VPT) procedures are biologically-based therapies aimed at preserving pulp-vitality. Historically, calcium-hydroxide was the 'gold-standard' VPT-material, however, recently a tricalcium-silicate material, ProRoot-mineral-trioxide-aggregate (MTA) has emerged as the material of choice for pulpal-application in permanent teeth. ProRoot-MTA also has drawbacks, including long-setting time, handling-difficulties and post-application crown-discolouration. Relatively recently, another tricalcium-silicate material, Biodentine, has been indicated for VPT. **Objectives** The aim of this review was to compare from relevant laboratory, biological and clinical-studies whether Biodentine is a better material than ProRoot-MTA for use in pulpal applications in permanent teeth. **Methods** A comprehensive MEDLINE search was used to identify manuscripts, which directly compared the materials in relation to dental-pulp applications. **Results** Literature analysis demonstrated that most of the comparative research is *in vitro* cell-culture studies demonstrating a wide range of methodologies and conflicting findings. In contrast there is a paucity of clinical studies comparing the pulpal response to the materials in permanent teeth. Histological evidence suggests similar pulpal responses, while clinical outcome studies, although preliminary, show equally high material efficacy. Other physical characteristics diverge with Biodentine setting quicker and staining less than ProRoot-MTA, however, the radiopacity of Biodentine is below testing standards making identification difficult. **Conclusions** Biodentine does present an evidence-based biologically-based alternative VPT material to ProRoot-MTA. Future research should be directed at long-term clinical outcome studies and the interaction of Biodentine with the dentine matrix.

Introduction

Exposure of the pulp is a common clinical occurrence due to trauma, caries or iatrogenic reasons. The pulp is protected by an outer shell of enamel and dentine; when this protection is breached the pulp is colonised by microbes with the simulation of a pulpal inflammatory response.[1] If the pulpitis is untreated, ultimately, pulp necrosis occurs.[2] Pulp vitality can be maintained if the irritant stimulus is removed and the tooth restored.[1] The importance of retaining all or part the pulp has been highlighted as it is more conservative, less technically demanding and more biologically-based compared with pulpectomy procedures.[3,4]

The aim of the vital pulp treatment (VPT) is to preserve the vitality and function of the pulp, while stimulating hard tissue repair processes.[5,6] VPT encompasses procedures with no pulp tissue removal, ie pulp capping (indirect and direct) as well as techniques with varying degrees of pulp excision, that is, pulpotomy (partial or complete).[5] Several factors influence the success of VPT procedures including the level of pre-operative pulp inflammation,[7] the post-operative prevention of further microbial insult[8] and the material used to interface with the biological tissue.[9] Historically, VPT was considered as an unpredictable procedure.[10] Calcium hydroxide has been the material of choice for many years,[11,12] but is limited by poor mechanical properties, non-specific mechanism of action,[13] absence of sealing properties[14] and incomplete hard tissue formation over the pulp wound.[8,9] Developments in our understanding of pulp defence mechanisms[4] and the advent of tricalcium silicate materials have created new opportunities and enthusiasm for VPT.[15] The tricalcium silicate, mineral trioxide aggregate (MTA), has demonstrated superior histological[9,16] and clinical outcome compared with calcium hydroxide in VPT procedures.[17]

The original, most researched and, within the United Kingdom, the market leading commercial MTA product, ProRoot MTA (Dentsply Sirona, Ballaigues, Switzerland), is not an ideal material with several disadvantages highlighted including a long-setting time,

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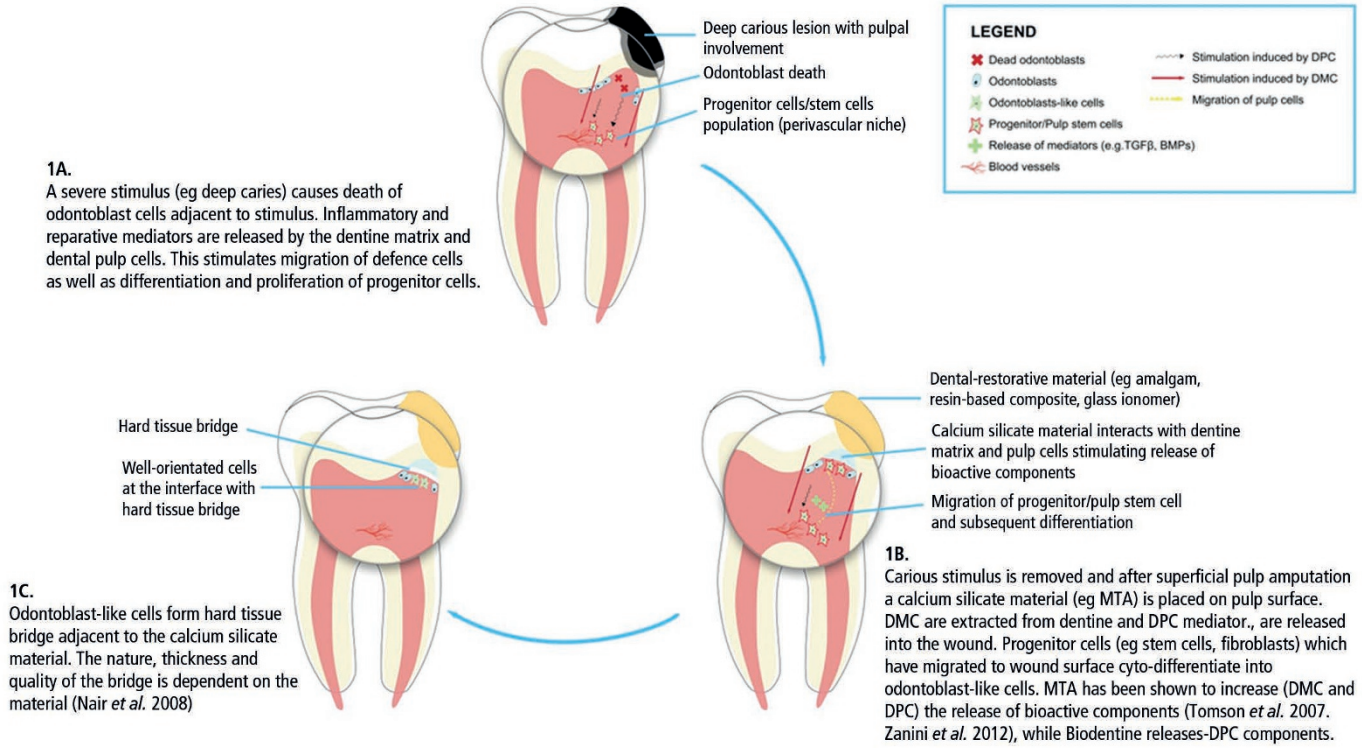

