

Review Article

Current trends and future perspectives of dental pulp capping materials: A systematic review

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Abstract: To systematically review the literature to analyze the current trends and future perspectives of dental pulp capping materials through an analysis of scientific and technological data. This study is reported in accordance with the PRISMA Statement. Nine databases were screened: PubMed (MedLine), Lilacs, IBECs, BBO, Web of Science, Scopus, SciELO, Google Scholar, and The Cochrane Library. Additionally, the following patent applications were searched online in Questel Orbit (Paris, France), USPTO, EPO, JPO, INPI, and Patentscope databases. A total of 716 papers and 83 patents were included. Calcium hydroxide was the main type of material studied, especially for direct pulp capping, followed by MTA. Patents related to adhesives or resins increased from 1998 e 2008, while in the last years, a major increase

was observed in bioactive materials (containing bioactive proteins), materials derived from MTA (calcium silicate, calcium phosphate and calcium aluminate-based cements) and MTA. It was possible to obtain a scientific and technological overview of pulp capping materials. MTA has shown favorable results in vital pulp therapy that seem to surpass the disadvantages of calcium hydroxide. Recent advances in bioactive materials and those derived from MTA have shown promising results that could improve biomaterials used in vital pulp treatments. © 2017 Wiley Periodicals, Inc. *J Biomed Mater Res Part B: Appl Biomater* 00B: 000–000, 2017.

Key Words: dental pulp capping, pulp capping agents, pulpotomy, dental materials, review

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INTRODUCTION

Minimal intervention dentistry aims to promote the preservation of the tooth structure in an effort to avoid damage to the dentin–pulp complex.¹ The morbidity associated with untreated pulp infection often requires either root canal treatment or tooth extraction with further replacement, which could require multiple appointments and considerable expenses apart from being less cost-effective.^{2,3} Vital pulp therapy (VPT) has been practiced for over 200 years. This procedure may involve the application of a protective biomaterial (called of pulp capping agent) on the remaining thin layer of dentin over: a nearly exposed pulp (indirect capping); an exposed coronal pulp (direct capping); or over

partially removed coronal pulp tissue (pulpotomy).¹ The first procedure described was the application of a lead foil cap on an exposed pulp performed by Pfaff in 1756.^{2,3} About 100 years later, materials containing calcium hydroxide were first described for treating exposed pulp. However, the use of calcium hydroxide gained importance only after Hermann's publication in 1930, and since then, this has been one of the materials most commonly used in VPT.^{3,4}

However, the high solubility, lack of adhesion and poor physico-mechanical properties had become relevant clinical issues. Consequently, the quest to find an ideal pulp capping agent has led to other biomaterials being suggested in the literature, such as mineral trioxide aggregate (MTA), dental

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TABLE I. Search Strategy Used in PubMed (MedLine)

	Search Terms
#4	Search #1 AND #2 AND #3
#3	"Pulp Capping and Pulpectomy Agents"[Mesh] OR "Pulp Capping and Pulpectomy Agents" OR "Mineral Trioxide Aggregate" OR "MTA Cement" OR "MTA Aggregate" OR "aggregate ProRoot" OR "Pulp Capping Agent" OR "Pulp Capping Agents" OR "Agent, Pulp Capping" OR "Agents, Pulp Capping" OR "Capping Agent, Pulpb" OR "Capping Agents, Pulp" OR "Pulp Capping Agent" OR "Agents, Pulpectomy" OR "Pulpectomy Agent" OR "Calcium Hydroxide" OR "Hydroxide, Calcium" OR "Mineral Trioxide Aggregate" OR "Cavity Linings, Dental" OR "Lining, Dental Cavity" OR "Linings, Dental Cavity" OR "Cavity Lining, Dental" OR "Dental Cavity Linings" OR "Varnish, Cavity" OR "Cavity Varnish" OR "Cavity Varnishes" OR "Varnishes, Cavity" OR "Cavity Lining Varnish" OR "Varnish, Cavity Lining" OR "Cavity Lining Varnishes" OR "Varnishes, Cavity Lining" OR "Cavity Liner, Dental" OR "Cavity Liners, Dental" OR "Liner, Dental Cavity" OR "Dental Cavity Liners" OR "Liners, Dental Cavity" OR "Dental Cavity Liner" OR "Theracal" OR "Biodentine" OR "Emdogain" OR "MTA"
#2	"Dental Pulp Capping" [Mesh] OR "Dental Pulp Capping" OR "Pulp Capping, Dental" OR "Pulp Capping" OR "Capping, Pulp" OR "Cappings, Pulp" OR "Pulp Cappings" OR "Capping, Dental Pulp" OR "Cappings, Dental Pulp" OR "Dental Pulp Cappings" OR "Pulp Cappings, Dental" OR "Pulpotomy" OR "Dental Pulp Exposure" OR "Exposure, Dental Pulp" OR "Pulp Exposure, Dental" OR "Pulp Exposures"
#1	"Dental Materials"[Mesh] OR "Dental Materials" OR "Materials, Dental" OR "Dental Material" OR "Material, Dental" OR "Oral medicine" OR "Medicine, Oral" OR "Dentistry" OR "Odontology" OR "Biomaterials"

