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The use of bioinductor materials for vital pulp therapy in immature permanent teeth - Narrative review

Fernando Pessoa University

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"Work presented to Fernando Pessoa University as part of the requirements for obtaining a degree in dentistry."

Maria Cristina Varela Montilla

ABSTRACT

Background: Dental pulp preservation is essential, especially in young permanent teeth. Nowadays, with the development of biomaterials and advances in pulp biology, the preservation of dental pulp based on regenerative therapies with the use of new biomaterials could be achieve.

Objective: Analyse the use of bioinductive materials for vital pulp therapy in immature permanent teeth.

Materials and methods: A narrative review of publications, between the years 2000 and 2021, retrieved from "PubMed and B-ON" database and search engines of indexed scientific journals. 29 articles were selected according with the inclusion criteria of comparing bioinductive materials used in pulp treatment, based on biological principles and the behaviour of such materials in pulp treatment.

Conclusions: Vital pulp therapy in immature permanent teeth has been successful, especially, with the use of bioinductive materials like Mineral Trioxide Aggregate which is the most recommended.

Key words: dental pulp capping, immature permanent teeth, biomimetic materials, tricalcium silicate.

RESUMO

Introdução: A preservação da polpa dentária é essencial, principalmente em dentes permanentes jovens. Atualmente, com o desenvolvimento dos biomateriais e avanços na biologia pulpar, pode-se alcançar a preservação da polpa dentária baseada em terapias regenerativas com o uso de novos biomateriais.

Objetivo: Analisar o uso de materiais bioindutivos na terapia da polpa vital em dentes permanentes imaturos.

Materiais e métodos: Uma revisão narrativa de publicações, entre os anos de 2000 e 2021, recuperadas dos motores de busca "PubMed e B-ON" de revistas científicas indexadas. 29 artigos foram selecionados de acordo com os critérios de inclusão de comparação de materiais bioindutivos utilizados no tratamento da polpa, com base nos princípios biológicos e no comportamento desses materiais no tratamento da polpa.

Conclusões: A terapia da polpa vital em dentes permanentes imaturos tem tido sucesso, principalmente, com o uso de materiais bioindutivos como o Agregado de Trióxido Mineral que é o mais recomendado.

Palavras-chave: capeamento da polpa dentária, dentes permanentes imaturos, materiais biomiméticos, silicato tricálcico

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I would like to thank God for giving me health and the opportunity to achieve my goals.

To my son who daily teaches me and gives me the necessary motivation to be a better human being.

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LIST OF ABBREVIATIONS

BA	Bioaggregate
BEC	Bioactive Endodontic Cement
BMP	Bone Morphogenetic Protein
$Ca(OH)_2$	Calcium Hydroxide
CEM	Calcium Enriched Mixture
CSMs	Calcium Silicate materials
EMD	Enamel Matrix Derivative
FDA	Food and Drug Administration
IPC	Indirect pulp capping
IRM	Intermediate Restorative Material
MTA	Mineral Trioxide Aggregate
MMTA	Micromega MTA
PMTA	ProRoot® MTA

I. INTRODUCTION

An immature permanent tooth had recently erupted in the oral cavity and presents an incomplete root formation. In this sense, it must be remembered that the complete root development normally takes place two or three years after the tooth has erupted (Veleiro, 2010). In general, the interruption of this dental development tooth occurs because of pulp necrosis, which is usually caused by carious lesions or by various types of trauma that generate complications. In consequence, an altered crown-root ratio, roots with thin dentin walls, which in turn increases the risk of fractures, and open apices, among others, may occur (Trope et al., 2016).

For Gonzales et al. (2008), the basis of successful pulp treatment is based on the assertive diagnosis of the pathology, which implies the need to collect information based on a series of signs and symptoms, that make up the medical picture that will allow the identification of the lesion. However, this task is more difficult in children, since their clinical history is often confusing, especially in the youngest ones (6 to 10 years old), because they have not yet developed the skills that allow them to discriminate their sensations.

The same authors also refer the need to preserve teeth in the paediatric population as it is associated with the discouraging statistics on teeth loss, mostly young permanent teeth, at an early stage. Despite the adoption of measures such as fluoridation and other preventive methods, the preservation of young permanent teeth, whose pulps have been exposed or harmed due to caries, trauma, or even the toxicity of restorative materials, remains a fundamental objective of paediatric endodontics.

In this regard, Tropes et al., 2016 refer that reparative therapies of young permanent teeth (like pulp capping and apexification) are aimed at preserving the health and integrity of the tooth and its supporting tissues. Thus, the understanding and comprehension of the relationship between the materials used and the pulp tissue, constitutes the starting point for the knowledge of repair mechanisms: regenerative, inductive and biological effects as maintenance of dental pulp vitality and the complete formation of the root in young permanent teeth, which are the answer and propitious for a diversity of clinical research studies.

According to Teicher et al. (2019), the current knowledge of the molecular mechanisms that modulate dentinogenesis during pulp tissue repair has prompted the search for materials with biostimulating characteristics that are not only mechanically stable (i.e. good adhesion and sealing), but also potentially bactericidal, biocompatible and healing; materials that are not merely fixative (formocresol) or devitalizing, which do not present mutagenicity or cytotoxicity and have the property of accompanying the biological and functional cycle of the tooth.

The property associated with the ability to induce the differentiation of new odontoblasts allows the formation of reparative dentin at the dentin-pulpal junction, blocking external stimuli, and, thus, preventing possible microbial contamination. Many different factors influence the interaction between the material and the tissues: the chemistry of its composition (few are truly inert), and the degradation of the products and the way in which the tissue manages to respond in its dynamic environment (Tziafas et al., 2001).

