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# Pulp Capping Agents: An Evolutionary Review

[1]Dr. Snigdho Das, MDS, Conservative Dentistry & Endodontics

**Corresponding Author:** Dr. Snigdho Das, MDS, Conservative Dentistry & Endodontics

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## Abstract

The vitality of the pulp is important for the maintenance of the structural integrity and normal physiological characteristic of teeth. The development of minimally invasive biologically based therapies aimed at preservation of the pulp vitality; remains the key issue in modern-day Endodontics. A vast number of studies are present in the literature evaluating the efficacy of Calcium hydroxide, MTA, and other bio-ceramic materials as pulp-capping agents. However, the recent decade has seen the emergence of new bioactive materials which possess the potential to prolong the expectancy of tooth life. This comprehensive review thus discusses the current pulp-capping materials along with state-of-the-art products who could be potential forayers in future therapies; upholding the theme of "prevention of extension".

**Keywords:** Bio-Active, Biodentine, Chitosan, Enzymes, MTA, PRF, Pulp Capping Agent, Stem Cells, Vital Pulp Therapy.

## Introduction

Traditionally, deep caries management often resulted in pulp exposure and subsequent ensuing of root canal treatment. The promotion of biologically-based treatment strategies has been advocated for partial caries removal aimed at avoiding carious pulp exposure. Indeed, recent reports have stated that the complete or non-selective carious removal is now considered overtreatment.[1] Recent years have seen a paradigm transition towards minimally invasive techniques in all spheres of Dentistry. Similarly, a shift has been evident in Endodontics from complete pulp tissue removal towards vital pulp treatment(VPT) techniques such as pulp capping, partial and complete pulpotomy.[2] Historically, vital pulp therapy was first considered by performing pulp amputation at the root orifices and placing calcium hydroxide. The aim was to form dentin over the surface of the exposed pulp and wall off the pulp from the cavity. It was reported in an initial study of vital pulp therapy that 71% of 150 cases showed no radiographic changes at follow-up. Today, vital pulp therapy is still considered a successful treatment option. [3] This aim of retaining the pulp vitality triggered the search for a "bio-active" material which would form a surface layer of an apatite-like material in the presence of an inorganic phosphate solution . [4]

**Deep Caries and Pulp Exposure Management with VPT**

According to the latest (2019), European Society of Endodontology (ESE)-approved definitions and terminology, Indirect Pulp Capping (IPC) due to removal of both soft and firm carious dentine until hard dentine is reached, is nowadays considered aggressive, and in many cases may be acknowledged as overtreatment. [5] It involves the preservation of the deepest layer of affected dentin overlying the pulp and application of a suitable biomaterial to enhance reparative dentin formation, followed by placement of a permanent restoration. The above-mentioned procedures can be carried out in a single visit or two visits.

Direct Pulp Capping (DPC) on the other hand is ensued when a pulp horn exposure is seen, either due to deep caries excavation or an iatrogenic mishap. The exposed pulp is then treated by placement of a biomaterial directly over it, followed by restoration with an intermediate material. In subsequent visits, the permanent restoration is placed. [5] In contrast to the above-mentioned procedures, partial pulpotomy involves the removal of 2-3 mm of the coronal pulp, as pulp capping procedures aims only at protecting the pulpal tissue, but no reversal of the inflammatory processes is seen. It is also advocated that if hemostasis is not achieved within 5 minutes, further caries excavation is required after exposure; and a complete pulpotomy should be planned. [6]