bonding agents, formocresol, ferric sulfate, and materials derived from MTA, such as calcium silicate, calcium phosphate and calcium aluminate-based cements.⁵⁻⁹ An ideal pulp capping material should adhere to tooth substrate; maintain a sufficient seal, be insoluble in tissue fluids; dimensionally stable, non-resorbable, nontoxic, noncarcinogenic, nongenotoxic, radiopaque, and exhibit biocompatibility and bioactivity.^{6,10,11} Unfortunately, none of the biomaterials currently available have been able to satisfy all the requirements of an ideal VPT.¹¹

Therefore, since the evolution of dentistry, various dental materials have been developed to obtain maximum benefit from them, and generate the most beneficial tissue response. With the better understanding of the dentin-pulp complex repair and regeneration process, advances in biomaterials have emerged for maintaining pulp vitality, by using minimal invasive dentistry.^{3,4} With a wide variety of biomaterials used for VPT, it is a problem to identify the best pulp capping agent for each clinical case. Thus, the aim of this systematic review was to analyze the scientific and technological information related to dental pulp capping materials in order to determine the state of the art in this area. Additionally, we aimed to verify the current trends and future perspectives in the development of new biomaterials for VPT.

MATERIALS AND METHODS

The report of this systematic review was adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.¹²

Electronic searches

The reviewers performed the literature search until November of 2015. Eight databases were selected to conduct the search: PubMed (MedLine), Web of Science, The Cochrane Library, Scopus, Scielo, Ibecs, Lilacs, BBO, and Lilacs. Additionally, patent applications were searched and analyzed by

means of the online system Questel Orbit (Paris, France) that allows the patent search of over 80 authorities. Other patent databases screened were USPTO (United States Patents and Trademark Office), EPO (European Patent Office), JPO (Japan Patent Office), INPI (National Institute of Intellectual Property of Brazil) and Patentscope. The search strategy used in PubMed (MedLine) was adapted for use in the other databases (Table I).

Furthermore, a preliminary patent search was conducted to identify relevant International Patent Classifications (IPC) in order to optimize the patent search process. The aim of identifying these codes was to create a specific tool for patent search, and the following codes were crossed with the search terms to enhance the retrieval of relevant patents: A61K (preparations for medical, dental, or toilet purposes); A61K 6/02 (use of preparations for artificial teeth, for filling or for capping teeth) and A61C 5/00 (filling or capping teeth). The papers were imported to the software Endnote X7 (Thompson Reuters, USA) to remove duplicates.

Screening and study selection

Studies and patents were initially analyzed by screening the titles and abstracts. Reviewers selected only studies and patents related do dental pulp capping materials in accordance with the eligibility criteria (Table II). There was no limit on year of publication. Documents that appeared to meet the inclusion criteria or had insufficient data in the title and abstract to make a clear decision were selected for full analysis. Any disagreement as regards the inclusion of studies was resolved by discussion and consensus. Thus, only documents that fulfilled all of the eligibility criteria were included.

Data extraction

The reviewers (ARC, TMS, LCM, and ADG) tabulated the scientific and technological data of interest, and another reviewer (WLOR) revised all data. From the studies included, the following data were tabulated: type of study

TABLE II. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
- Studies that evaluated pulp capping agents to vital pulp therapy - Patents related to dental materials and protection of dentin-pulp complex	- Studies that evaluated only techniques and not materials - Review articles, abstracts from congress, case reports, case series, thesis and dissertations - Studies published in a language other than English, Spanish or Portuguese

(*in vitro*, clinical and/or animal study), year of publication, country of corresponding author, vital pulp treatment (direct/indirect pulp capping, pulpotomy), type of material evaluated. The type of teeth evaluated by clinical studies was also analyzed (permanent/primary teeth). Moreover, the characteristics of the patents included, such as priority and year of publication, priority and country where the patent was deposited, type of depositor (personal, university, company, and public foundation) and type of material patented were also tabulated in order to obtain the technological information. The materials were classified according to their main compositions, as described in Table III.

RESULTS

Descriptive analysis

Initially, 4742 studies and 367 patents were identified from all databases. After screening, a total of 716 papers and 83 patents were included in this systematic review, as described in Figure 1. Out of the studies included, 24% were *in vitro*; 38% animal experiments and 38% clinical trials.

