NARRATIVE REVIEW

Bio-active cements-Mineral Trioxide Aggregate based calcium silicate materials: a narrative review

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Abstract

Recent advances in the field of endodontics have greatly improved the outcome and success rate of dental materials. For last three decades, there has been great interest in the development of bioactive dental material with the ability to interact and induce surrounding dental tissues to promote regeneration of pulpal and peri-radicular tissues. As these bioactive materials are mainly based on calcium silicates, they are also referred to as Calcium Silicate materials. The first material introduced was Mineral Tri-oxide Aggregate, which, due to its favourable biological properties, gained importance initially. However, later, due to its drawbacks, like discolouration, long setting time and difficult manipulation, several modifications were done and newer bioactive materials, such as Biodentine, BioAggregate, Endosequence, Calcium-Enriched Mixture etc., were developed. The main applications of these materials are for pulp capping (direct/indirect), pulpotomy, perforation repair, resorption defects, , apexogenesis and as retrograde filling materials, apexification and endodontic sealers. This review discusses the various types of bioactive materials, their composition, setting mechanism, and literature evidence for current applications.

Keywords: Bioactive materials, Calcium silicate, MTA, Biodentine, Bioceramics, Calcium-enriched mixture, BioAggregate, Endosequence.

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Introduction

In modern dentistry, the field of endodontics is also improving with the advent of new materials and techniques.[1] The term bioactivity is defined as materials that are durable in tissues and have the capability to undergo interfacial changes with surrounding tissues. When these bioactive materials contact the tissue fluids, they release calcium hydroxide ($Ca[OH]_2$), which can interact with and induce surrounding tissues to promote their regeneration.[2] The major emphasis has been on the development of bioactive and biocompatible materials that can specifically promote regeneration of pulpal and peri-radicular tissues rather than repair.[3] Among the bio-materials that have gained great importance in regenerative endodontics, calcium silicate (CS)-based materials, like Mineral Tri-oxide Aggregate (MTA), Biodentine, Bioceramics, calcium-enriched mixture etc., are common.[4] CS-based materials are defined as those that are composed of either di/tri/tetra- CS phases with a basic setting mechanism involving hydration process resulting in the formation of leachate and crystalline phases.[3] CS-based materials were first used in dentistry in 1878 when Portland cement was used to fill the root canals. They later became common in practice and remained so till the 1990s when MTA was first introduced.[5] The main indication of these CS materials are pulpal and hard tissue regeneration, such as pulp capping, pulpotomy, apexogenesis, apexification, endodontic sealers, root perforation repair and as retrograde filling materials.[6] There are certain common desirable characteristics of CS-based materials (Table 1). On the basis of chemistry, a classification of CS-based materials has been mentioned in literature[3] (Table 2). The current narrative review was planned to discuss bioactive cements, their basic composition, manipulation, mechanism of setting reaction and clinical applications,

Table-1: Common properties of Bioactive materials

Adequate strength
Antimicrobial properties
Biocompatible
Bioactivity (capability of stimulation and modulation of native tissue)
Dimensionally stable
Easy manipulation
Sealing ability
Lacks moisture sensitivity
Non-resorbable
Non-toxic, non-carcinogenic, non-genotoxic
Radio-opaque

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Table-2: Classification of Bioactive materials.

Generation	Bio-Active materials
Generation I	Grey MTA
	White MTA
Generation II	Modifications to MTA
	MTA Angelus
Generation III	Endo CPM (Cement Portland Modified)
	iRootSP (also retailed as Endosequence BC and SmartPaste Bio)
	MTA Obtura,
	Tech Biosealer Endo
	- New Endodontic Cement/Calcium Enriched Mixture
	- Bioaggregate
	- Biodentine
	-Ortho MTA
	-MTA plus
	-Generex A, Generx B
Generation IV	Hybrid cements:
	- Calcium phosphate/Calcium silicate/Bismutite cement
	- NRC (Incorporating HEMA)
	- MTA with 4-META/MMA-TBB (4-methacryloxyethyl trimellitate anhydride in methyl methacrylate initiated by tri-n-butyl borane)
	- Light-cured cements including (TheraCal LC)

MTA: Mineral Tri-oxide Aggregate; HEMA: 2-hydroxyethyl methacrylate

drawbacks, and modifications.