Table 1: Composition of Available Pulp Capping Agents

| Sl. No. | Pulp Capping Agent | Composition |
|---|---|---|
| 1. | Calcium hydroxide (Dycal®) | • Base paste - titanium dioxide and barium sulfate in glycol disalicylate<br>• Catalyst paste - calcium hydroxide, zinc oxide, and zinc stearate in ethyl toluene sulphonamide |
| 2. | Mineral Trioxide Aggregate(MTA) based materials | |
| | i. ProRoot MTA | • Powder- tricalcium silicate, dicalcium silicate, tricalcium aluminate, bismuth oxide, gypsum<br>• Liquid- water |
| | ii. MTA Angelus | • Powder-tricalcium silicate, dicalcium silicate, tricalcium aluminate, silicon oxide, potassium oxide, aluminum oxide, sodium oxide, iron oxide, calcium oxide, bismuth oxide, magnesium oxide, insoluble residues of crystalline silica<br>• Liquid: water |
| | iii. Retro MTA | • Powder-calcium carbonate, silicon dioxide, aluminum oxide, calcium zirconia complex<br>• Liquid- water |

| | | |
|---|---|---|
| | iv. NeoMTA Plus | • Powder- Tricalcium silicate ($Ca_3SiO_5$), Dicalcium silicate ($Ca_2SiO_4$), and Tantalum oxide ($Ta_2O_5$).<br>• Liquid- Water ($H_2O$) and proprietary polymers |
| 3. | Biodentine | • Powder-tricalcium silicate, dicalcium silicate, calcium oxide, calcium carbonate, zirconium oxide, iron oxide<br>• Liquid: calcium chloride, water-soluble polymer, water |
| 4. | Endosequence Root Repair Material (ERRM ) | • calcium silicate, monobasic calcium phosphate, zirconium oxide, tantalum oxide, and filler agents<br>• available as a paste in preloaded syringes and also in a moldable putty form |
| 5. | Thera Cal | Light-curing single paste- resin bis-phenyl glycidyl methacrylate (BisGMA) & polyethylene glycol dimethacrylate (PEGD) modified calcium silicate filled with CaO, calcium silicate particles (type III Portland cement), Strontium glass, fumed silica, barium sulfate, barium zirconate |

**Overview of the different Pulp Capping Materials**

**Calcium hydroxide**

Historically, Calcium hydroxide(Composition in Table 1) has been considered the standard of care because of beneficial properties such as induction of mineralization, high pH, and low cytotoxicity. Its usage as pulp capping material dates back to 1934.[7] However, its usage has seen a decline due to several drawbacks such as poor sealing ability, insufficient adherence to dentinal walls, and multiple tunnel-defects in the induced dentinal-bridges; to name a few.[8] Calcium hydroxide has been thought to display its mechanism of action, owing to its high basicity(pH 11–12.5); by forming a layer of necrotic tissue, and indirectly triggering an inflammatory response to lay down a barrier of calcific material. But long-term clinical studies have proved its futility in maintaining vitality.[9]

**Mineral Trioxide Aggregate (MTA)**

The advent of Mineral Trioxide Aggregate (MTA) demonstrated great potential in endodontic therapies, and modifications and improvements of this bio-ceramic gave rise to many materials. MTA is a bioactive cement pioneered by Torabinejad *et al.* in the early 1990s as an endodontic repair and root-end filling material. The powder of MTA is a mixture of a purified Portland cement and bismuth oxide (Composition in Table 1) to provide radiopacity. The main constituent phases of cement are tricalcium and dicalcium silicate and tricalcium aluminate.[10] ProRoot MTA, which was the first to be developed is extremely biocompatible but carried the disadvantages of high setting time (228-261 minutes). This drawback has urged the development of new types of MTA-based materials. Recently, MTA Angelus has been developed with a setting time of 24-83 minutes[11], whereas Retro MTA has a much lesser final setting time of only 12 minutes.[12] MTA exhibits its acting by releasing calcium