Fig. 1 Schematic theoretical representation of the process of reparative dentinogenesis after a VPT procedure using calcium silicate cement

tooth discolouration and high-cost.[17–20] New generation tricalcium silicate-based cements have been introduced, which attempt to address many of the shortcomings of ProRoot MTA. Biodentine (Septodont, Sant-Maur-des-Ditch Cedex, France) is a tricalcium silicate cement marketed specifically for use in VPT procedures. Publications have highlighted its positive effects on pulp mineralisation processes, shorter setting-time, improved mechanical resistance and ease of use compared with ProRoot MTA for use in VPT procedures.[21–24]

ProRoot MTA is chemically composed of Portland cement with bismuth oxide added as a radiopacifier.[25] There are now a range of other commercial MTA products available, including Angelus MTA and Angelus HP (The Angelus, Londrina, Brazil), MM–MTA (Micro-Mega, Besancon, France), Retro/ Ortho MTA (BioMTA, Seoul, Republic of Korea) and MTA Plus (Avalaon Biomed, Houston, USA), which share the presence of di and tricalcium silicates, as well as radiopacifiers.[26] These products vary in their radiopacifiers (bismuth oxide, zirconia, calcium tungstate and tantalite), but also have minor differences including the presence of calcium sulphate, calcium carbonate and phyllosilicates.[26] Biodentine is similar to ProRoot MTA, but does not contain calcium aluminate, calcium sulphate or bismuth oxide, while zirconium oxide is the radiopacifier.[26] The absence of bismuth oxide in Biodentine is significant not only for radiopacity, but also for other properties such as staining potential, setting time and micro-hardness.[27,28] Due to differences in chemical formulation a recent review has suggested that these materials could be grouped as 'bioactive endodontic cements (BECs)' rather than calcium silicate materials.[29]

From a reparative perspective, the role of the odontoblast cell is critical, forming the primary dentine during development, secondary dentine throughout the life of the tooth and when challenged the deposition of tertiary dentine in an attempt to 'wall off' the irritation.[30] Depending on the severity of the stimulus, tertiary dentine deposition can be reactionary or reparative.[31] Reactionary dentine being formed by an upregulation of surviving post-mitotic odontoblasts exposed to the influence of relatively mild stimuli, while reparative dentine is formed generally after a stronger stimuli, which has led to death of the odontoblast cell.[31,32] At a cellular level reparative dentine is believed to be produced following cyto-differentiation of pulpal progenitor cells and the formation of a new generation of odontoblast-like cells.[31,32] Alternative theories suggest that other cells such as fibroblasts may cyto-differentiate to produce the mineralised tissue.[33] The cellular differentiation is likely to be guided by the influence of growth factors and bioactive molecules derived from both the dentine and the pulp matrix.[34,35] Although reactionary and reparative dentinogenesis are for didactic purposes considered separately, in the event of pulp exposure reparative dentine will form the mineralised bridge, while at the periphery of the cavity reactionary dentinogenesis will occur simultaneously.[3]

Inflammation is also an important stimulus to drive the reparative process with odontoblasts involved in initial sensory stimulus transmission from the dentine and also an immunocompetent role in cellular defence.[36,37] Indeed the low level release of inflammatory mediators such as interleukins (for example, IL–1α, –1β, –2, –6) in mineralising cells in contact with MTA supports the need for a degree of inflammation in promoting regenerative processes.[38] A wide range of bioactive dentine matrix components are 'fossilised' in the mineralised tissue being released into pulp during caries or trauma.[3,39,40] Demineralisation of dentine and indeed contact with materials such as Pro Root MTA, calcium hydroxide and other agents release a plethora of bioactive molecules including members of the TGF–β superfamily which can stimulate a complex cascade of molecular events that promote pulp repair.[34,41–43] Notably, no evidence suggests that Biodentine is capable of sequestering dentine matrix components so comparative bioactivity analysis with ProRoot MTA is not possible.

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Table 1 Biological laboratory *in vitro* studies comparing the efficacy of ProRoot MTA (PrMTA) and Biodentine (BD) within the same publication

Reference	Methodological approach and species	Materials investigated	Variables analysed	Principal results
Pérard *et al.* 2013[69]	• *In vitro* • Two murine pulpal cell-lines (MDPC-23, OD-21)	• BD • PrMTA	• Cell viability (acid phosphatase assay) • Gene expression (qRT-PCR) OP, ALP, Runx2,Col1a1 • Phenotypic analysis (SEM)	• MDPC-23 cells cultured with PrMTA superior viability to BD at 7d • PrMTA and BD reduced cell proliferation compared with control • Colla1 expression reduced in PrMTA compared with BD
Corral Nunez *et al.* 2014[101]	• *In vitro* • Murine embryo fibroblast cell line (3T3)	• BD • PrMTA • GIC	• Cell viability (Alamar blue assay) and proliferation • Cell morphology in response to dental material (SEM) • Cytokine expression (Semi Quantitative RT-PCR) for IL1β, IL6	• Similar cell viability for BD and PrMTA at 72h, reduced for GIC. • BD showed increased cell growth and development (extended cellular processes) in comparison with PrMTA and GIC • No difference in IL-1β expression, all groups. PrMTA showed increased IL6 expression at 3 hrs compared with BD, but not at 24 hrs
Widbiller *et al.* 2015[70]	• *In vitro* • Human DPSCs	• BD • PrMTA • GIC	• Cell viability (MTT assay) • ALP activity • Gene expression (Quantitative RT-PCR) for ALP, Runx2, Col1a1, DSPP, RPS18	• BD showed higher cell viability than control. PrMTA had reduced viability at 7d; however, at 10d and 14d the difference not significant, instead GIC significantly lower cell viability • Reduction of ALP activity with PrMTA and BD compared to control • Gene expression of Col1a1 initially increased with PrMTA before decline. DSPP expression increased in BD and PrMTA. Expression of Runx2 down-regulated.
Poggio *et al.* 2015[72]	• *In vitro* • Murine pulpal cell-line (MDPC-23)	• Dycal • Calcicur • Calcimol • TheraCal • PrMTA • AMTA • BD	• Cytotoxicity • Cell viability (MTT, Alamar blue assay) • Cell damage/apoptosis (Confocal Laser Scanning Microscope)	• BD, AMTA, PrMTA not cytotoxic; Calcimor, Calcicur, Theracal slightly more cytotoxic than control; Dycal high cytotoxicity. • BD cell viability remains stable, PrMTA and AMTA showed slightly decreased viability at 72h, Calcicur maintained discrete cell viability while Calcimol and Theracal have important reduction at 72h. Dycal less cell viability
Margunato *et al.* 2015[71]	• *In vitro* • Stem cells isolated from human mandibular bone marrow (hBMSCs)	• BD • PrMTA • MM-MTA	• Cell viability (ELISA) • ALP activity • Mineralisation (Alizarin Red) • Gene expression (qRT- PCR) for Col1a1, ON, Runx2	• Similar cell viability in all groups • ALP activity increased in both PrMTA species in relation to control group, BD decreased • Increased gene expression of Runx2 and ON compared to control group. • No significant differences in mineralisation between materials