Mineral Tri-oxide aggregate (MTA)

In the quest for bioactive and osteo-conductive materials, the introduction of MTA in 1993 by Dr. Mahmoud Torabinejad led to a paradigm shift in the application of dental materials in endodontics.[3] Some of the notable properties of MTA are its good physical properties and its capability to stimulate hard tissue regeneration as well as good pulpal response. MTA, when in contact with dentine of the pulp chamber, stimulates the production and release of signalling molecules, which are essential for the formation of new tissue in the pulp space.[6] MTA is also capable of activation of cementoblast and regeneration of periodontal ligament.[7]

Composition

The principal constituents of MTA powder are tricalcium silicate (52-53%), dicalcium silicate (23%), tricalcium aluminate (0-4%), calcium sulphate (1.5%), and bismuth oxide (20%) as radio-opacifier.[8]

Availability

MTA is a fine hydrophilic powder available in single-use sachets (1gm) with some manufacturers providing pre-measured water sachets for the ease of use.[9] The first commercially available product was ProRoot MTA,[3] in the form of grey-coloured powder owing to the presence of iron (ferrous oxide). As this grey colour affected the aesthetics, the composition was later modified to replace ferrous oxide with magnesium oxide and marketed as white ProRoot MTA in 2002.[10]

Setting reaction

MTA, being a hydrophilic cement, requires moisture to set. The presence of moisture during the setting also improves flexural strength.[11] The powder is mixed with water and a chemical reaction occurs known as hydration. On hydration, colloidal gel composed of calcium oxide crystals in an amorphous structure is formed.[12-15] The initial setting time for grey and white MTA is 2.45 hours and 2.20 hours, respectively. On mixing ,the immediate value of potential hydrogen (pH) is 10.2 which increases to 12.5 after 3 hours of mixing. This is comparable to $Ca(OH)_2$. [16]

Manipulation

Manipulation of MTA is difficult owing to its granular consistency, making it difficult to manage and deliver at clinical site.[17] Specialised carriers such as retro-amalgam carrier, MTA carrier, Micro-apical placement system etc. were made available to tackle and enhance manipulation.[3]

Modifications of MTA

The main drawbacks of MTA are its long setting time, discolouration potential, manipulation that makes its utilisation difficult and sometimes requiring multiple visits for treatment completion. To minimise these limitations, and enhance clinical utilisation, the composition of MTA was modified, and MTA Angelus was introduced in 2001, in which calcium sulphate was eliminated from its composition to decrease the setting time.[18] A fast-setting nano-white MTA (NW-MTA) was also introduced that reduced particle size, resulting in increased surface area (7.8mg), leading to decrease in initial setting time from 43 minutes (White MTA) to 6 minutes for NW-MTA. NW-MTA also contains strontium salts in its composition, improving the bio-activity.[17] Addition of sodium hypochlorite (NaOCl) gel has also been reported to reduce (30-60%) the setting times of MTA. [17]

Light cured based MTA was also introduced to control

the setting reaction. Further, 2-hydroxyethyl methacrylate (HEMA) and triethylene glycol dimethacrylate (TEGDMA) were added to the liquid component to initiate the setting reaction.[19] Various other types of MTA, such as Micro-Mega (MM) MTA, and Ortho MTA, were formulated to improve the limitations of conventional materials.