Scientific production of pulp capping materials related to different treatment protocols are represented in Figure 2. The number of papers published was higher than that of patent applications or published annually in almost the entire period analyzed (Figure 2a). Clinical studies mainly evaluated permanent teeth with regard to direct pulp capping, while primary teeth were the most analyzed for pulpotomy and indirect pulp capping (Figure 2b).

Main countries with patent application were United States (25 patents), Japan (22 patents), China (7 patents), Australia (6 patents) and Germany (6 patents) (Figure 3); and main origin of papers (according to corresponding authors) and patents (priority countries). The United States and Japan were also the main countries of origin of patents related to this area. Moreover, Brazil (24%), United States (15%) and Japan (8%) had the majority of papers published in this field of research.

Figure 4 represents the main type of biomaterial studied and patented. As regards annual technological production, calcium hydroxide-based materials were the most patented for a long time, in the past (Figure 4a). Patents related to

adhesives or resins as pulp capping agents increased especially from 1998 to 2008. While in the last decade, a major increase was observed in bioactive materials (containing bioactive proteins), MTA and materials derived from MTA (calcium silicate, calcium aluminate, calcium phosphate-based cements). Calcium hydroxide was the biomaterial most studied, followed by MTA (Figure 4b). Direct pulp capping was evaluated in 68% of studies with calcium hydroxide, followed by pulpotomy (24%) and indirect pulp capping (8%). Besides, MTA was applied in 53% of studies where pulpotomy was evaluated, and in 48% direct pulp capping. Considering all biomaterial, the majority of studies evaluated calcium hydroxide and adhesives/resins for indirect pulp capping. Whereas, for pulpotomy, many studies were related to calcium hydroxide, formocresol, and MTA.

Additionally, the main patent depositors were companies (36%) and universities (33%). Personal deposit represented 26% of all patents applications, and public foundations deposited the least 8%.

DISCUSSION

This review allowed mapping of the knowledge available about pulp capping materials by means of scientific and technological analysis. There was a gradual increase in studies and patents related to these biomaterials over the years, which reflects the constant evolution of treatments in this topic. Furthermore, patents are an important source of technological information,^{13,14} and the scientific and technological scenario observed differed with regard to the main types of materials studied and patented, which means that the search and analysis of papers only might show a limited overview of this area. Moreover, within each VPT, several biomaterials were found, which will be discussed further on, in order to present their current trends, recent advances and future perspectives.

Current trends in vital pulp treatments

Indirect pulp capping. There are different clinical procedures to preserve pulp vitality in teeth with deep caries: either with total carious tissue removal or partial caries removal; either during the same appointment (complete caries excavation) or in one or more treatment steps (stepwise excavation).²⁻⁴ The complete removal of all carious substrate is no longer considered mandatory; and in recent years indirect pulp capping with partial caries removal has been advocated in studies.^{3,4} The preservation of carious dentin along the pulpal floor is the goal of contemporary conservative dentistry based on retaining healthy tooth tissues. By leaving the deepest layer of carious dentin undisturbed, the risk of pulp exposure and post-operative pulp symptoms is significantly reduced, and favorable clinical results have been reported with residual dentin remineralization.⁴

Calcium hydroxide was the main material evaluated in indirect pulp capping, probably because it has important biological and antimicrobial properties. Additionally, it has the longest track record of clinical success.¹⁵ The high alkalinity of calcium hydroxide has been believed to cause

TABLE III. Classification of Main Pulp Capping Materials Identified in the Literature