Abbreviations: ALP = Alkaline phosphatase, AMTA = Angelus-MTA, Col1a1 = Collagen type I alpha 1 chain, DSPP = Dentin sialophosphoprotein, GIC = Glass ionomer, IL = Interleukin, IRM = Intermediate Restorative Material, PrMTA = ProRoot MTA, OP = Osteopontin, Runx2 = Runt-related transcription factor 2, RPS18=Ribosomal protein S18

Using biologically-based dental materials that promote the healing process are paramount in vital pulp therapy and other irrigation strategies are being developed which enhance the release of bioactive molecules from dentine to improve the wound repair.[44,45] Over the last ten years, tricalcium silicate materials, including ProRoot MTA and Biodentine, have demonstrated superior histological response compared with the gold standard material calcium hydroxide in VPT.[9,24] It is assumed that tricalcium silicates work more efficiently than calcium hydroxide and in a similar way to each other (Fig. 1).[13,24] ProRoot MTA and Biodentine have shown the capacity to promote the early synthesis of reparative dentine, perhaps due to enhanced regulation of TGF-F-β1, osteopontin and other growth factors.[23,24]

The aim of this review was to comprehensively analyse only the laboratory and clinical studies which compared the most commonly used and researched tricalcium silicate materials, ProRoot MTA and Biodentine, specifically in relation to the dental pulp.

Review

Search strategy

A comprehensive MEDLINE search up to November 2017 was conducted using medical subject headings (MeSH) in combination with 'and' or 'or'. The major MeSH terms searched were 'Endodontics', 'Dental Pulp Disease', 'Dental Pulp Test', 'Pulpotomy' and 'Dental Pulp Capping'. In addition, the following terms were added 'Biodentine', 'Mineral Trioxide Aggregate', 'MTA', 'calcium silicate cements', 'calcium silicate materials', 'calcium silicates' as well as 'di and tricalcium silicates'. Bibliographies of all relevant papers and previous review articles were hand-searched for further studies of relevance. Any relevant work published in the English language and presenting pertinent information related to this review was considered for inclusion. Titles were excluded if they were conference reports. Laboratory (biocompatibility, biological, material aspects) studies were considered if Biodentine and MTA were compared within the same study. Clinical studies focused on comparative responses in permanent teeth.

How are the success of ProRoot MTA and Biodentine in VPT procedures compared clinically?

The aim of VPT is to maintain the vitality of the tooth in the absence of an apical radiolucency and, in case of immature teeth, achieve apexogenesis. Therefore, outcome should be assessed from both a clinical and radiographic perspective.[5,46] Clinically, the treated tooth should respond positively to pulp sensibility testing (if possible to assess) and not present any sign or symptoms such as pain, tenderness to percussion or presence of a sinus tract.[6,47] The radiographic examination should demonstrate no signs of apical periodontitis, no evidence of internal resorption, present evidence of mineralised bridge formation and continued root development in immature teeth.[6,48,49] A follow-up appointment no longer than six months postoperatively is recommended and a recall of one year; long-term follow up is also

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Table 2 Laboratory and clinical comparison of ProRoot MTA (PrMTA) and Biodentine (BD) as an ideal material for vital pulp treatment according to criteria listed in Ingle's Endodontics (Bogen & Chandler 2008)[73]

Ideal material characteristic	Reference	Comparative results
Stimulate reparative dentine formation	Nowicka *et al.* 2015[67]	Clinical trial, histological *ex vivo* study. Tested CH single bond universal RBC, PrMTA, BD. Both PrMTA and BD materials induced a similar hard tissue bridge. The bridge (BD and MTA) was homogeneous with no tunnel defects. MTA, BD and CH, showed a thicker dentine bridge than RBC.
	Bakhtiar *et al.* 2017[74]	Clinical trial, histological *ex vivo* study. Tested BD, PrMTA and TCal. Teeth vital at eight weeks with all materials. Significant increase inflammation, tissue disorganisation and incomplete hard tissue bridge formation with TCal when compared to BD and PrMTA. Similar results for BD and PrMTA (lack of inflammation and good tissue organisation); however, BD group showed complete dentinal bridge formation in all teeth with TCal (11%) and PrMTA (67%), respectively.
	Brizuela *et al.* 2017[59]	Randomised clinical trial. Tested CH, BD and PrMTA. No significant difference between the materials, selected failures in PrMTA and CH groups, but BD had success rate of 100%.
Maintain pulpal vitality	Nowicka *et al.* 2013 & 2015[23,67]	Both PrMTA and BD maintain pulp vitality in 'sound' teeth over the duration of the study (six weeks). Same duration in both studies.
	Brizuela *et al.* 2017[59]	Both PrMTA and BD maintain pulpal vitality. Even if no statistically significant MTA showed one case of failure
Release fluoride		No fluoride release from BD or MTA commercial materials
Bactericidal or bacteriostatic	Bhavana *et al.*2015[75]	PrMTA, BD and GIC tested against: *S. mutans*, *E. faecalis*, *E. coli* and *C. albicans*. BD showed best antimicrobial activity. Both MTA and BD are more effective than GIC.
	Ceci *et al.* 2015[102]	PrMTA, AMTA, BD and IRM were checked against *S. mutans*, *S. salivarius* and *S. sanguis*. PrMTA AMTA and IRM showed better results against *S. mutans* and *S. salivarius*. BD showed better results against *S. sanguis*, but was not active against *S. mutans*.
Adhere to dentine	Guneser *et al.* 2013 [78]	Tested by push out strength test BD, PrMTA, IRM, Amalgam, Dyract AP. BD demonstrated greater adherence to dentine than PrMTA.
	Nagas *et al.* 2016[79]	Compared PrMTA and BD by push out strength testing. BD better adhesion to dentine.
Adhere to restorative material	Altunsoy *et al.* 2015[103]	Compared AMTA, CEM, BD (not PrMTA). BD showed the weakest adhesion to flowable composites.
Resist forces during subsequent restoration placement		No good evidence
Long-term insolubility restoration	Kaup *et al.* 2015[76]	Both materials fulfil the ISO standards of solubility but BD is significantly more soluble than PrMTA.
Sterile		Not mentioned in the manufacturer's instructions for either material
Radiopaque	Kaup *et al.* 2015[76]	Tested PrMTA and BD. MTA higher radiopacity, BD below ISO standards.
Provide seal against bacterial ingress	Nowicka *et al.* 2013[23] Tsesis *et al.* 2017 [77]	Both PrMTA and BD did not allow bacterial infiltration. Tested BD, PrMTA, IRM. All materials allow bacterial colonisation at the interface material/dentine, but bacteria showed the less viability in samples treated with BD/IRM compared with MTA.