The following narrative review is an analysis of the use of bioinductive materials for vital pulp therapy in immature permanent teeth, through a review of publications about this issue, since 2000, so that the latest research trends can be examined for generalization of valid conclusions that may contribute to this area of scientific knowledge.

1. Materials and methods

i. Eligibility /Exclusion Criteria.

The eligibility criteria included scientific papers comparing bioinductive materials used in direct and indirect pulp capping, based on biological principles and the behaviour of such materials in pulp treatment. Studies published between 2000 and 2021 were included, written in English, Spanish and Portuguese. There were no restrictions regarding population bias.

The exclusion criteria were researches on pulp treatment of primary teeth or immature permanent teeth with pulp necrosis.

ii. Sources of information

The present review consisted on an electronic search of articles from specialised scientific journals in the MEDLINE/PubMed and B-ON search engines/databases.

iii. Search strategy

The search strategy was defined by the following Mesh terms: pulp capping, biomimetic materials, tricalcium silicate, mineral trioxide aggregate; and the keywords: vital pulp therapy, young permanent teeth, materials, biomaterials, immature permanent teeth, pulp capping, biodentine. The search strategy is described in table 1:

Table 1. Search strategy

Search data base	Queries	Results
Pubmed	immature permanent teeth **AND** vital pulp therapy **AND** materials **AND** pulp capping	37
B-ON	immature permanent teeth **AND** vital pulp therapy **AND** materials **AND** pulp capping	205

Source: Own elaboration (2021)

Five studies of notable assertiveness with the inclusion criteria were used to identify results from the Pubmed and B-On databases. From there, keywords were identified by searching for matches in titles and abstracts. As defined in the eligibility criteria, the search filtered out studies that were not in English, Spanish or Portuguese, and that were within the date ranges between 2000 and 2021. Search terms were also identified and checked using PubMed PubReMiner, a word frequency analyser.

iv. Selection process

Researchers (MV and Dr CS) reviewed titles and abstracts of the first 57 records with the most important keywords, defining the criteria that will allow the selection of the records according with the investigation goal. Then, this same researcher screened and reviewed all articles verifying they met the inclusion criteria.

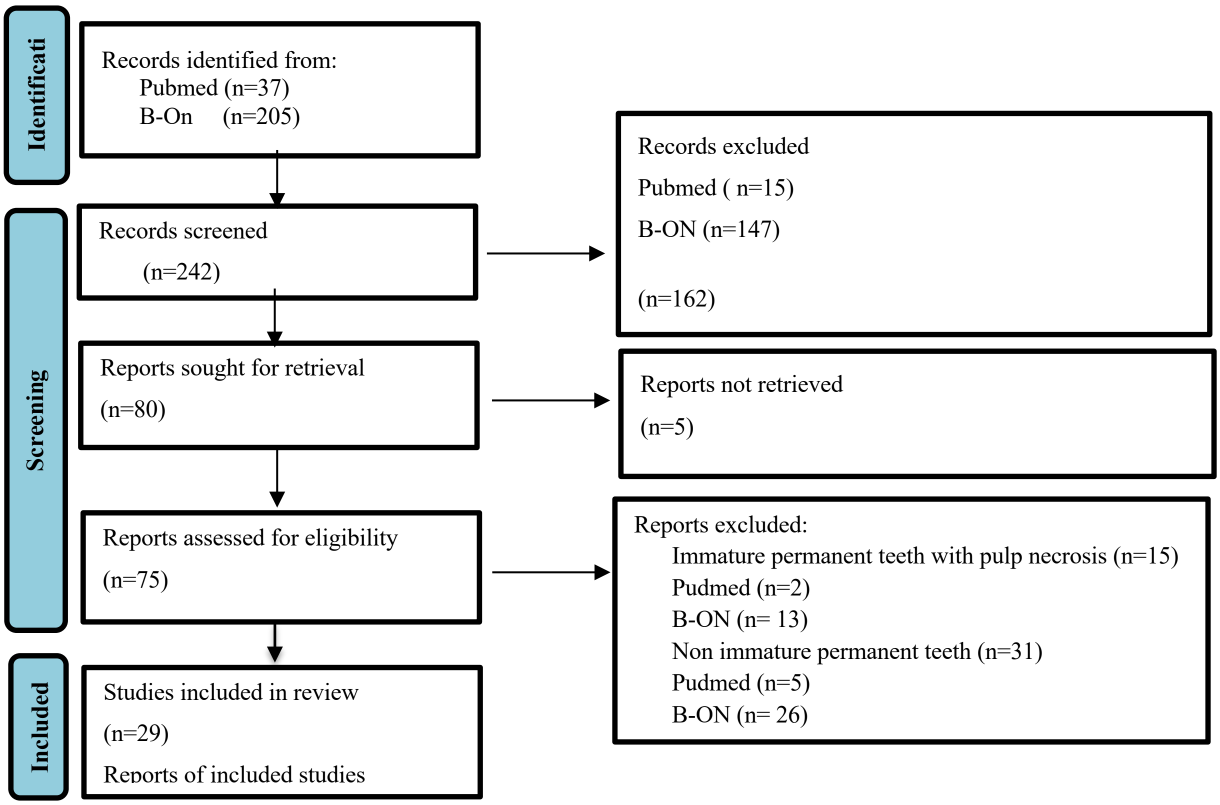

Figure 1: Flow diagram of the article selection process.

II. DEVELOPMENT

2. Immature permanent teeth

When a tooth makes its appearance in the mouth, its root is not yet completely formed; its length is between half and two thirds (²/₃) of the final length. It takes approximately three years for the root to complete its growth and apical closure (Boj et al., 2005; Canalda and Brau, 2014).