ions which then reacts with the phosphate ions present in the tissue fluid, to form hydroxyapatite. [13] A study of literature states that MTA has lower rates of failure (19.7 %) compared to Calcium Hydroxide which had shown a failure rate of 31.5 % after 2 years of follow-up. A review of a few clinical studies revealed a success rate of 92.5-97.6% after 9-10 years of observation. [14,15]. Also, a histological study conducted by Laurent P. *et al.* stated that an application of MTA was associated with an increase in TGF-β secretion from pulp cells, [16] which promotes the migration of the progenitor cells to the pulp-material interface, thus inducing the differentiation of odontoblasts to form reparative dentin. Micro- CT imaging techniques have revealed a more homogenous reparative dentinal layer with uniform thickness with MTA when compared to Biodentine.[17] A bioactive material is also expected to be compatible with the overlying restoration to warrant a permanent seal. Recent studies have suggested that placement of composite used with a two-step etch and rinse adhesive (E&R) over white MTA performed significantly better than an all-in-one system in terms of bond strength [18] Other studies concluded that the highest bond strength was obtained when the E&R adhesive was used after 24 h resulting in shear bond strength (SBS) of 7.3±1.49 MPa. Also, MTA has been found to mature up to 1 year beyond the setting time with impacts on its mechanical integrity and hence SBS values. [6,19]

**Newer generation MTA-Based Bioactive materials**

Neo MTA Plus (Avalon Biomed Inc., Houston, TX, USA) is a novel MTA- based restorative material (Composition in Table 1) in which the component bismuth oxide is replaced by tantalum oxide, to overcome the adverse effect of tooth discoloration. A higher crystallinity, better apatite formation, and better bioactivity have also been observed in Neo MTA Plus compared to its previous counterpart. [20]

Light-curable resin-modified calcium-silicate based materials have also been developed. Compared to conventional MTA materials, the resin-modified light-curable cement has several advantages like immediate light-polymerization, prevention of materials washing out, and superior physical properties. However, it is reported that the resin-modified light-curable MTA cement showed more cytotoxic than resin-free calcium silicates/MTA.[21] Studies conducted in the past revealed their dominance over calcium hydroxide as pulp capping agents. However further research is needed to validate this claim.

**Biodentine**

Biodentine (Septodont, France) is a newer tricalcium silicate-based restorative material, which was explicitly designed as a “dentine replacement” material has drawn interest in recent years due to its wide plethora of applications in Restorative Dentistry and Endodontics namely root perforations, apexification, resorption repair, retrograde fillings and as a pulp-capping agent. Biodentine is commercially available in the form of a capsule containing powder (Composition in Table 1) and a liquid containing calcium chloride as an accelerator. The material exhibits its mechanism of action by releasing calcium silicate hydrate, calcium, and hydroxide when in solution. The inclusion of calcium carbonate acts as a nucleation site for the growth of hydroxyapatite crystals, thus enhancing its microstructure.[22] When compared with MTA, Biodentine has shown faster setting time, good biocompatibility, and a better initial cohesiveness. Biodentine and MTA have comparable success rates when used as direct pulp capping or pulpotomy material in permanent mature teeth with carious exposure. (Biodentine—91.7% and MTA—96.0%)[23]. A randomized clinical trial was conducted to explore the outcome of the

DPC procedure of permanent young teeth with Biodentine; it showed no failures after 12 months, while both calcium hydroxide and MTA had a 13.6% failure rate after the same time period.[24] In terms of quality of induced calcific bridge formation, although MTA surpasses Biodentine. But, in later stages, it has been seen to have performed better. A notable increase in alkaline phosphatase expression and calcium nodule formation.[25] Though superior to MTA in many ways, Biodentine has presented with significantly lower shear bond strength values than MTA to composite, which can be attributed to its prolonged intrinsic maturation(2 weeks) .[26]

**Endosequence Root Repair Material (ERRM )**

Endosequence Root Repair Material (ERRM; Brasseler USA, Savannah, GA) has been recently introduced as a potential pulp capping material. This bio-ceramic material is hydrophilic, radiopaque, and aluminum-free (Composition in Table 1) and has a high pH . In vitro studies have reported that ERRM had a similar antibacterial effect on Enterococcus faecalis than MTA.[27] Hirschman WR *et al.* compared four pulp capping material for their cytotoxicity on cultured adult human dermal fibroblasts.[28] They concluded that ERRM had the highest cell viability than MTA, Dycal, and Ultra-blend Plus(resin-based calcium hydroxide liner).