Material	Main Indications	General Composition	Commercial Example
Calcium hydroxide	Direct/indirect pulp capping, pulpotomy	Base paste: titanium dioxide, calcium tungstate 1,3-butylene glycol disalicylate Catalyst paste: calcium hydroxide, zinc oxide, zinc stearate, ethyl toluene sulfonamide	Dycal ^a (Dentsply, United States), Life (Kerr, United States)
Mineral trioxide aggregate (MTA)	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: tricalcium silicate, dicalcium silicate, tricalcium aluminate. Liquid: distilled water	MTA Angelus ^a (Angelus, Brazil), MTA ProRoot (Dentsply, United States)
Calcium silicate based	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: tricalcium silicate, dicalcium silicate, calcium carbonate, zirconium dioxide Liquid: water, calcium chloride, modified polycarboxylate (superplasticizing agent)	Biodentine ^a (Septodont, France), TheraCal LC (Bisco, United States), Tech Biosealer capping (Isasan, Italy)
Calcium phosphate based	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: calcium compounds such as calcium oxide, calcium phosphate, calcium carbonate, calcium silicate, calcium sulfate, calcium hydroxide, calcium chloride Liquid: distilled water	Calcium Enriched Mixture (CEM) Cement ^a (Bionique-Dent, Iran)
Calcium aluminate cement	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: aluminum oxide, calcium oxide, silicon dioxide, magnesium oxide, iron oxide, bismuth oxide Liquid: distilled water	Endobinder ^a (Binderware, Brazil)
Adhesive systems	Indirect pulp capping	Primer: 10-methacryloyloxydecyl dihydrogen phosphate (MDP), dimethacrylate monomer, hydroxyethyl methacrylate (HEMA), silica, N,N-diethanol-p-toluidine, canforoquinone Bond: Hydroxy ethyl methacrylate (HEMA), dimethacrylate monomer, bisphenol A glycidyl methacrylate (Bis-GMA), N,N-diethanol-p-toluidine silica, canforoquinone	Clearfil SE Bond ^a (Kuraray Medical, Japan), Optibond S (Kerr, United States), Prime&Bond 2.1 (Dentsply, United States)
Zinc oxide and eugenol	Indirect pulp capping	Powder: zinc oxide, polymethyl methacrylate (PMMA) pigment. Liquid: eugenol, acetic acid	IRM ^a (Dentsply, United States), Temp Bond (Kerr, United States), Relix Tempo (3M ESPE, United States)
Formocresol	Pulpotomy	Formaldehyde, ortho-cresol, glycerol, ethyl alcohol	Buckley's Formocresol* (Sultan Healthcare, United States)
Ferric sulfate	Pulpotomy	Ferric sulfate, silica, aqueous vehicle	ViscoStat ^a (Ultradent, United States), Astringedent (Ultradent, United States)
Bioactive materials (containing bioactive proteins)	Direct/indirect pulp capping, pulpotomy	Enamel matrix proteins, water, propylene glycol alginate.	Emdogain ^a (Straumann, Switzerland)

^a Material with general composition informed.

irritation of the pulp tissue when in contact with it; this could stimulate the repair process through the release of bioactive molecules sequestered within dentin, such as bone morphogenic protein-7 (BMP-7) and transforming growth factor- β 1 (TGF- β 1).¹⁶ Despite the wide use of calcium hydroxide, this material provides a poor seal; does not adhere to tooth substrates; and the self-cure formulations are soluble.^{2,17}

To overcome the disadvantages of calcium hydroxide, dental adhesive systems were suggested for use as potential pulp capping material about 20 years ago,¹⁸ which has probably led to a further increase in patent deposition observed especially from 1998 to 2008. Although bonding to tooth substrates could improve cavity sealing with restorative materials, in clinical situations, sound dentin is not the substrate most frequently found in deep carious lesions, but

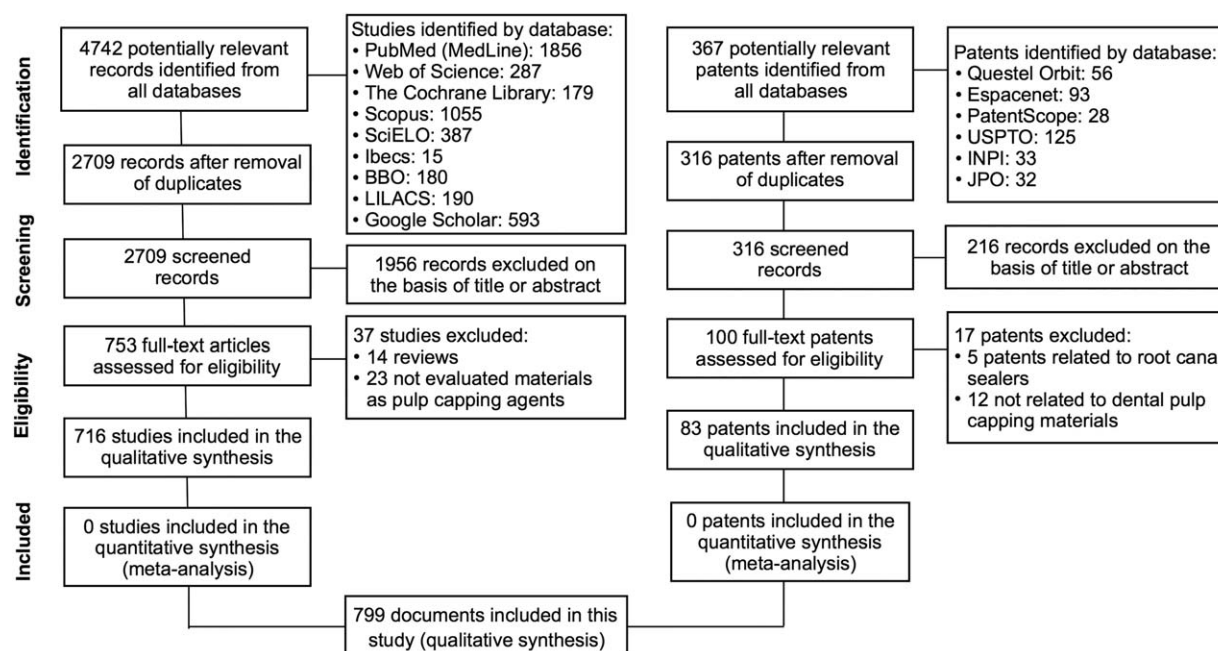


FIGURE 1. Search flow (adapted from the PRISMA statement).