In general, the complications of an open apex are essentially the compromise of the normal crown/root ratio, as well as the difficulty of achieving an apical seal with a conventional endodontic filling (Torabinejad & Walton, 1999).

i. Classification of root and apical development in immature permanent teeth.

There is a very didactic classification of immature teeth, published by Patterson (1958), who distinguishes five classes, according to root and apical development:

I - Root development, at one half (½) of its total length; open funnel apex.

II - Root development at two thirds ($^2/_3$) of its total length; divergent apex walls.

III - Root development at three-fourths (¾) of its total length; parallel-walled apex.

IV - Root development complete; open apex.

V - Root development complete; closed apex.

ii. Histological characteristics of immature permanent teeth.

The pulps of immature permanent teeth have few fibres and many cells, so they have a great capacity for defence and response to biological treatments and pulp stimulation. They are characterized by (Fanning, 1962):

- Great potential for cellular differentiation, which gives them a greater capacity to react to attacks by external agents.
- Great vascularization, which provides them with an abundant nutritional supply.
- Intense calcifying activity, to continue maintaining the production of secondary dentin together with the existing one, which, together with cement, will form the root apical third.

iii. Pulp therapy of immature permanent teeth.

The main objective of pulp therapy is to preserve the integrity and health of teeth and their supporting tissues. It is practiced as a treatment to maintain the vitality of the pulp of a tooth affected by caries, traumatic injury, or other causes.

However, if the pulp tissue is irreversibly inflamed or in necrotic conditions, it is necessary to remove this tissue. Nevertheless, conventional endodontic treatment is very difficult be performed due to the presence of an open apex.

Depending on the degree of pulp involvement and the stage of root development, it is possible to differentiate between two therapeutic techniques: apicogenesis and apicoformation (Canalda and Brau, 2014).

Apicogenesis is performed in teeth with vital pulp. Its purpose is to maintain pulp vitality permanently or temporarily, in order to achieve complete apical closure. There are three different techniques to be applied, according to the degree of pulp involvement: indirect pulp treatment, direct pulp capping and pulpotomy (partial or total).

Apicoformation is performed in a tooth with incomplete rhizogenesis and pulp necrosis, with the purpose of inducing or allowing the formation of a calcified barrier that obliterates the apical foramen or that allows complete root development. Another clinical procedure consists of placing an artificial apical barrier, prior to the filling of the root canal system. Apical closure can occasionally occur, with an increase in previous root length and narrowing of the canal lumen.

3. Bioinductive endodontic materials

The bioactivity of a restorative material generally denotes that it has a biological effect or is biologically active. Such a characteristic refers to the potential to induce a specific and intentional mineral adhesion to the dentin substrate (Hench, 2005); therefore, they are also called bioinductive materials. In terms of restorative dentistry, a bioactive material is described as one that forms a surface layer of an apatite like material, in the presence of an inorganic phosphate solution (Jefferies, 2014). Therefore, remineralization of demineralized dentin is the process of mineral restoration through the formation of inorganic mineral matter (Cao et al., 2015).

As a bioinductive materials the calcium silicate gradually are making their way through the various materials used in restorative dentistry (Corral et al., 2016). While it is true that they have long been used in endodontics, their introduction in restorative dentistry is more recent, the first apparition of this type of materials was in 1995 with the MTA, as a result of the favorable properties of biocompatibility and bioactivity of this first material, many manufacturers developed other products, such as MTA Angelus, Theracal LC and Biodentin (Watson et al., 2014). Better mechanical properties and shorter curing times make them suitable for a variety of applications in which they are used as a substitute of dentin, including direct/indirect pulp capping and as cavity base/liner (Parirokh et al., 2010, Corral et al., 2016).

Many biomaterials have been proposed to induce complete root formation and preserve pulp vitality at the same time. Due to direct contact with vital tissue, capping biomaterials must be biocompatible, implantable, and demonstrate a regenerative effect *in vitro* and *in vivo* (Thuy et al., 2020). An ideal pulp capping material should provide easy handling, infection control, good sealing ability, and induce dentinal bridge formation (Saghiri et al., 2016).

Untreated pulp exposures to the oral cavity are the cause of pulpitis and pulp necrosis (Komabayashi et al., 2016). Either direct pulp capping or pulpotomy can be performed to prevent pulp death.

Direct pulp capping is used to treat the exposed vital pulp, to facilitate the formation of reparative dentin. The most commonly used materials are calcium hydroxide paste ($Ca(OH)_2$), mineral trioxide aggregate (MTA) and modified MTA/calcium silicate cement. Additionally, a next generation of direct pulp capping materials as other bioceramics and bioactive glass-based cements produce chemical stimulation of pulp. The development of a novel therapy that induces wound healing and dentinogenesis similar to the natural process is expected. Growth factors are future candidates for direct pulp capping agents, due their hability to develop a novel therapy that induces wound healing and dentinogenesis, similar to the natural process. One of them is a bone morphogenetic protein (BMP) that has been approved by the United States Food and Drug Administration (FDA) for clinical use (Morotomi et al., 2019).

i. Calcium hydroxide

Calcium hydroxide ($Ca(OH)_2$) consists of a white powder obtained by calcination of calcium carbonate and its transformation into calcium oxide (Rodriguez et al., 2005). It is classified into 2 types: Aqueous calcium hydroxide and Calcium hydroxide based cement. Aqueos calcium hydroxide is used for direct pulp-capping, the major disadvantages are their lack of setting, weak physical properties, and gradual dissolution (Eleazar et al., 1981 and Hassan et al., 1966). To improve these disadvantages, a cement type of calcium hydroxide with setting characteristics was developed, Calcium hydroxide based cement and has been widely used in clinical practice since the 1960s (Komabayashi et al., 2016). Long term clinical observations of $Ca(OH)_2$ are incomparable to any other bioactive material, as the first reports of successful pulpal healing using this terapheutic were published between 1934 and 1941. Among several materials, ($Ca(OH)_2$) was one of the most common materials used in pulp capping, and was considered the gold standard until the 90's with the introduction of new materials. The alkaline pH can present anti-inflammatory effects, activate transforming growth factor β (TGF-β), increase the activity of alkaline phosphatase (ALP), and enhance the dissolution of dentine extracellular matrix (Saghiri et al., 2016).