**TheraCal**

TheraCal LC (Bisco, Schaumburg, IL, USA) was introduced in 2011 to overcome poor bonding of Calcium Silicate Materials (CSMs) to resins in final restorations. TheraCal LC is a light-cured, resin-modified calcium silicate (Composition in Table 1) filled liner designed for use in direct and indirect pulp capping, as a protective base/liner under composites, amalgams, cements, and other base materials. TheraCal LC performs as an insulator/barrier of the dentin-pulp complex. TheraCal LC releases calcium which further stimulates hydroxyapatite formation and subsequently dentinal bridge formation. TheraCal LC is a light-cured, resin-modified calcium silicate filled liner designed for use in direct and indirect pulp capping, as a protective base/liner under composites, amalgams, cements, and other base materials. Gandolfi *et al.*[29], compared the physicochemical properties of TheraCal, ProRoot MTA, and Dycal and concluded that TheraCal displayed higher calcium releasing ability and lower solubility than either ProRoot MTA or Dycal.[30] A study reported that TheraCal is toxic to pulp fibroblasts and has a higher inflammatory effect and a lower bioactive potential than Biodentine,[31] but exhibits superior bonding ability to composite or glass-ionomer cements than the latter.[32] Although sufficient bioactivity, superior handling properties, and superior quality of bonding with the final overlaying restoration could validate the use of TheraCal LC as the IPC agent, further in vitro and in vivo studies are still required.[6]

**Orientation for the Future**

**Enzymes - Heme-Oxygenase-1:** Heme oxygenase-1(HO-1) is the rate-limiting enzyme in heme catabolism. Odontoblasts and oxidatively stressed dental pulp cells express HO-1, indicates that the pulp might respond to oxidative stress at the molecular level. HO-1 induction protects against hypoxic stress and nitric oxide-mediated cytotoxicity. It has been reported that HO-1 might play a cytoprotective role against pro-inflammatory cytokines and nitric oxide in human pulp cells. Besides, bismuth oxide containing Portland cement (BPC) induced HO-1 expression in dental pulp cells plays a protective role against the cytotoxic effects of BPC.[33] A study by Kim *et al.* reported that Cobaltic protoporphyrin IX (CoPP) induction of HO-1 in HDPCs increased cell growth and mineralization and up-regulated the messenger RNA expression of odontoblastic markers such as alkaline phosphatase, osteopontin, bone sialoprotein, protein-1

matrix dentin, and phosphoprotein dentin sialo. It described HO-1 ' s capability as a material for pulp capping.[34]

**Simvastatin:** Statins are structural analogs of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A). These drugs are the first-line for hyperlipidemia and it has been documented to be safe. Moreover, statins have multiple functions including anti-inflammation, induction of angiogenesis, and improvement of the vascular endothelial cell function. Also, it has been shown to promote osteogenesis. [35] They promote mineralization in non-mineralizing osteoblasts through induction of BMP-2 and osteocalcin. Karanxha L. *et al.*[36] inferred through their study that Simvastatin promotes odontoblastic differentiation of human dental pulp cells (hDPCs) via the extracellular-signal-regulated kinase (ERK) signaling pathway and simvastatin-induced differentiation is facilitated by co-treatment with Enamel Matrix Derivative; which suggests a new strategy to induce odontoblastic differentiation of hDPCs.