Abbreviations: AMTA = Angelus MTA, CEM = Calcium-enriched mixture cement, CH = $Ca(OH)_2$, GIC = Glass-ionomer cement, IRM = Intermediate restorative material, TCal = TheraCal

required to assess the success of the procedure.[6]

VPT materials should ideally be compared in adequately powered, randomised clinical trials (RCT), which are free from bias.[17,50–52] The clinical performance of new materials can also be investigated, but not compared in case series and case reports.[53–55] Clinical trials comparing ProRoot MTA and Biodentine pulpotomy procedures in carious deciduous molars have demonstrated that the two materials have equally effective outcomes in young patients.[57,58] Unfortunately, there is a paucity of clinical studies comparing the outcome of Biodentine and ProRoot MTA in VPT procedures in permanent teeth. One recent RCT compared Biodentine and ProRoot MTA as pulp capping materials in asymptomatic cariously-exposed permanent molar teeth and reported no difference between the materials after one-year recall.[59] In this study, 169 patients with carious exposures of one permanent molar were treated with calcium hydroxide, ProRoot MTA or Biodentine with no significant differences between the materials and very few failures reported in any of the experimental groups at one year, however, for practical reasons (handling, placement) it was concluded that Biodentine and ProRoot MTA offered advantages over calcium hydroxide.[59] This clinical trial investigated tricalcium silicate pulp capping on carious exposures in permanent teeth of a young patients (seven to 16 years), which by the author's admission contained significant numbers of teeth with open apices[59]. To homogenise the patient sample other studies investigated VPT procedures in older patients, 15 to 30 years and 18 to 40 years.[60,61] A small clinical trial of 24 patients with cariously exposed molars were pulp capped with either Biodentine or ProRoot MTA and reviewed up to six months; ProRoot MTA was reported to perform better but the results were not significantly different.[60] Another small retrospective pulp capping study investigating the two materials in carious molars concluded after 18 months that both materials performed predictably and equally, however care must be taken in extrapolating the results because the sample size in both studies was

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Table 3 Comparison of practical issues and drawbacks of Biodentine (BD) and ProRoot MTA (PrMTA) investigated *in vivo* and *in vitro*

Issue	MTA	Biodentine	References
Discolouration	• PrMTA reported to cause crown discolouration. • Related to the presence of bismuth oxide	• No or less disclouration reported. • Generally less compared with Pr MTA. • Only one study reports more discolouration than PrMTA (Beatty & Svec 2015)[91]	Bortoluzzi *et al.* 2007, Lenherr *et al.* 2012, Felman & Parashos, 2013, Marciano *et al.* 2014, Camilleri 2015, Kohli *et al.* 2015, Vallés *et al.* 2015, Beatty & Svec 2015, Keskin *et al.* 2015, Yoldas *et al.* 2016 [8,20,27,85–91]
Setting time	• Long setting time between 15 min (MTA Angelus) and >2 hours (ProRoot MTA)	• BD manufacturer setting time of 12 minutes • Reported up to to sevenfold longer • No significant difference between BD and MTA Angelus reported	Torabinejad *et al.* 1995, Kogan *et al.* 2006, Wiltbank *et al.* 2007, Grech *et al.* 2013, Kaup *et al.* 2015[76,94,96–98]
Handling	• Handling is considered difficult because of formulation and difficulties in compacting • Can mix to desired consistency	• BD is generally considered easier to use and mix • Cannot mix to desired or bespoke consistency	Kogan *et al.* 2006, Wiltbank *et al.* 2007, Ma *et al.* 2011, Butt *et al.* 2014 [94,98–100]
Cost	• High cost	• High cost	Chin *et al.* 2016[19]
Radiopacity	• Good radiopacity above ISO radiopacity standards	• BD difficult to visualise as radiopacity similar to dentine • Below ISO standards for radiopacity of dental materials	Tanalp *et al.* 2013, Kaup *et al.* 2015, Lucas *et al.* 2017 [76,92,93]

inadequate to potentially recognise any statistical difference between the materials.[61]

From the limited evidence available, the success rate for VPT procedures is high with both materials, however, existing studies are preliminary, limited by small numbers and short follow-up period, and only investigate pulp capping, not pulpotomy procedures. Other important clinical variables including calcium silicate-associated discolouration was only reported in one study.[61]

How are Biodentine and ProRoot MTA compared in the laboratory with respect to the pulp?

The majority of research comparing the histological response to VPT materials is carried out in sound teeth, which limits confounding factors and enables comparison, but decreases the clinical relevance of the study.[33,62] Recruiting human subjects who are prepared to consent to a VPT procedure on a sound tooth before later scheduled extraction is challenging and as a result the majority of *ex vivo* studies are carried out using animal models, which have their own limitations.[63–65] Several qualitative and quantitative *ex vivo* human studies comparing a range of VPT materials have been published.[9,16,23,66,67] These studies should carefully evaluate histologically with serial sections the soft tissue response – inflammation, necrosis, odontoblast-like cell presence, bacterial infiltration, pulpal calcifications – as well as hard tissue bridge formation, recording its thickness, homogeneity and the cellular interface with the materials.[9,23] Cone-beam computed tomography (CBCT) has been used to assess the hard tissue bridge before the histological exam.[67] One recent histological study compared Biodentine and ProRoot MTA (as well as calcium hydroxide and composite resin) and concluded that both ProRoot MTA and Biodentine materials induced a similar mineralised bridge formation at the pulp-material interface. The bridges from Biodentine and ProRoot MTA were homogeneous and with minimal tunnel defects.[67]

In addition to a limited number of *ex vivo* studies, other *in vitro* biological studies have compared Biodentine with ProRoot MTA within the same study (Table 1). There have been cell culture studies using primary cells (rodent or human dental pulp cells) or odontogenic cell lines (for example, MDPC–23), which analyse cellular processes such as cytotoxicity, migration, viability, differentiation, inflammation and mineralisation (Table 1).[21,68–71] Although these laboratory studies represent the majority of research on this subject, unfortunately, it is not possible to conclude from these biological studies comparing Biodentine and ProRoot MTA that one material is consistently better than the other (Table 1).