$Ca(OH)_2$ still has several drawbacks: insufficient adherence to dentinal walls, multiple tunnel defects in the induced dentin bridges, poor sealing ability, dissolution over time and lack of antibacterial properties (Aguilar and Linsuwanont 2011). Long-term clinical studies showed success rates of pulp capping with calcium hydroxide on carious exposures to be highly variable, generally unpredictable, and often unsuccessful. Indeed, calcium hydroxide no longer seems to be the best possible material of choice. Due to its high basicity, calcium hydroxide in direct contact with the pulp locally destroys a layer of pulp tissue, and thus creates an uncontrolled necrotic zone (Eleazar et al., 1981; Komabayashi et al., 2016 and Kunert et al., 2020).

Several studies examining toxicity inflammatory response to the use of $Ca(OH)_2$ generally demonstrated a mild inflammatory reaction with an influx of foreign body giant cells. In addition, they showed mild to moderate tissue irritating activities, however, it may also cause adverse reactions, damaging bone and soft tissues, either by direct contact after poor implementation or after ion diffusion. It has also been described inferior or alveolar nerve paraesthesia caused by displacement of calcium hydroxide paste through the apex during endodontic treatment. The severity and extent of lesions depends on the quantity and concentration used, as well as on the time of contact (Cardoso-Silva et al., 2019).

ii. Mineral Trioxide Aggregate

Mineral Trioxide Aggregate (MTA) is a bioactive endodontic cement, composed mainly of calcium and silicate elements (Abueniel et al., 2020). It was first described in the dental scientific literature by Lee et al. in 1993 and patented in 1995 by Torabinejad and White. In 1998, it was approved by the US Food and Drug Administration as a therapeutic endodontic material for humans.

MTA is a mixture of a refined Portland cement, composed by dicalcium silicate, tricalcium silicate, tricalcium aluminate, gypsum and tetracalcium aluminoferrite. It also presents bismuth oxide, which makes it radiopaque. *In vitro* and *in vivo* investigations have shown that MTA has many properties such as excellent biocompatibility, an alkaline pH, radiopacity, a high sealing capacity and the fact that it hardens in the presence of humidity 2–4 h after mixing (Scheerer et al., 2001; Aeinehchi et al.; 2003 and Sakar et al., 2005). MTA can also induce the formation of dentine, cement and bone (Roberts et al., 2008). It is an antibacterial material that has a high bioactivity (Teicher et al., 2019).

When MTA was first commercialized it had a grey colouration but in 2002 a new formula was created, the white MTA, to improve on the dark colour properties exhibited by Grey MTA. It has been recently optimized in many aspects including the setting time and calcium ion release (Saghiri et al., 2016). Several MTA derived materials have been provided in order to overcome the disadvantages of the original MTA. For example, the addition of calcium chloride to MTA resulted in a lower setting time and good biocompatibility, and replacing the Portland cement component in MTA with pure tricalcium silicate resulted in a biomaterial with improved physic/mechanical properties (Morotomi et al., 2018).

MTA has been used in a variety of clinical situations, such as pulp capping, pulpotomies, closure of perforations and apexification of permanent teeth (Holan et al., 2005; Damamaschke et al., 2005; Roberts et al., 2008; Cardoso-Silva et al., 2010). Its clinical efficacy in the reparative response of the dental pulp is undoubted as well as its very high clinical and radiographic success rates, but it presents difficulties associated with handling techniques and costs (Teicher et al., 2019).

iii. Endocem-Zr®

Pozzolan-based cement contains oxides of calcium, silicon, and aluminium. The radiopacifier is zirconium oxide. Endocem-Zr® was introduced as a retrograde filling and repair material, but few studies were done to assess the mineralization and biocompatibility of the cement which gave an insight into whether it could be used for pulp capping (Sharma et al., 2020). Li et al. in 2013, stated that the addition of nano-sized particles of zirconium oxide fastens the setting reaction of Portland cement, thereby reducing the setting time. This decrease in the setting time of Endocem-Zr® leads to an increased strength of the material during the early phase and increased resistance toward washout.

iv. Biodentine™

Biodentine™ is a calcium silicate-based material (Septodont, Saint Maur des Fosses, France), based on active biosilicate technology, which can be used in coronary and root treatments due to its mechanical properties similar to dentin (Arora et al., 2013; Malkondu et al.; 2014). It is characterized as an inorganic and non-metallic material (Teicher et al., 2019). Biodentine™ presents high biocompatibility with human dental pulp cells. The pulp tissue in contact with Biodentine™ does not show an irreversible inflammatory response (Chinadet et al., 2019).