Applications and Literature review

Studies have shown good clinical success of MTA when used as retrograde filling[20-21] perforation repair, pulp capping,[22,23] apexification[24] and pulpotomy.[25] Formation of natural hard tissue barrier on the surface of apical plug is important owing to the requirement of providing biological seal around apical plug. Systematic reviews and meta-analysis comparing $Ca(OH)_2$ and MTA in successfully forming hard tissue barrier around open apices were not significant, but the time needed by MTA to form apical barrier was significantly lower than $Ca(OH)_2$.[24,26] As a perforation repair material (non-surgical), systematic reviews and meta-analysis reported the overall success rate of 81% of MTA.[27] Another systematic review evaluating the revitalisation and apical placement reported high success rate and successful outcome.[28] When used as root-end filling material after peri-apical surgery, MTA is considered the gold standard, with systematic reviews and meta-analyses reporting significantly better outcome when compared with gutta percha, glass ionomer cement and amalgam.[29] However, MTA was not significantly different than intermediate restorative material.[29,30] Evidence regarding the use of MTA as an indirect pulp capping is scarce. A study compared ProRoot MTA and Dycal as an indirect pulp capping agent and reported non-significant results at 6 months in terms of calcific bridge thickness.[31] As a direct pulp capping agent, MTA had significantly better outcome with regard to complete calcific bridge formation and reducing the inflammation when compared to Dycal.[31-35] A recent systematic review concluded that the risk of failure was significantly lower when MTA was used as a direct pulp capping agent in permanent teeth.[36] When considered as pulpotomy medicament in primary teeth, several systematic reviews and meta-analyses reported superiority of MTA in comparison to the other currently used materials, but they studies failed to find significant difference between $Ca(OH)_2$ and MTA when used as pulpotomy agent over cariously exposed pulps.[37-41]

To further overcome the drawbacks of MTA, newer bioactive cements have been introduced, with characteristics similar to MTA but without its disadvantages.

Biodentine

Biodentine (Septodont) has now been recognised as a promising material, serving as a chief representative of the CS family,[42] first marketed in 2009. Biodentine has a wide range of applications, including pulp capping, pulpotomy medicament, and as an endodontic repair (perforation repair, resoprtive lesions, root-end filling material), and can be regarded as a dentine replacement material. Biodentine, which is technically based on MTA technology, is formulated to overcome the deficiencies of MTA.[43]

Composition

The setting time of the material is 12-13 minutes, which is significantly less than the MTA.[42] This fast-setting reaction is attributed to the increased particle size, addition of calcium chloride ($CaCl_2$) in the liquid component, decreasing the liquid content.[43] Studies have also linked the short setting time to the absence of di-calcium silicate from the composition of biodentine, which was associated with a slow hydration reaction.[44] Another important difference was the addition of calcium carbonate which can act as a nucleation site for calcium-silicate-hydrate (CSH), hence accelerating the setting reaction.[36]

Setting reaction

The setting reaction of biodentine is similar to MTA and results in the formation of CSH and $Ca(OH)_2$. Biodentine additionally contains calcium carbonate in the powder which explains the presence of carbonate phase. The tri-calcium silicate grains in the biodentine are finer than MTA and the addition of hydrophilic polymer in the composition makes the manipulation and handling easier. [44]

Applications and literature review

When used as a root-end filling material, biodentine showed significantly better sealing ability in comparison to MTA and intermediate restorative material (IRM).[46,47] No significant difference was found when biodentine

and ProRoot MTA were tested in acidic environment.[47] Studies have also reported superior compressive strength[48,49] flexural strength, microhardness, and push-out bond strength and calcium ion release when compared to other CS-based cements.[50-53] However, studies have shown conflicting results regarding radio-opacity of biodentine, and its colour stability.[53,54] Direct contact of biodentine with dentine provided significantly thicker reparative dentine formation in comparison to Dycal.[55] When biodentine was compared with MTA, no significant difference was found with regard to calcific bridge formation after pulp capping.[33] Studies comparing outcomes of biodentine and MTA as pulpotomy agent in primary teeth also reported insignificant results.[56-60]