How do Biodentine and ProRoot MTA compare to the criteria for an ideal VPT material?

If additional evidence is collated from clinical, *ex vivo* and *in vitro* studies and analysed with respective to Ingle's criteria, (Table 2) it is evident that Biodentine compares equally to ProRoot MTA for reparative dentine formation, maintaining pulp vitality, anti-bacterial properties, long-term insolubility and preventing coronal leakage.[23,50,67,73–77] Notably, Biodentine performed consistently better than ProRoot MTA in adherence to dentine measured by push-out testing, however, ProRoot MTA was more radiopaque than Biodentine, which consistently fell below ISO standards (Table 2).[76,78,79] Certainly within these studies Biodentine compares favourably to ProRoot MTA and both tricalcium silicate materials are superior to other materials tested including glass ionomer cement (GIC), Dycal (calcium hydroxide), Theracal (resin-modified tricalcium silicate), Calcimol (calcium hydroxide), Calcicur (calcium hydroxide) and zinc-oxide eugenol cements such as IRM.

How are the practical aspects of Biodentine and MTA compared in the laboratory and clinic?

Crown discolouration as a result of VPT does not signify a failure of the procedure, however, patients are understandably concerned about potential shade change and staining issues as a result of any dental treatment.[6] Comparative studies carried out on extracted teeth (animal and human) have concluded that Biodentine has less staining potential compared with ProRoot MTA (Table 3).[80–83]

Initially, ProRoot MTA was only available in a grey formulation, which was later superseded by a white formula for use in aesthetic areas. White ProRoot MTA has been demonstrated to discolour teeth, particularly in the presence of sodium hypochlorite and blood.[18,84,85] This discolouration has been attributed to the radiopacifier bismuth oxide.[27] The anaerobic environment of the root canal system and light irradiation have been reported to enhance

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formation of stains, while presence of oxygen reduces discolouration.[80] Biodentine contains zirconium oxide rather than bismuth oxide, which has been attributed to reduced colour change in Biodentine treated teeth.[86–88] While, it is acknowledged that tooth discolouration remains possible with all tricalcium silicate materials, particularly in the presence of blood products, in general Biodentine induced staining significantly less than ProRoot MTA or MTA Angelus.[89,90] Indeed, only one study reported that Biodentine induced a higher incidence of stains than ProRoot MTA (Table 2).[91] Although the absence of the radiopacifier bismuth oxide in Biodentine has been attributed to the lack of discolouration, the radiopacity of Biodentine is consistently reported as being below ISO 6876 standard of 3 mm of equivalent aluminium for a 1 mm thick sample, and indeed cannot be clearly visualised as distinct to dentine by the operator.[76,92,93]

An important practical limitation of ProRoot MTA is the time taken to set.[94,95] This process takes several hours. As a result new calcium silicates such as Biodentine were developed to reduce this time with a setting time of 12 minutes claimed by the manufacturers. This shortened setting time is not predictable, however, with times of up to 100 minutes reported.[76,96] Direct comparison of setting times between studies is problematic to compare as the ISO methods require careful training and execution. For instance Biodentine may not set as quickly as the manufacturer claims, but it does set faster than ProRoot MTA.[76,94,97,98] One study reported a similar setting time between that MTA Angelus and Biodentine.[99]

ProRoot MTA has been reported to be difficult to handle, while Biodentine is considered easier to mix and use.[94,98–100] Many dentists avoided using any calcium trisilicate materials in VPT, citing cost, lack of training and difficulties in handling.[19]

Conclusions

The choice of material for pulpal application is critical with tricalcium silicates established as the gold standard. Comparative analysis of Biodentine and ProRoot MTA within this review revealed a plethora of biological *in vitro* studies, with a range of methodologies and conflicting findings, however, both materials' pulpal interaction is consistently better that other materials investigated. There are a small number of short-term, but no long-term clinical studies comparing the pulpal response to the materials in permanent teeth. Of the available evidence, histological evaluation highlights a similar response, while VPT outcome studies, although preliminary and under-powered, show high material-efficacy. Currently, practical issues consistently separate the materials, with ProRoot MTA causing more tooth staining, but having greater radiopacity than Biodentine. In the future, there is an urgent need for well-designed, adequately-powered, clinical trials in this area, as well as improved functional understanding of the interaction of Biodentine with the dentine-matrix.