Previous studies have reported that Biodentine™ has high antibacterial effect and antifungal activity. Its bacterial action is determined by the dissociation of its calcium and hydroxyl ions that increase the pH of the solution, thus preventing bacterial growth and improving biocompatibility (Bhavana et al.; 2015). The angiogenic effect of this cement was evaluated by Laurent et al. who suggested that Biodentine™ can induce early mineralization in dental pulp due to an increase in release of TGF-β1, a pro-angiogenic factor produced by pulp cells. The easy manipulation of Biodentine™ is the result of hydrosoluble polymer in the liquid component, which is based on polycarboxylate, a component that induces flocculation and increases flowability at low water/cement ratios (Chinadent et al.; 2019).

v. TheraCal LC

TheraCal LC (Bisco Inc, Schaumburg, IL, USA) is a light-cured resin-modified calcium silicate filled material designed for direct and indirect pulp capping. It consists of approximately 45% wt mineral material (type III Portland cement), 10% wt radiopaque component, 5% wt hydrophilic thickening agent (fumed silica), and approximately 45% resin. It also shows physiochemical bonding to dentin, good sealing abilities, and it is well tolerated by immortalized odontoblast cells (Deepthi, et al. 2018). It was introduced in 2011 to overcome poor bonding of calcium silicate materials (CSMs) to resins in final restorations (Kuner et at., 2020).

vi. BioAggregate

Bioaggregate is manufactured in Canada (Innovative Bioceramix,Vancouver, Canada). Its recommended applications are the same as those of MTA. This new material has received less research attention than other materials. Park et al., 2014 examined the chemical composition of BioAggregate and reported that it contained a significant amount of tantalumoxide instead of bismuth oxide.

vii. Activa Bioactive

Activa bioactive-base/liner (Pulpdent, USA) was launched in 2014 claiming the strength, aesthetics and physical properties of composites and increased release and recharge of calcium, phosphate and fluoride, in comparison with glass ionomer (Kuner et at., 2020). It was presented as a "light-cured resin-modified calcium silicate" combining uncompromised attributes of both composite and glass ionomer. However, investigations of the biological activities in mammalian cells that result from its use are limited (Karabulut, B. et al. 2020). It is a material that combines the optimal mechanical and aesthetic properties of resin materials with the ion release capacity of GICs, theoretically making it an excellent material for paediatric dentistry. It contains a blend of urethane and methacrylates with modified polyacrylic acid (44.6%), reactive glass filler (21.8%), inorganic filler (56%), patented rubberized resin (Embrace), and water. It has greater release and recharge of calcium, phosphate, and fluoride than glass ionomers in a strong, resilient resin matrix that will not chip or crumble. It also stimulates apatite formation at the material-tooth interface. The base/liner adheres to dentin and does not require etching or bonding agents (Karabulut, B. et al. 2020). However, no information is available on its cytotoxicity (López et al*.,* 2019).

viii. Acemannan

Acemannan is a natural polysaccharide extracted from Aloe vera which has many medicinal properties, as cell proliferation, osteogenic, immunomodulation, and antimicrobial properties, that promote wound healing. In Dentistry, Acemannan induces pulp healing and dentin formation *in vitro* and in *vivo* (Vu, et al., 2020; Le Van et al., 2020). Acemannan also induces osteoblast progenitor proliferation and differentiation, and mineral deposition (Boonyagul et al., 2014) The regenerative effect of acemannan in hard tissue and soft tissue has been intensively studied (Songsiripradubboon et al,. 2017). No fibrous capsule or ankylosis was reported when implanting acemannan sponges in calvaria defects, tooth extraction sockets, pulp capping, and class II furcation defects (Chantarawaratit et al., 2014).

ix. Calcium Enriched Mixture

Calcium enriched mixture (CEM) is water based cement first introduced to endodontic treatment by Asgary in 2006 (Asgary et al., 2008). It is a mixture of different calcium compounds including, calcium oxide, calcium phosphate. It shows similarities with MTA in its sealing ability, biocompatibility and the potential to induce hard tissue (Esmaeili et al., 2016 and Chen et al., 2019). This agent also shows its advantages in less tooth discoloration and stronger antibacterial ability (Tarbasy et al., 2010)

III. DISCUSSION

Although the implementation of pulp therapy of immature permanent teeth depends on multiple variables, this treatment has repeatedly shown to be successful and, therefore, should be routinely recommended. As such, vital pulp therapy has a high success rate if the following conditions are met: the pulp must not be inflamed, haemorrhage can be properly controlled, a nontoxic capping material will be applied, and the capping material and restoration can seal out bacteria (Cohenca et al., 2013).

In the context of minimally invasive dentistry, the direct pulp capping procedure with a reliable biomaterial can be considered as an alternative, providing the pulp a favourable status. Bioinductor materials can be used when the pulp diagnosis is normal pulp or no more than reversible pulpitis (Hedge et al., 2017), having these diagnosis, treatment with $Ca(OH)_2$, MTA, Biodentine or glass ionomer cement, are protective coatings and is also recommended (American Academy of Paediatric Dentistry, 2010/2011). The term ‘bioactive endodontic cement’ is using this overview because the new materials have a variety of chemical compositions; however, they all have one common capability, that is bioactivity. This implies releasing calcium ions, electrocon-ductivity, production of calcium hydroxide, formation of an interfacial layer between the cement and dentinal wall and formation of apatite crystals over the surface of the material in a synthetic tissue fluid environment such as phosphatebuffer saline (Parirokh & Torabinejad 2014).

Many clinical reports demonstrated that the success rate of direct pulp capping was higher with MTA than with $Ca(OH)_2$ (Morotomi et al., 2019). Particularly, several authors (Cho et al., 2013; Hegde et al., 2017; Kunert & Lukomska, 2020) recommend the use of MTA as the best option for pulp capping treatments, as well as some of its equivalent products, outperforming $Ca(OH)_2$ (Cohenca et al., 2013). However, in the opinion of Parirokh et al. (2018), the absolute superiority of MTA over $Ca(OH)_2$ for all vital pulp therapy procedures is poorly documented, as well as that of other bioactive endodontic cements (BEC). What is irrefutable is that vital pulp therapies have been highly successful with the introduction of MTA and bioceramics (Patel et al., 2019).