Calcium-enriched mixture cement (CEC)

Calcium-enriched cement (CEC) was introduced in the field of dentistry in 2006 as an endodontic filling material.[61] It has also got favourable physical characteristics, like film thickness, flow and setting time. It also has the capability to set in wet conditions in a shorter time compared to MTA.[61,62] The clinical applications of CEC are similar to MTA and biodentine, and it has demonstrated encouraging success when used as capping, pulpotomy, resorption or repair material.[63-65]

Composition

CEC is very similar to MTA.[66] In contrast to MTA, CEC has similar composition to dentine containing hydroxyapatite.[67]

Setting reaction

When CEC powder is mixed with water-based solution, bioactive calcium and phosphate-enriched materials are formed as a result of hydration reaction. In addition, calcium and phosphorous ions are released that are consumed in the formation of hydroxyapatite.[68] CEC appeared to exhibit better physical properties, such as consistency, manipulation, setting time, antibacterial and antifungal properties, biocompatibility, lack of staining and better sealing ability.[69]

Literature review

A recent review reported that CEC is a suitable alternative material for vital pulp therapies of primary molars (mature/immature) with reversible / irreversible pulpitis.[69] Asgary et al. reported 5-year success of CEC-pulpotomy when compared with root canal treatment in mature permanent teeth with the established diagnosis of irreversible pulpitis.[70] Most of the literature on CEC is currently based on case reports and case series which are considered weak levels of evidence. More clinical trials are needed to be conducted to assess the role of CEC as a wide-range endodontic application so that concrete level of evidence is generated.

Bio Aggregate

It is a new tailored adaptaption of MTA now available for endodontic repair utilising the advanced science of nanotechnology.

Composition

It is composed of nano-particle-sized tricalcium silicate, tantalum penta oxide, calcium phosphate and silicon dioxide, and presents improved performance compared to MTA.[71] Tricalcium silicate is the main component phase.[71] This material is claimed to be an aluminium-free ceramic biomaterial. Replacing bismuth oxide with tantlum penta oxide for radio-opacity makes it different from MTA.[71]

Setting reaction

The powder has to be mixed with deionized water in a ratio of 1 g/0.38 mL for 2-5 minutes. The material takes 4 hours to set, and permanent restoration has to be done after the final set. This turns out to be a clinical disadvantage if the final restoration has to be placed on the same day. A nano-composite network of Hydrated Calcium Silicate (HCS) gel forms a firm tight seal at the site.[71,72]

Literature review

It is reported to be biocompatible in human fibroblast cells and stimulates osteoblastic differentiation in osteoblasts.[73] BioAggregate (Innovative Bioceramix) stimulates odontoblastic differentiation of human dental pulp cells.[72] Its efficiency in odontoblastic and mineralisation differentiation is comparable with MTA. The results are comparable with those observed with human dental pulp cells (HDPCs) exposed to MTA. Clinical application of BioAggregate as pulp capping agent promotes mineralisation of dentine beneath the capping material, and then stimulates reparative odontogenesis

from the injured dental pulp tissue.[72] There were concerns regarding cytotoxicity of BioAggregate but Yen et al. found it to be nontoxic to human cells and it also had the ability to induce differentiation of human periodontal ligament (PDL) fibroblasts.[74]

Clinical Application

It is similar to MTA with respect to sealing ability and biocompatibility, but it has more potential to form hard tissue barrier at the site. This advantage is due to the presence of Pi source present in the material. It is indicated for root perforation repair, root resorption repair, root-end filling, apexification and pulp capping.[75] Its hard tissue-forming potential is expected to be greater than MTA because of the presence of Pi source in Bio-Aggregate, but the poorer mechanical properties and long setting time of BioAggregate limits the situations where it could replace MTA.[71]

Table-3: Composition of bioactive cements.