**Growth Factors and Signaling molecules:** A growth factor, as initially defined as a secreted biologically active molecule that can affect the growth of cells. It encompasses secreted molecules that promote or inhibit mitosis or affect cellular differentiation. Growth factors act on specific cell surface receptors that can later transmit their growth signals to other intracellular components and eventually result in altered gene expression.[37]

**Bone Morphogenic Protein (BMP):** BMP belongs to a superfamily transforming growth factor-beta (TGF-β). TGF β is a potent modulator of tissue repair in different situations. BMP-2, 4, and 7 plays a role in the differentiation of adult pulp cells into odontoblasts during pulpal healing. [30] Lianjia et al., found that BMPs are responsible for dentinogenesis, inducing non-differentiated mesenchymal cells from the pulp to form odontoblast-like cells, obtaining osteodentin, and tubular dentin deposition when used as direct protectors. [38] Al-Agele *et al.* in 2019 detailed that BMP-7 application in direct pulp capping can enhance and accelerate pulp healing moreover the combined application of laser irradiation with BMP-7 may induce an additional effect over the application of BMP-7 itself.[39]

**Other growth factors:** Recombinant Insulin-Like Growth Factor-I (rhIGF-I) and Transforming Growth Factor Beta-1 (TGF-β 1) have been shown to enhance dentinal bridge formation in at molars. A possibility of immunological problems due to repeated implantation of active molecules also exists from these materials.[40,41]

**Heat Shock Proteins:** Direct pulp capping procedures include administration of Local Anesthesia and cavity preparation. This exposes the pulp to heat stress and reduced blood flow. Due to its inherent nature, pulp possesses the ability to resist this thermal stress and ischemia. It was also demonstrated that pre-treated odontoblastic cells with the fever-range heat stress (41°C) survived with odontoblast-like properties after lethal heat stress, with the accumulation of heat shock proteins (HSPs) and the cell-cycle arrest.[42] Accumulation of HSPs and cell-cycle arrest induce cellular resistance to various stimuli.[43] Therefore, HSPs may also be one of the biological molecules which can be considered as pretreatment agents for direct pulp capping.[42]

**Macromolecular Translocation Inhibitor II Peptide Anti-Inflammatory Drug (MPAID :** Lately, it was found that a macromolecular translocation inhibitor II (MTI-II) peptide anti-inflammatory drug (MPAID) may regulate the inflammatory response and maintain a protective response of dental pulp. [44] MTI-II is a small nuclear acidic protein, which was previously demonstrated to be an enhancer of the transcriptional activity of glucocorticoid-bound glucocorticoid receptor, and MPAID was

bioengineered from the structure of MTI-II as an inhibitor of Nuclear Factor kappa-light chain-enhancer of activated B-cells(NF-κB) transactivation.[45] Anti-inflammatory agents similar to MPAID could be contenders for direct pulp capping or pretreatment agents.

**Stem cells:** Adult stem cells possess the capacity of self-renewal and multilineage differentiation which helps in playing a crucial role in postnatal tissue development and provide an attractive progenitor cell source for tissue engineering and regenerative medicine. Dental pulp stem cells (DPSCs), Stem cells from Human Exfoliated Deciduous Teeth (SHED), and bone marrow stem cells (BMSCs) [46] which can differentiate into multiple mesenchymal cell lineages are putative candidate cells for tooth and bone tissue engineering. Nakamura S *et al.* compared the proliferation and stem cell marker of SHED, DSPCs, and Bone Marrow-Derived Mesenchymal Stem Cells (BMMSCs) and concluded that SHED has got significantly higher proliferation rate than that of DSPCs and BMMSCs and this could be a desirable choice as a cell source for therapeutic applications.[47]

**Scaffolds:** Scaffolds are three-dimensional (3D) porous solid biomaterials designed which promote cell-biomaterial interactions, cell adhesion, and ECM deposition; permit sufficient transport of gases, nutrients, and regulatory factors to allow cell survival, proliferation, and differentiation; while causing less toxicity.[48]