In the treatment of immature permanent teeth, MTA and Biodentine™ have shown excellent results as pulpotomy materials (Abueniel et al. 2020; Awawdeh et al., 2018; Chinadet et al., 2019; Linsuwanont et al., 2016). However, compared with Biodentine™, teeth treated with MTA show more frequent discoloration (Abueniel et al., 2020; Parinyaprom et al.,2017). Although it could be considered as a negligible adverse effect, according to Paula et al. 2019. MTA has been recently optimized in many aspects including the setting time and calcium ion release (Saghiri, et al., 2016). Many studies found out colour changing as a result of using MTA, but, nowadays, it is possible to use MTA without having this disadvantage, with very similar success rates as Biodentine™. The fact that Biodentine™ requires the use of a capsule for each treatment might result in greater material waste, whereas MTA can be dosed, manipulating only the necessary material, which represents an advantage of this material.

Biodentine™ has a shorter setting time than MTA, as the result of calcium chloride in its liquid component. The easy manipulation of Biodentine™ is the consequence of hydrosoluble polymer in the liquid component, which is based on polycarboxylate, a component that induces flocculation and increases flowability at low water/cement ratios. Biodentine™ has higher flexural strength, compressive strength, and modulus of elasticity than does MTA (Chinadent et al.; 2019).

When compared with MTA, advances in Biodentine™ properties, such as setting time, mechanical qualities, and initial cohesiveness, led to a widened range of applications, including endodontic repair and vital pulp therapy (Parinyaprom et al., 2018). It is resin-free and mainly composed of pure tricalcium silicate. The chemical composition differs from MTA by the addition of calcium carbonate to the powder. The liquid constituted a hydrated calcium chloride (as an accelerator to reduce setting time) and a water-reducing agent. It is considered an encouraging material due to its antimicrobial influence (Malkondu et al., 2014). Its antibacterial mechanism of action is achieved through its high pH and its ability to increase the osmotic pressure which can inhibit many bacteria and through inducing mineralization on bacterial surfaces. Biodentine™ has shown better compression and surface properties than other tricalcium silicate-based materials (Sheth et al., 2020).

In pulp therapy of vital teeth, lack of cytotoxicity and biocompatibility are the significant factors concerning pulp capping agents that directly affect the clinical outcome. Based on the evaluation of pulpal responses in partial pulpotomy cases in dogs by Kurner et al. in 2020, a complete dentine bridge was observed in only 33% of the specimens. It was observed that TheraCal LC produced the least favourable pulpal responses compared to ProRoot MTA and RetroMTA. Overall, the research reported that TheraCal specimens had lower quality calcified barrier formation, extensive inflammation and less favourable odontoblastic layer formation.

According with Sharma et al. 2020, the major components of MTA and ENDOCEM are very similar, as both contain oxides of calcium, silicon, and aluminium. However, the radiopacifier in MTA, i.e., bismuth oxide, has been substituted by zirconium oxide in ENDOCEM-Zr.®; there was no significant difference in the outcome between MTA and ENDOCEM-Zr® groups, suggesting that both materials are equally effective as an IPC agent. This result is comparable with the study by Jang et al. 2015, which demonstrated similar cumulative successes of MTA and ENDOCEM as pulp capping materials evaluated in a year. Another study by Park et al. 2014, that evaluated the formation of dentin bridge histologically in rat teeth detected no statistically significant difference between ENDOCEM and MTA.

On the other hand, ACTIVA BioACTIVE Base/Liner is a new dental material recommended for pulp capping (López-García et al., 2019). The material has the advantage of stimulating mineral apatite crystal formation. Karabulut et al. 2020, included it in their study to evaluate the reactions in subcutaneous tissue. Histological response to ACTIVA BioACTIVE Base/Liner was very similar to Biodentine™ and ProRoot MTA. All materials were well tolerated by the tissues in the 60 days of evaluation period. One notable result was the presence of dystrophic calcification in the connective tissue adjacent to the newly developed BioACTIVE Base/Liner material. Therefore, this new base/liner material may be a potential pulp capping material.

The use of MTA and Biodentine™ is difficult to handle, ACTIVA BioACTIVE Base/Liner can be an alternative to these materials. Further, MTA and Biodentine™ are expensive materials, suggesting an additional motivation to investigate whether ACTIVA BioACTIVE Base/Liner can be used as a pulp capping material (Tran, et al., 2019).

Koutroulis et al. 2019 compared the role of calcium ion release on biocompatibility and antimicrobial properties of several hydraulic cements, and the results showed that ACTIVA BioACTIVE Base/Liner presented characteristic microstructure of glass ionomer with negligible calcium release, acceptable biocompatibility, and moderate antibacterial activity.

In addition, Long et al., 2017, reported that sol-gel derived BioACTIVE glass, when used for direct pulp capping, stimulated the formation of a compact dentin bridge with inflammatory responses alike MTA, as shown in mechanically exposed pulps of rats. They have reported that the extended setting time and undesired physical properties of

MTA can be modified by the addition of BioACTIVE glass. Sheng et al. 2016 and Anthoney et al., 2020 reported that BioACTIVE glass could promote mineral formation on dentin surfaces, BioACTIVE glass has been examined for pulp capping by virtue of its supposed dentinogenesis property.

Likewise, according to Jun et al. 2017, ACTIVA BioACTIVE exhibited the potential to stimulate biomineralization at the same level as MTA, Biodentine, and TheraCal LC based on releasing the same amount of Ca and OH ions.

Other bioinductive materials currently used for vital pulp therapy are: Portland cement, potassium nitrate, dimethylisosorbide, polycarboxylate cement, enamel matrix derivative (Gudkina et al., 2012) and Acemannan (Thuy et al., 2020). Additionally, it has to be mentioned that materials used in vital pulp therapy such as $Ca(OH)_2$, MTA, calcium enriched mixture (CEM), Biodentine, Enamel Matrix Derivative (EMD), glass ionomer and bioactive resins may also have positive effects on angiogenesis events (Saghiri et al., 2016).