rather sclerotic, caries-infected or caries-affected dentin.¹⁹ The bond strength of adhesives to caries-affected dentin has been reported to be lower than it is to sound dentin.^{20–22} Taking into consideration that these effects are dependent on how deep the carious lesion is, this could affect the clinical success of this treatment.⁴ Furthermore, the components of adhesive systems have been shown to be cytotoxic to pulp cells, and they are not currently recommended to direct pulp capping.^{23–25} Furthermore, the therapy of deep cavitated lesions should require less focus on complete carious removal than on adequate sealing with restorative materials.^{26,27}

Direct pulp capping. Direct pulp capping treatment has been suggested when pulp exposure occurs due to caries, traumas or accidents during cavity preparation, without the presence of irreversible pulp inflammation.^{6,45,46} The biomaterial used should have some fundamental properties to maintain tooth vitality, such as stimulating tertiary dentin formation, providing an adequate bacterial seal and then promoting pulp healing.⁶ Our review demonstrated that calcium hydroxide-based materials and MTA were the two most studied materials in pulp exposures.

Calcium hydroxide had been considered the “gold standard” for years, recently MTA has been widely investigated as a material for direct pulp capping, and it has shown good results in clinical trials.^{28,29} The major benefits include good biocompatibility, radiopacity, sealing ability, low solubility, long-term stability, prevention of bacterial infiltration, and the dentinogenic and osteogenic potentials.⁸ In addition, MTA could reduce the levels of pulp inflammation, hyperemia and necrosis,^{2,30} and could also solubilize bioactive proteins involved in the tooth repair process.³¹ On the other

hand, it was reported that MTA presents disadvantages such as discoloration³² - a critical factor in anterior teeth; the presence of toxic elements (i.e., arsenic) in the material composition³³; higher cytotoxicity in its freshly mixed state³⁴; long setting time,³⁵ high pH during setting³⁶; and difficult handling characteristics.³⁷

Nowadays, MTA is the present reference control recommended by ISO 7450 (2008)³⁸ or ANSI/ADA no. 41.³⁹ Moreover, recent studies have demonstrated that MTA presented higher clinical success rates than calcium hydroxide in direct pulp capping.^{28,29} Current evidence suggests that MTA presented an overall success rate of 80.5% compared with the 59% of calcium hydroxide in up to 123 months,²⁸ and at present, it seems to be the best indicated biomaterial for this therapy.

Pulpotomy. In the presence of pulpal inflammation, teeth can be clinically managed either by attempting to preserve the tissue in cases of reversible pulpitis, or removing it and sealing the root canal in irreversible pulpitis. Considerable controversy surrounds this issue, and pulpotomy should be considered for treating a few affected teeth in which the pulp exposure occurred through sound dentin or through carious lesions in symptom-free teeth.^{4,17,40,44} Pulpotomy consists of the surgical amputation of coronally inflamed pulp, and the surface of the remaining radicular pulp may be treated with a medicament or pulp capping agent in an endeavor to maintain vitality.⁴⁰ Furthermore, pulpotomy is often indicated for immature teeth, which are frequently associated with child patients, and pulp testing in these subjects is a complex and subjective procedure.⁴⁰

The main biomaterials that have been evaluated for pulpotomy include formocresol, ferric sulfate, zinc oxide and