Products	Composition
ProRoot MTA (Dentsply, Tulsa, OK, USA)	Portland cement, bismuth oxide (MSDS)
MTA-angelus (Londrina, PR, Brazil)	Tricalcium silicate, dicalcium silicate, tricalcium aluminate, tetracalcium aluminoferrite, bismuth oxide (MSDS)
MM-MTA (MicroMega, Besançon, France)	Mixture of several mineral oxides and bismuth oxides (MSDS)
Ortho MTA (BioMTA, Seoul, Korea)	Calcium carbonate, silicon dioxide, aluminum oxide, dibismuth trioxide (MSDS)
Biodentine (Septodont, St. Maur-des-Foss´es, France)	Powder: Tricalcium silicate, calcium carbonate and oxide, iron oxide, zirconium oxide Liquid: calcium chloride (accelerator), hydrosoluble polymer (water reducing agent)
Calcium enriched mixture	Calcium oxide, sulphur tri-oxide, P205, Si02. The other main components are calcium hydroxide, calcium phosphate, and calcium silicate. Minor components are Al203, Na20, MgO, Cl.
Bioaggregate (Diadent, Burnaby, Canada)	Tricalcium silicate, dicalcium silicate, tantalum pentoxide, calcium phosphate monobasic, amorphous silicon oxide (MSDS)
Endosequence	Zirconium oxide, calcium silicates, calcium phosphate monobasic, calcium hydroxide, filler and thickening agents.

MTA: Mineral Tri-oxide Aggregate

Endosequence

Endosequence BC sealer (Brasseler USA) is another bioactive material that is highly radiopaque, dimensionally stable, hydrophilic, and forms hydroxyapatite upon setting. It is a material that needs natural canal moisture in the dentinal tubule for setting reaction.

Composition

It is a pre-mixed CS in the form of syringe-able paste or putty with easier handling and more feasible in application compared to MTA (Table 3).[61] The manufacturer claims that the material is aluminium-free, less soluble, and dimensionally more stable during setting.[76]

Setting reaction

It is a radiopaque material with a setting time of 2-4 h.[77] Micro hardness reduces in the presence of environmental moisture whereas premature setting accelerates.[78] It complies with the International Organisation for Standards (ISO) in terms of dimensional accuracy, solubility and film thickness. It penetrates dentinal tubules due to its nano particles. Dentine liquid will create a mechanical bond with material upon setting. This results in less shrinkage, thus maintaining dimensional stability.[79] Sealing ability of endosequence is as good as MTA when used as root-end filling material.[80] In contact with saliva, it forms a hydroxyapatite layer on the surface.[81] Hard tissue is deposited due to calcium release as it has an alkaline pH. It also has antibacterial properties against enterococcus faecalis owing to its high pH.[82]

Literature Review

An in vitro study has reported that this material up-regulates alkaline phosphatase (ALP) and denitine sialoprotein (DSP) genes, suggesting greater odontoblastic differentiation potential. In addition, Runx2 determines the lineage of osteoblasts and odontoblasts from mesenchymal cells, and its expression is high in response to bioceramics and MTA. [83]

Lovato and Sedgley[83] investigated the antibacterial activity of Endosequence against enterococcus (E.) faecalis and found that Endosequence root repair material (ERRM) and white ProRoot MTA demonstrated similar antibacterial efficacy against clinical strains of E. faecalis. Additionally, another study found that the ERRM had cell viability similar to MTA.[84] These materials are still evolving and are under research.

Clinical Application

It is a suitable material for perforation repair, apical surgery, apical plug, and pulp capping. It has strengths and biological properties comparable with MTA .[71] It is easy to handle and apply, and thus can be considered an alternative to MTA.

Conclusion

MTA has been proven as a table-turner in bio-active materials and has a wide horizon of applications in endodontics and restorative dentistry. The newer modifications and materials are continuously on the verge of improving the properties by combating the drawbacks of the previous material. The newer materials could be seen as the promising alternative to MTA, but more long-term follow-up studies are needed to this notion.

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