In Dentistry, evaluating the biocompatibility of new products has vital importance. Before marketing and using dental materials, it is mandatory to ensure that these materials have no side effects when in contact with tissues (Martinez et al., 2009).

IV. CONCLUSIONS

Nowadays, the preservation of dental pulp vitality is an integral part of our daily therapies. A good diagnosis, a proper treatment plan, the evaluation of each possible alternative regarding materials to be used in specific cases, its capacity to induce the formation of high quality mineralized tissue, will imply in the future preservation of the health of young permanent teeth affected.

Bioinductive materials make possible to preserve young permanent teeth which, for various reasons, may require pulp treatment. Materials as MTA and Biodentine present advantages and a high success rate by inducing the remineralization of the remaining affected tissue. Materials as BioACTIVE presents a high rate of dentin bridge formation, and additionally a better setting time. However, treatments with Biodentine can result in a very high costed therapy. On the other hand, MTA older formulations pigmented the teeth, a handicap that has been overcomed by recent formulas.

Vital pulp therapy in immature permanent teeth is effective when a proper diagnosis and a treatment that respects the corresponding technique are performed. Although there is no ideal material, a good diagnosis based on knowledge of the biology and the patient will allow the selection of the most suitable one for each case. Calcium silicate-based cements, used as pulp capping materials, provide an optimal environment for pulp healing, resulting in a reparative dentin resembling on certain points of the primary dentin and the regeneration of the pulp. Of all the materials evaluated, MTA, stands out as the bioinductor par excellence, highlighting its antimicrobial properties, biocompatibility, no cytotoxicity, which leads to dentin-pulp complex regeneration.

REFERENCES

Abuelniel, G. M., Duggal, M. S. and Kabel, N. (2020). A comparison of MTA and Biodentine as medicaments for pulpotomy in traumatized anterior immature permanent teeth: A randomized clinical trial. *Dental Traumatology*, 36(4), pp. 400–410.

Aguilar, P. and Linsuwanont, P. (2011). Vital pulp therapy in vital permanent teeth with cariously exposed pulp: A systematic review. Journal of Endodontics, 37(5), pp. 581–587.

Aboy Pazos, S. et al. (2016). Regeneración pulpar en diente permanente con ápice inmaduro. RCOE: Revista del Ilustre Consejo General de Colegios de Odontólogos y Estomatólogos de España, 21(4), pp. 201–207.

AB, F. (1999). Pulp therapy for the primary dentition. In: Pinkham JR (ed.). *Pediatric Dentistry, Infancy Through Adolescence , 3rd edn. Philadelphia, PA: W. B. Saunders*, pp. 341–353.

Amaireh, A. I., Al-Jundi, S. H. and Alshraideh, H. A. (2019). In vitro evaluation of microleakage in primary teeth restored with three adhesive materials: ACTIVA^{TM}, composite resin, and resin-modified glass ionomer. *European Archives of Paediatric Dentistry*, 20(4), pp. 359–367.

Aeinehchi, M. et al. (2003). Mineral trioxide aggregate (MTA) and calcium hydroxide as pulp-capping agents in human teeth: A preliminary report. International Endodontic Journal, 36(3), pp. 225–235.

Asgary, S., Eghbal, M. J. and Parirokh, M. (2008). Sealing ability of a novel endodontic cement as a root-end filling material. Journal of Biomedical Materials Research - Part A, 87(3), pp. 706–709.

Arora, D. V. (2013). Bioactive dentin replacement. *IOSR Journal of Dental and Medical Sciences*, 12(4), pp. 51–57.

Awawdeh, L. *et al.* (2018). Outcomes of Vital Pulp Therapy Using Mineral Trioxide Aggregate or Biodentine: A Prospective Randomized Clinical Trial. *Journal of Endodontics*, 44(11), pp. 1603–1609.

Boonyagul, S. et al. (2014). Effect of acemannan, an extracted polysaccharide from Aloe vera, on BMSCs proliferation, differentiation, extracellular matrix synthesis, mineralization, and bone formation in a tooth extraction model. Odontology, 102(2), pp. 310–317.

Bhavana, V. *et al.* (2015). Evaluation of antibacterial and antifungal activity of new calcium-based cement (Biodentine) compared to MTA and glass ionomer cement. *Journal of Conservative Dentistry*, 18(1), pp. 44–46.

Boj, J.; Catalá, M.; García, C.; Mendoza, A. (2005). Odontopediatría. Primera Edición. Barcelona: Masson; pp.55-64, pp.185-190.

Brännström, M. and Lind, P. O. (1965). Pulpal Response to Early Dental Caries. *Journal of Dental Research*, 44(5), pp. 1045–1050.

Canalda, C.; Brau, E. (2014). Endodoncia: técnicas clínicas y bases científicas. Tercera Edición., Barcelona: Masson, pp. 259–270.

Cao, C. Y. *et al.* (2015). Methods for biomimetic remineralization of human dentine: A systematic review. *International Journal of Molecular Sciences*, 16(3), pp. 4615–4627.

Cardoso-Silva, C. et al. (2011). Clinical study of Mineral Trioxide Aggregate in primary molars. Comparison between Grey and White MTA - A long term follow-up (84 months). Journal of Dentistry, 39(2), pp. 187–193.

Cardoso-Silva, C., Llanes, M. and Barbería, E. (2020). Bone Necrosis After Pulp Treatment of Temporary Molar with Calcium Hydroxide: In Vivo Confirmation. Acta Scientific Dental Scienecs, 5(1), pp. 93–99.