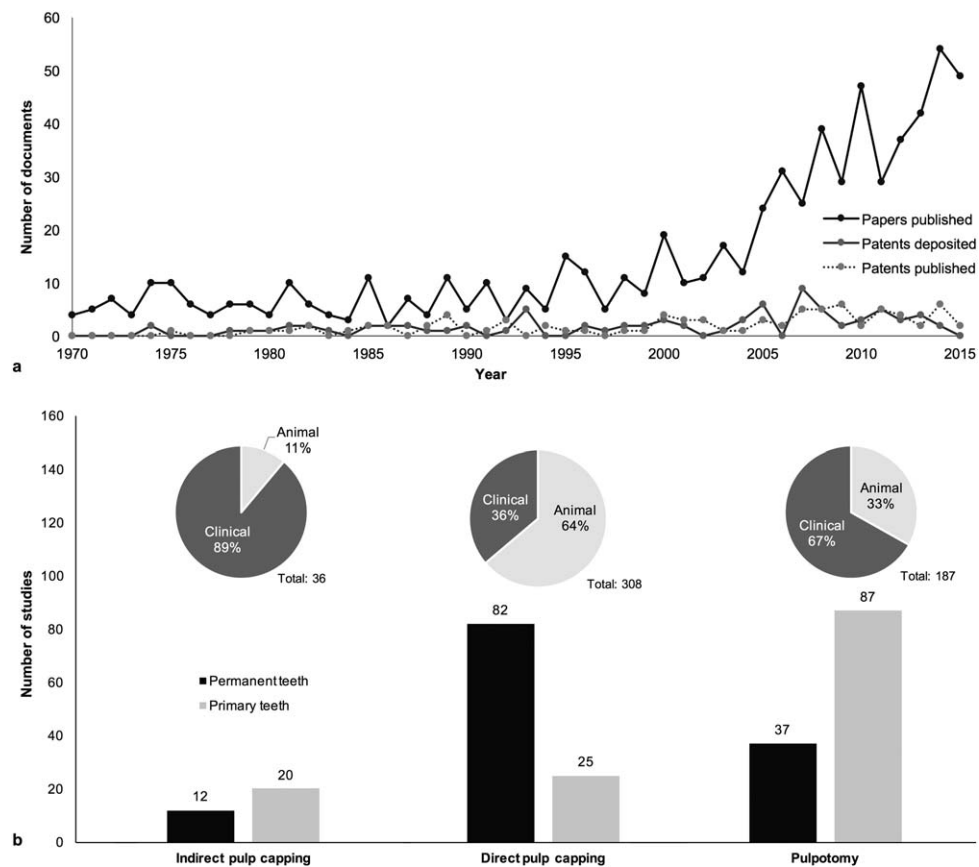


FIGURE 2. Studies and patents related to pulp capping materials (a) annual evolution of the scientific (papers published) and technological production (patents applications and later published) (1970–2015); (b) number of studies related to type of study (clinical or animal study), pulp treatment (direct or indirect pulp capping, pulpotomy) and type of teeth (permanent or primary).



FIGURE 3. Scientific and technological production of pulp capping materials in the world. Main countries with patents applications; and main origin of papers (according to corresponding authors) and patents (priority countries).