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1. Tronstad L, Mjör I A. Capping of the inflamed pulp. *Oral Surg Oral Med Oral Pathol* 1972; **34:** 477–485.
2. Farges J C, Alliot-Licht B, Renard E *et al.* Dental pulp defence and repair mechanisms in dental caries. *Mediators Inflamm* 2015; 230–251.
3. Smith A J, Duncan H F, Diogenes A, Simon S, Cooper P R. Exploiting the bioactive properties of the dentin-pulp complex in regenerative endodontics. *J Endod* 2016; **42:** 47–56.
4. Özyürek T, Demiryürek E. Comparison of the antimicrobial activity of direct pulp-capping materials: Mineral trioxide aggregate-Angelus and Biodentine. *J Conserv Dent* 2016; **19:** 569–572.
5. Witherspoon D E. Vital pulp therapy with new materials: new directions and treatment perspectives-permanent teeth. *J Endod* 2008; **34:** S25–S28.
6. European Society of Endodontology. Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. *Int Endod J* 2006; **39:** 921–930.
7. Mejàre I, Cvek M. Partial pulpotomy in young permanent teeth with deep carious lesions. *Dent Traumatol* 1993; **9:** 238–242.
8. Cox C F, Keall C L, Keall H J, Ostro E, Bergenholtz G. Biocompatibility of surface-sealed dental materials against exposed pulps. *J Prosthet Dent* 1987; **57:** 1–8.
9. Nair P N R, Duncan H F, Pitt Ford T R, Luder H U. Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: A randomized controlled trial. *Int Endod J* 2008; **41:** 128–150.
10. Barthel C R, Rosenkranz B, Leuenberg A, Roulet J. Pulp capping of carious exposures: treatment outcome after 5 and 10 years: a retrospective study. *J Endod* 2000; **26:** 525–528.
11. Zander H A, Glass R L. The healing of phenolized pulp exposures. *Oral Surg Oral Med Oral Pathol* 1949; **2:** 803–810.
12. Pitt Ford T R, Roberts G J. Immediate and delayed direct pulp capping with the use of a new visible light-cured calcium hydroxide preparation. *Oral Surg Oral Med Oral Pathol* 1991; **71:** 338–342.
13. Sangwan P, Sangwan A, Duhan J, Rohilla A. Tertiary dentinogenesis with calcium hydroxide: A review of proposed mechanisms. *Int Endod J* 2013; **46:** 3–19.
14. Browne R M, Tobias R S, Crombie I K, Plant C G. Bacterial microleakage and pulpal inflammation in experimental cavities. *Int Endod J* 1983; **16:** 147–155.
15. Simon S R, Tomson P L, Berdal A. Regenerative endodontics: regeneration or repair? *J Endod* 2014; **40:** S70–S75.
16. Aeinehchi M, Eslami B, Ghanbariha M, Saffar A S. Mineral trioxide aggregate (MTA) and calcium hydroxide as pulp-capping agents in human teeth: a preliminary report. *Int Endod J* 2003; **36:** 225–231.
17. Hilton T J, Ferracane J L, Mancl L *et al.* Comparison of CaOH with MTA for direct pulp capping. *J Dent Res* 2013; **92:** S16–S22.
18. Lenherr P, Allgayer N, Weiger R, Filippi A, Attin T, Krastl G.Tooth discolorization induced by endodontic materials: a laboratory study. *Int Endod J* 2012; **45:** 942–949.
19. Chin J S, Thomas M B, Locke M, Dummer PMH. A survey of dental practitioners in Wales to evaluate the management of deep carious lesions with vital pulp therapy in permanent teeth. *Br Dent J* 2016; **221:** 331–338.
20. Bortoluzzi E A, Niu L N, Palani C D *et al.* Cytotoxicity and osteogenic potential of silicate calcium cements as potential protective materials for pulpal revascularization. *Dent Mat* 2015; **31:** 1510–1522.
21. Zanini M, Sautier J M, Berdal A, Simon S. Biodentine induces immortalized murine pulp cell differentiation into odontoblast-like cells and stimulates biomineralization. *J Endod* 2012; **38:** 1220–1226.
22. Kim J R, Nosrat A, Fouad A F. Interfacial characteristics of Biodentine and MTA with dentine in simulated body fluid. *J Dent* 2015; **43:** 241–247.
23. Nowicka A, Lipski M, Parafiniuk M *et al.* Response of human dental pulp capped with biodentine and mineral trioxide aggregate. *J Endod* 2013; **39:** 743–747.
24. Tran X V, Gorin C, Willig C *et al.* Effect of a calcium-silicate-based restorative cement on pulp repair. *J Dent Res* 2012; **91:** 1166–1171.
25. Camilleri J. The chemical composition of mineral trioxide aggregate. *J Conserv Dent* 2008; **11:** 141–143.
26. Ha W N, Bentz D P, Kahler B, Walsh LJ. D90: The Strongest Contributor to Setting Time in Mineral Trioxide Aggregate and Portland Cement. *J Endod* 2015; **41:** 1146–1150.
27. Marciano M A, Costa R M, Camilleri J, Mondelli R F, Guimarães B M, Duarte M A. Assessment of colour stability of white mineral trioxide aggregate angelus and bismuth oxide in contact with tooth structure. *J Endod* 2014; **40:** 1235–1240.
28. Grazziotin-Soares R, Nekoofar M H, Davies T E *et al.* Effect of bismuth oxide on white mineral trioxide aggregate: Chemical characterization and physical properties. *Int Endod J* 2014; **47:** 520–533.
29. Parirokh M, Torabinejad M, Dummer P M H. Mineral trioxide aggregate and other bioactive endodontic cements: An updated overview – part I: Vital pulp therapy. *Int Endod J* 2017; **51:** 177–205.
30. Simon S, Smith A J, Lumley P J *et al.* Molecular characterization of young and mature odontoblasts. *Bone* 2009; **45:** 693–703.
31. Lesot H, Smith A J, Tziafas D, Begue-Kirn C, Cassidy N R J. Biologically active molecules and dental tissue repair: a comparative review of reactionary and reparative dentinogenesis with the induction of odontoblast differentiation *in vitro*. *Cells Mater* 1994; **4:** 199–218.
32. Smith A J, Cassidy N, Perry H, Begue-Kirn C, Ruch J V, Lesot H. Reactionary dentinogenesis. *Int J Dev Biol* 1995; **39:** 273–280.
33. Ricucci D, Loghin S, Lin L M, Spångberg L S W, Tay F R. Is hard tissue formation in the dental pulp after the death of the primary odontoblasts a regenerative or a reparative process? *J Dent* 2014; **42:** 1156–1170.
34. Cassidy N, Fahey M, Prime S S, Smith A J. Comparative analysis of transforming growth factor-beta isoforms 1–3 in human and rabbit dentine matrices. *Arch Oral Biol* 1997; **42:** 219–223.
35. Smith A J.Vitality of the dentin-pulp complex in health and disease: growth factors as key mediators. *J Dent Educ* 2003; **67:** 678–689.
36. Cooper P R, Takahashi Y, Graham L W, Simon S, Imazato S, Smith A J. Inflammation-regeneration interplay in the dentine-pulp complex. *J Dent* 2010; **38:** 687–697.
37. Couve E, Osorio R, Schmachtenberg O. The amazing odontoblast: activity, autophagy, and aging. *J Dent Res* 2013; **92:** 765–772.
38. Huang T H, Yang C C, Ding S J, Yeng M, Kao C T, Chou M Y. Inflammatory cytokines reaction elicited by root-end filling materials. *J Biomed Mater Res – Part B Appl Biomater* 2005; **73:** 123–128.
39. Rutherford R B, Wahle J, Tucker M, Rueger D, Charette M. Induction of reparative dentine formation in monkeys by recombinant human osteogenic Protein-1. *Arch Oral Biol* 1993; **38:** 571–576.
40. Nakashima M. Induction of dentin formation on canine amputated pulp by recombinant human bone morphogenetic proteins (BMP)-2 and-4. *J Dent Res* 1994; **73:** 1515–1522.
41. Graham L, Cooper P R, Cassidy N, Nor J E, Sloan A J, Smith A J. The effect of calcium hydroxide on solubilisation of bio-active dentine matrix components. *Biomaterials* 2006; **27:** 2865–2873.