**Platelet-rich fibrin (PRF):** Platelet-rich fibrin (PRF), belongs to the second generation of platelet concentrate products, named Choukroun's PRF after its inventor. It has favorable properties, which include osteogenic ability, simple preparation, and no added biological agents. PRF was demonstrated to promote cell proliferation and osteogenic differentiation in human dental pulp cells (HDPCs). The procedure consists of drawing blood which is collected into test tubes without an anticoagulant and is centrifuged immediately. A tabletop centrifuge can be used for 10 min at 3000 rpm or 12 min at 2700 rpm.[49] The product separates into three layers with the PRF clot in the middle. PRF can be considered as an immune concentrate with a specific composition and a 3D architecture. It contains a multitude of growth factors such as Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor β1 (TGF β1), and Insulin-Like Growth Factor (IGF). It consists of an intimate assembly of cytokines, glycan chains, structural glycoproteins enmeshed within a slowly polymerized fibrin network. These biochemical components have well known synergistic effects on healing processes. Fibrin is the natural chaperon of angiogenesis. Fibrin constitutes natural support to immunity. [50] A study [51] had inferred that PRF had similar mineralization capacity as that of MTA, implying its possible future application as a pulp capping material. however, suggesting evidence is in dearth in the literature to reach a consensus about the same, hence, future investigations are required.

**Concentrated Growth Factors (CGF):** Concentrated growth factor (CGF) is a novel 2nd generation platelet-concentrate which are also derived from autologous blood and produced using a special centrifuge device (Medifuge Silfradent s.r.l. Sofia,Italy). On centrifugation it separates out in 3 phases- a superior phase represented by the serum (blood plasma without fibrinogen and coagulation factors, platelet poor plasma, PPP); an interim phase represented by a very large and dense polymerized fibrin block containing the CGFs, white blood cells and stem cells; and the lower erythrocytes layer.[52]Compared to the previous generation platelet concentrate products, the different centrifugation speeds allow the isolation of a fibrin matrix that is considerably larger, denser, and richer in growth factors.[53] CGF contains numerous growth factors and CD34+ stem cells with advantages including osteogenic

ability, simple preparation process, good biological properties, and lack of added biological agents. Dou L. *et al.* [51] investigated the effect of calcium hydroxide, mineral trioxide aggregate (MTA), iRoot BP, platelet-rich fibrin (PRF), and concentrated growth factors (CGF) on the proliferation, viability, apoptosis, and mineralization of human dental pulp cells (HDPCs), and concluded that CGF has comparable cell proliferation ability as that of MTA and can be a potential candidate for pulp capping material.

**Chitosan:** Chitosan is produced commercially by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (such as crabs and shrimp) and cell walls of fungi. The properties of chitosan affect the formation of pores in the scaffolds, thereby influencing the mechanical and biological properties. [54] Chitosan is nontoxic, easily bioabsorbable, shows antibacterial activity, has the gel-forming ability, increases alkaline phosphatase activity, shows fibroblast, and odontoblastic proliferation. It is porous and promotes cell attachment effortlessly.[55]

Recently a study was conducted by Subhi H. *et al.* [56] where they evaluated the effects of an experimental Gypsum-based Chitosan (Gp-CT) material on cell viability, Alkaline Phosphatase (ALP) activity, and cell attachment when incorporated with BMP-2 and compared the material with Dycal. They concluded that the ALP activity of Stem Cells from Human Exfoliated Deciduous Teeth (SHED) in the Chitosan group was significantly higher than that of the Dycal group, with the scanning electron microscopy (SEM) image revealing the distribution and adherence of the flattened cells to the material surface. Thereby, Gp-CT material seemed to show an aptitude as a potential material for direct pulp capping.

**Conclusion**

Recent advancements in biomedical engineering have urged the transition towards minimally invasive therapy techniques in the field of Restorative Dentistry & Endodontics. This review has detailed the current and the future materials which are/can be employed to preserve the vitality of the pulp. However, further in-vivo and in-vitro studies are required to validate the importance of the newer generation materials available with a simultaneous comparison with the traditional agents. Also, the properties of the pulp- capping agents in terms of cytotoxicity, cell viability, quality of hard tissue barrier formation, and shear bond strengths with the overlying permanent restorative materials; should be a matter of address in the impending researches.

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