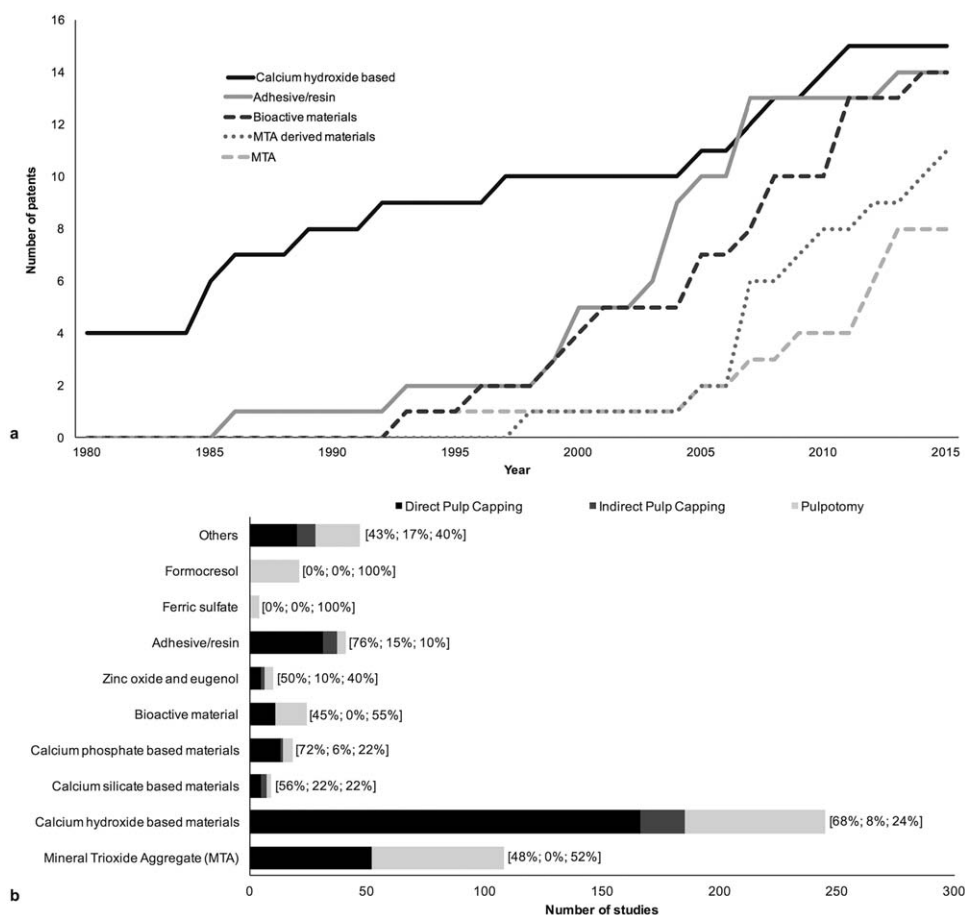


FIGURE 4. Scientific and technological production of pulp capping materials: (a) annual production (cumulative) of main type of pulp capping materials patented (1980–2015); and (b) type of material evaluated according to pulp treatments.

eugenol, calcium hydroxide, MTA. Despite the long history of calcium hydroxide in VPT, the issue is still controversial as regards pulpotomy in primary teeth, due to its caustic actions.¹⁷ Because of this, formocresol was introduced in 1904 by Buckley for the treatment of the putrescent pulp in animal teeth. Later, he introduced a commercial formula that consisted of 19% formaldehyde, 35% cresol and glycerin in distilled water.⁴⁰ Although formocresol has long been considered the gold standard in pulpotomy, researchers have been questioning its use due to possible toxic effects.⁴¹

MTA was also recently indicated for pulpotomy, and showed favorable pulpal responses in both permanent and primary teeth. In permanent teeth, MTA demonstrated satisfactory treatment outcomes in studies with pulpotomy after pulp exposure due to caries.^{22,42,43} However, a study reported that the incidence of unfavorable outcomes in periods of up to 2 years tended to be higher in teeth with larger pulp exposure areas.⁴² In addition, regarding the current evidence about pulpotomy, a systematic review demonstrated that MTA as a pulpotomy agent had a favorable success rate in treating carious exposure of permanent teeth with closed root apices.⁴⁴ In primary teeth, MTA presented higher clinical success rates than formocresol.^{17,43,45,46}

When comparing all the main materials used for pulpotomy of primary teeth, a recent meta-analysis demonstrated that the success rate of MTA (94.6%) was higher than that of formocresol (87.4%), ferric sulfate (86.6%) and calcium hydroxide (60.5%).⁴⁷ Although MTA presented some drawbacks, as previously mentioned, at present it seems to be the best treatment option for pulpotomy in primary and permanent teeth.

Recent advances and future perspectives in vital pulp therapy

There is a need to discover a pulp capping material that potentiates the natural pulp healing process; is biocompatible and exceeds the benefits of biomaterials at present available on the market. In an endeavor to develop products that satisfied the easy to use requirements and ideal pulp capping agent criteria, the composition of materials continues to change as the manufacturers try to improve their efficacy. We also included patent data in our analysis as source of technological information, and scientific production in this area is not being properly followed by technological prospecting. Many studies were focused on evaluating already available pulp capping materials than on developing and improving them. The trend observed in

technological data suggested that while focus in the past was on calcium hydroxide based cements, and afterwards on adhesives or resins, in the last few years it seems that MTA and bioactive materials have gained attention. The countries with high counts of patents applications were the United States and Japan, which probably reflects the most important markets for this technology. Considering that the main depositors of patents were companies, the results also suggest the need for a close relationship between the university and industry to improve the integration between scientific and technological knowledge. There are potential areas to be explored with new innovative pulp capping materials that could disrupt existing business models and provide newer and better treatment options for patients.

In this context, new materials derived from MTA have been suggested in recent years as pulp capping agents. These materials have improved properties of MTA, such as good sealing correlated to expansion, the ability to set in the presence of fluids^{35,48,49}; release of ions such as calcium⁵⁰ and good biological properties.^{51–54} The addition of calcium chloride resulted in a cement with a lower setting time and good biocompatibility.^{55–57} Moreover, attempts at replacing the Portland cement component of MTA with tricalcium silicate resulted in a biomaterial with improved physico-mechanical properties.⁵⁸ The most studied calcium silicate based cement was Biodentine (Septodont, France), that had been recommended even for temporary restorative material. Similar outcomes as regards tertiary dentin formation and inflammatory response between Biodentine and MTA were demonstrated in an animal experiment⁵⁹; in an *ex vivo* study with human teeth⁶⁰; and in a recent clinical trial when used for pulpotomies of primary molars after 12 months of follow-up.⁴¹ Moreover, when used for indirect pulp capping, Biodentine showed similar clinical results to those of a glass ionomer cement (Fuji IX, GC Corporation, USA) after 12 months of follow-up.⁶¹