42. Duncan H F, Smith A J, Fleming G J P, Reid C, Smith G, Cooper P R. Release of bio-active dentine extracellular matrix components by histone deacetylase inhibitors (HDACi). *Int Endod J* 2017; **50:** 24–38.
43. Ferracane J L, Cooper P R, Smith A J. Can interaction of materials with the dentin-pulp complex contribute to dentin regeneration? *Odontology* 2010; **98:** 2–14.
44. Widbiller M, Eidt A, Hiller K A, Buchalla W, Schmalz G, Galler K M. Ultrasonic activation of irrigants increases growth factor release from human dentine. *Clin Oral Investig* 2017; **21:** 879–888.
45. Haskell E W, Stanley H R, Chellemi J, Stringfellow H. Direct pulp capping treatment: a long-term follow-up. *J Am Dent Assoc* 1978; **97:** 607–612.
46. Mass, Zilberman M. Clinical and radiographic evaluation of partial pulpotomy in carious exposure of permanent molars. *Paediatr Dent* 1993; **15:** 257–259.
47. Fuks A B, Bielak S, Chosak A. Clinical and radiographic assessment of direct pulp capping and pulpotomy in young permanent teeth. *Paediatr Dent* 1982; **4:** 240–244.
48. Mente J, Geletneky B, Ohle M *et al.* Mineral Trioxide Aggregate or Calcium Hydroxide direct pulp capping: An analysis of the clinical treatment outcome. *J Endod* 2010; **36:** 806–813.
49. Katge F A, Patil D P. Comparative analysis of 2 calcium silicate-based cements (Biodentine and Mineral Trioxide Aggregate) as direct pulp-capping agent in young permanent molars: a split mouth study. *J Endod* 2017; **43:** 507–513.
50. Grewal N, Salhan R, Kaur N, Patel H. Comparative evaluation of calcium silicate-based dentin substitute (Biodentine®) and calcium hydroxide (pulpdent) in the formation of reactive dentin bridge in regenerative pulpotomy of vital primary teeth: Triple blind, randomized clinical trial. *Contemp Clin Dent* 2016; **7:** 457–467.
51. Malekafzali B, Shekarchi F, Asgary S. Treatment outcomes of pulpotomy in primary molars using two endodontic biomaterials. A 2-year randomised clinical trial. *Eur J Paediatr Dent*. 2011; **12:** 189–193.
52. Asgary S, Ehsani S. Permanent molar pulpotomy with a new endodontic cement: A case series. *J Conserv Dent* 2009; **12:** 31–36.
53. Borkar S, Ataide I. Biodentine pulpotomy several days after pulp exposure: Four case reports. *J Conserv Dent* 2015; **18:** 73–78.
54. Patel R, Cohenca N. Maturogenesis of a cariously exposed immature permanent tooth using MTA for direct pulp capping: A case report. *Dent Traumatol* 2006; **22:** 328–333.
55. Asgary S, Eghbal M J, Parirokh M, Ghoddusi J, Kheirieh S, Brink F. Comparison of Mineral Trioxide Aggregate's composition with portland cements and a new endodontic cement. *J Endod* 2009; **35:** 243–250.
56. Kusum B, Rakesh K, Richa K. Clinical and radiographical evaluation of mineral trioxide aggregate, biodentine and propolis as pulpotomy medicaments in primary teeth. *Restor Dent Endod* 2015; **40:** 276–285.
57. Cuadros-Fernàndez, C, Rodríguez A I L. Short-term treatment outcome of pulpotomies in primary molars using mineral trioxide aggregate and Biodentine: a randomized clinical trial. *Clin Oral Inv* 2015; **20:** 1639–1645.
58. Brizuela C, Ormeño A, Cabrera C *et al.* Direct pulp capping with calcium hydroxide, Mineral Trioxide Aggregate, and Biodentine in permanent young teeth with caries: A randomized clinical trial. *J Endod* 2017; **43:** 1776–1780.
59. Linu S, Lekshmi M S, Varunkumar V S, Sam Joseph V G. Treatment outcome following direct pulp capping using bioceramic materials in mature permanent teeth with carious exposure: A pilot retrospective study. *J Endod* 2017; **43:** 1635–1639.
60. Hegde S, Sowmya B, Mathew S, Bhandi S H, Nagaraja S, Dinesh K. Clinical evaluation of mineral trioxide aggregate and biodentine as direct pulp capping agents in carious teeth. *J Conserv Dent* 2017; **20:** 91–95.
61. Fransson H, Wolf E, Petersson K. Formation of a hard tissue barrier after experimental pulp capping or partial pulpotomy in humans: An updated systematic review. *Int Endod J* 2016; **49:** 533–542.
62. Murray P E, Smith A J, Garcia-Godoy F, Lumley P J. Comparison of operative procedure variables on pulpal viability in an *ex vivo* model. *Int Endod J* 2008; **41:** 389–400.
63. Sazak H, Günday M, Alatli C. Effect of calcium hydroxide and combinations of Ledermix and calcium hydroxide on inflamed pulp in dog teeth. *J Endod* 1996; **22:** 447–449.
64. Shayegan A, Jurysta C, Atash R, Petein M, Abbeele A V. Biodentine used as a pulp-capping agent in primary pig teeth. *Paediatr Dent* 2012; **34:** 202–208.
65. Accorinte M L R, Loguercio A D, Reis A, Costa C A S. Response of human pulps capped with different self-etch adhesive systems. *Clin Oral Investig* 2008; **12:** 119–127.
66. Nowicka A, Wilk G, Lipski M, Kołecki J, Buczkowska-Radlińska J. Tomographic evaluation of reparative dentin formation after direct pulp capping with Ca(OH)2, MTA, Biodentine, and dentin bonding system in human teeth. *J Endod* 2015; **41:** 1234–1240.
67. Poggio C, Beltrami R, Colombo M, Ceci M, Dagna A, Chiesa M. *In vitro* antibacterial activity of different pulp capping materials. *J Clin Exp Dent* 2015; **7:** e584–e588.
68. Pérard M, Le Clerc J, Meary F, Pérez F, Tricot-Doleux S, Pellen-Mussi P. Spheroid model study comparing the biocompatibility of Biodentine and MTA. *J Mater Sci Mater Med* 2013; **24:** 1527–1534.
69. Widbiller M, Lindner S R, Buchalla W *et al.* Three-dimensional culture of dental pulp stem cells in direct contact to tricalcium silicate cements. *Clin Oral Investig* 2016; **20:** 237–246.
70. Margunato S, Taşli P N, Aydin S, Karapinar Kazandağ M, Şahin F. *In vitro* evaluation of ProRoot MTA, biodentine, and MM-MTA on human Alveolar bone marrow stem cells in terms of biocompatibility and mineralization. *J Endod* 2015; **41:** 1646–1652.
71. Poggio C, Ceci M, Dagna A, Beltrami R, Colombo M, Chiesa M. *In vitro* cytotoxicity evaluation of different pulp capping materials: A comparative study. *Arh Hig Rada Toksikol*. 2015; **66:** 181–188.
72. Bogen G, Chandler N. Vital Pulp Therapy. *In* Ingle JI, Bakland LK, Baumgartner J C (eds) *Ingle's Endodontics*. 6th edition. pp. 1310–1330. Hamilton, Ontario: BC Decker Inc, 2008.
73. Bakhtiar H, Nekoofar M H, Aminishakib P *et al.* Human pulp responses to partial pulpotomy treatment with theracal as compared with. *J Endod* 2017; **43:** 1786–1791.
74. Bhavana V, Chaitanya K P, Gandi P, Patil J, Dola B, Reddy R B. Evaluation of antibacterial and antifungal activity of new calcium-based cement (Biodentine) compared to MTA and glass ionomer cement. *J Conserv Dent* 2015; **18:** 44–46.
75. Kaup M, Schäfer E, Dammaschke T. An *in vitro* study of different material properties of Biodentine compared to ProRoot MTA. *Head Face Med* 2015; **11:** 16.
76. Tsesis I, Elbahary S, Venezia N B, Rosen E. Bacterial colonization in the apical part of extracted human teeth following root-end resection and filling: a confocal laser scanning microscopy study. *Clin Oral Investig* 2017; **22:** 267–274.
77. Guneser M B, Akbulut M B, Eldeniz A U. Effect of various endodontic irrigants on the push-out bond strength of biodentine and conventional root perforation repair materials. *J Endod* 2013; **39:** 380–384.
78. Nagas E, Cehreli Z C, Uyanik M O, Vallittu P K, Lassila L V J. Effect of several intracanal medicaments on the push-out bond strength of ProRoot M T A, Biodentine. *Int Endod J* 2016; **49:** 184–188.
79. Vall M, Duran-sindreu F. Influence of light and oxygen on the colour stability of five calcium silicate-based materials. *J Endod* 2013; **39:** 525–528.
80. Marconyak L J, Kirkpatrick T C, Roberts H W *et al.* A comparison of coronal tooth discoloration elicited by various endodontic reparative materials. *J Endod* 2016; **42:** 470–473.
81. Shokouhinejad N, Nekoofar M H, Pirmoazen S, Shamshiri A R, Dummer P M H. Evaluation and comparison of occurrence of tooth discoloration after the application of various calcium silicate-based cements: An *ex vivo* study. *J Endod* 2016; **42:** 140–144.
82. Mozyńska J, Metlerski M, Lipski M, Nowicka A. tooth discoloration induced by different calcium silicate-based cements: A systematic review of *in vitro* studies. *J Endod* 2017; **43:** 1593–1601.
83. Camilleri J. Colour stability of white mineral trioxide aggregate in contact with hypochlorite solution. *J Endod* 2014; **40:** 436–440.
84. Felman D, Parashos P. Coronal tooth discoloration and white mineral trioxide aggregate. *J Endod* 2013; **39:** 484–487.
85. Kohli M R, Yamaguchi M, Setzer F C, Karabucak B. Spectrophotometric analysis of coronal tooth discoloration induced by various bioceramic cements and other endodontic materials. *J Endod* 2015; **41:** 1862–1866.
86. Vallés M, Roig M, Duran-Sindreu F, Martínez S, Mercadé M. Colour stability of teeth restored with Biodentine: A 6-month *in vitro* study. *J Endod* 2015; **41:** 1157–1160.
87. Camilleri J. Staining potential of Neo MTA Plus, MTA Plus, and Biodentine used for pulpotomy procedures. *J Endod* 2015; **41:** 1139–1145.
88. Yoldas S E, Bani M, Atabek D, Bodur H. Comparison of the potential discoloration effect of bioaggregate, biodentine, and white mineral trioxide aggregate on bovine teeth: *in vitro* research. *J Endod* 2016; **42:** 1815–1818.
89. Keskin C, Demiryurek E O, Ozyurek T. Colour stabilities of calcium silicate-based materials in contact with different irrigation solutions. *J Endod* 2015; **41:** 409–411.
90. Beatty H, Svec T. Quantifying coronal tooth discoloration caused by Biodentine and EndoSequence root repair material. *J Endod* 2015; **41:** 2036–2039.
91. Tanalp J, Karapınar-Kazandati M, Dölekoğlu S, Kayahan M B. Comparison of the radiopacities of different root-end filling and repair materials. *Scientific World Journal* **2013:** 594, 950.
92. Lucas C P, Viapiana R, Bosso-Martelo R, Guerreiro-Tanomaru J M, Camilleri J, Tanomaru-Filho M. Physicochemical properties and dentin bond strength of a tricalcium silicate-based retrograde material. *Braz Dent J* 2017; **28:** 51–56.
93. Kogan P, He J, Glickman G N, Watanabe I. The effects of various additives on setting properties of MTA. *J Endod*. 2006; **32:** 569–572.
94. Lee J-B, Park S-J, Kim H-H, Kwon Y-S, Lee K-W, Min K-S. Physical properties and biological/odontogenic effects of an experimentally developed fast-setting α-tricalcium phosphate-based pulp capping material. *BMC Oral Health* 2014; **14:** 87.
95. Grech L, Mallia B, Camilleri J. Investigation of the physical properties of tricalcium silicate cement-based root-end filling materials. *Dent Mater* 2013; **29:** e20–e28.
96. Torabinejad M, Hong C U, McDonald F, Pitt Ford T R. Physical and chemical properties of a new root-end filling material. *J Endod* 1995; **21:** 349–353.
97. Wiltbank K B, Schwartz S A, Schindler W G. Effect of selected accelerants on the Physical Properties of Mineral Trioxide Aggregate and Portland Cement. *J Endod* 2007; **33:** 1235–1238.
98. Butt N, Talwar S, Chaudhry S, Nawal R R, Yadav S, Bali A. Comparison of physical and mechanical properties of mineral trioxide aggregate and Biodentine. *Indian J Dent Res* 2014; **25:** 692–697.
99. Ma J, Shen Y, Stojicic S, Haapasalo M. Biocompatibility of two novel root repair materials. *J Endod* 2011; **37:** 793–798.
100. Corral Nuñez C M, Bosomworth H J, Field C, Whitworth J M, Valentine R A. Biodentine and Mineral Trioxide Aggregate induce similar cellular responses in a fibroblast cell line. *J Endod* 2014; **40:** 406–411.
101. Ceci M, Beltrami R, Chiesa M, Colombo M, Poggio C.Biological and chemical-physical properties of root-end filling materials: a comparative study. *J Conserv Dent* 2015; **18:** 94–99.
102. Altunsoy M, Tanriver M, Ok E, Kucukyilmaz E. Shear bond strength of a self-adhering flowable composite and a flowable base composite to mineral trioxide aggregate, calcium-enriched mixture cement, and biodentine. *J Endod* 2015; **41:** 1691–1695.
103. Tomson P L, Grover L M, Lumley P J, Sloan A J, Smith A J, Cooper P R. Dissolution of bio-active dentine matrix components by mineral trioxide aggregate. *J Dent* 2007; **35:** 636–642.