Another material derived from MTA developed was a calcium aluminate-based cement, such as EndoBinder (Bind-erware, Brazil), which preserved the properties and clinical applications of MTA without some of its negative characteristics.^{62,63} Its components allowed control of impurities such as iron oxide⁶⁴ that promotes tooth discoloration, and free magnesium oxide and calcium oxide, which may be responsible for an undesirable expansion of the material in contact with moisture.⁶⁵ Animal experiments demonstrated that these cements presented tissue compatibility that allowed mineralized tertiary dentin formation after pulpotomy with similar morphology and integrity to those formed with MTA.^{59,66–68} Additionally, EndoBinder was biocompatible when tested in rat subcutaneous tissue.⁶³ However, further research is needed to evaluate the potential clinical benefits of these new biomaterial in VTP.

Calcium phosphate-based materials have also emerged in recent years: such as calcium enriched mixture (CEM) cement. This cement was first introduced by Asgary et al. in 2006,⁶⁹ and it is similar to MTA, but with better physical properties. When the CEM is mixed with water-based solution, it forms calcium and phosphate enriched mixture.⁷⁰

Mixed CEM cement then forms hydroxyapatite not only in simulated body tissue fluid but also in normal saline solution; the latter being unlike MTA.⁷¹ The properties of bioceramics are very advantageous to material sciences, because CEM cement has an antibacterial effect comparable with that of calcium hydroxide and superior to that of MTA⁷²; and sealing ability similar to that of MTA.⁷³ The biologic response of the pulpal tissue to MTA and CEM cement was shown to be similar in animal studies.⁷⁴ In addition, its biocompatibility, osseo-conductive property, ability to form hermetic seal, chemical bond to the tooth structure, insolubility in tissue fluids, good radiopacity, and easy handling characteristics have led to the widespread use of these materials in recent years.⁷⁰ A recent randomized clinical trial showed that VPT with CEM was a reliable technique for treatment of permanent molar teeth with pulpitis after 5 years of follow-up.⁷⁵

The knowledge about the repair and regenerative process in the dentin-pulp complex is being more extensively exploited by researches. There has been growing optimism about the use of a biologic approach for dental pulp treatments via the stimulation and formation of biological tissue. It was demonstrated that the repair mechanism may be due to the release of bioactive molecules from the dentin matrix, including bone-morphogenetic protein (BMP) and transforming growth factor-Beta-1 (TGF- β 1).^{16,76–79} Pulp capping agents containing bioactive proteins were evaluated with the commercially available Emdogain (Straumann, Switzerland). The biomaterial is an injectable gel solution consisting of enamel matrix proteins (amelogenin), water and a carrier (propylene glycol alginate).⁸⁰ Moreover, enamel matrix proteins act in cementogenesis and in the development of the periodontal attachment apparatus.^{81,82} This material presents multiple applications, and has been mainly indicated in periodontics with favorable results when applied in periodontal defects.⁸⁰ Emdogain was suggested as a possible pulp capping material due the presence of amelogenin in its composition, which is involved in the growth and maturation of dental pulp cells during odontogenesis.⁸³ Nevertheless, clinical trials that evaluated Emdogain for direct pulp capping in primary teeth⁸⁴ and pulpotomy in permanent teeth⁸⁵ failed to demonstrate improvement in tertiary dentin formation. It is not clear whether the components of Emdogain regulate pulp repair or the regenerative process, and probably there are dentin matrix proteins more involved in tertiary dentin formation.

On the other hand, many animal experiments with dentin matrix proteins have demonstrated their potential benefits in VPT, such as direct.^{86,87} and indirect pulp capping^{88,89}; as well as in pulpotomy.⁹⁰ The high cost of these biomaterials and mainly the setting time are still considerable drawback that compromises their popularization. Patent data also showed that the protection of materials containing bioactive proteins has grown in the last 10 years, and their use in microspheres, hydrogels, delivery systems, scaffolds was claimed.^{91–94} Novel dental materials containing these proteins open promising treatment options, and both basic and clinical research toward reaching this goal is

needed. Hence, the need arises to discover a biomaterial that potentiates the natural pulp healing process and is cost-effective.

Based on this systematic review it was possible to obtain a scientific and technological overview of pulp capping agents. Calcium hydroxide was the biomaterial most studied over time with favorable clinical outcomes; the current literature suggests MTA presents superior performance for direct pulp capping and pulpotomy. One limitation of the present study in terms of decision making is that results were focused in obtaining an overview of biomaterials for VPT; meanwhile, recent advances in materials derived from MTA (calcium silicate, calcium phosphate, calcium aluminate-based cements) and bioactive materials containing dentin proteins have shown promising results that could improve vital pulp treatments in the near future.

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