Chinadet, W., Sutharaphan, T. and Chompu-Inwai, P. (2019). Biodentine^{TM} Partial Pulpotomy of a Young Permanent Molar with Signs and Symptoms Indicative of Irreversible Pulpitis and Periapical Lesion: A Case Report of a Five-Year Follow-Up. *Case Reports in Dentistry*, 2019.

Chang, S. W. *et al.* (2014). Effects of ProRoot MTA, bioaggregate, and micromega MTA on odontoblastic differentiation in human dental pulp cells. *Journal of Endodontics*, 40(1), pp. 113–118.

Chen, Y. et al. (2019). Materials for pulpotomy in immature permanent teeth: A systematic review and meta-analysis. BMC Oral Health, 19(1).

Chantarawaratit, P. et al. (2014). Acemannan sponges stimulate alveolar bone, cementum and periodontal ligament regeneration in a canine class II furcation defect model. Journal of Periodontal Research, 49(2), pp. 164–178.

Cho, S. Y. *et al.* (2013). Prognostic factors for clinical outcomes according to time after direct pulp capping. *Journal of Endodontics*, 39(3), pp. 327–331.

Cohenca, N., Paranjpe, A. and Berg, J. (2013). Vital Pulp Therapy. *Dental Clinics of North America*, 57(1), pp. 59–73.

Corral, C. et al. (2016). The Current state of calcium silicate cements in restorative dentistry: A Review. Revista Facultad de Odontología Universidad de Antioquia, 27(2), pp. 425–441.

Daud Anthoney, S. Z. *et al.* (2020). Effectiveness of thymoquinone and fluoridated BioACTIVE glass/nano-oxide contained dentifrices on abrasion and dentine tubules occlusion: an ex vivo study. *European journal of dentistry*, 14(1), p. 45.

Deepthi, V. *et al.* (2018). Effect of acidic pH on microhardness and microstructure of theraCal LC, endosequence, mineral trioxide aggregate, and biodentine when used as root repair material. *Journal of Conservative Dentistry*, 21(4), pp. 408–412.

Dammaschke, T. *et al.* (2005). Chemical and physical surface and bulk material characterization of white ProRoot MTA and two Portland cements. *Dental Materials*, 21(8), pp. 731–738.

Dammaschke, T., Leidinger, J. and Schäfer, E. (2010). Long-term evaluation of direct pulp capping-treatment outcomes over an average period of 6.1 years. *Clinical Oral Investigations*, 14(5), pp. 559–567.

Dube, K. *et al.* (2018). Preventive endodontics by direct pulp capping with restorative dentin substitute-biodentine: A series of fifteen cases. *Indian Journal of Dental Research*, 29(3), pp. 268–274.

Esmaeili, B. et al. (2016). Coronal discoloration induced by calcium-enriched mixture, mineral trioxide aggregate and calcium hydroxide: A spectrophotometric analysis. Iranian Endodontic Journal, 11(1), pp. 23–28.

Eleazer, P. et al. (1981). The effect of unbound powdered materials on dog dental pulps. Journal of Endodontics, 7(10), pp. 462–465.

Gonzáles, A. et al. (2008). Terapia pulpar en niños, p. 142.Lima, Peru. Universidad Nacional Mayor de San Marcos. Facultad de Odontología.

Grossman, L. (1973). *Práctica Endodóntica*. Tercera edición. Buenos Aires: Editorial Mundi. Cap. 2.

Glossary of Endodontic Terms. http://www.aae.org/glossary/. (2003).

Guideline on pulp therapy for primary and immature permanent teeth. (2016). *Pediatric*

Gudkina, J. *et al.* (2012). Review of the success of pulp exposure treatment of cariously and traumatically exposed pulps in immature permanent incisors and molars. *Stomatologija / issued by public institution "Odontologijos studija" ... [et al.]*, 14(3), pp. 71–80.

Hassan, E. H., Van Huysen, G. and Gilmore, H. W. (1966). Deep cavity preparation and the tooth pulp. The Journal of Prosthetic Dentistry, 16(4), pp. 751–755.

Hegde, S. *et al.* (2017). Clinical evaluation of mineral trioxide aggregate and biodentine as direct pulp capping agents in carious teeth. *Journal of Conservative Dentistry*, 20(2), pp. 91–95.

Hench, L. L. (2005). Bioceramics. *Journal of the American Ceramic Society*, 81(7), pp. 1705–1728.

Holan, G., Eidelman, E. and Fuks, A. B. (2005). Long-term evaluation of pulpotomy in primary molars using mineral trioxide aggregate or formocresol. *Pediatric Dentistry*, 27(2), pp. 129–136.

Ingle, J. and Baklland, L. (1996). Patosis Pulpar. *Journal of Endodontics*.

Jang, Y. *et al.* (2015). A Randomized Controlled Study of the Use of ProRoot Mineral Trioxide Aggregate and Endocem as Direct Pulp Capping Materials: 3-month versus 1-year Outcomes. *Journal of Endodontics*, 41(8), pp. 1201–1206.

Jun, S. K., Lee, J. H. and Lee, H. H. (2017). The Biomineralization of a Bioactive Glass-Incorporated Light-Curable Pulp Capping Material Using Human Dental Pulp Stem Cells. *BioMed Research International*, 2017.

Jefferies, S. R. (2014). Bioactive and biomimetic restorative materials: A comprehensive review. part I. *Journal of Esthetic and Restorative Dentistry*, 26(1), pp. 14–26.

Karabulut, B. *et al.* (2020). Reactions of Subcutaneous Connective Tissue to Mineral Trioxide Aggregate, Biodentine®, and a Newly Developed BioACTIVE Base/Liner. *Scanning*, 2020.

Komabayashi, T. *et al.* (2016). Current status of direct pulp-capping materials for permanent teeth. *Dental Materials Journal*, 35(1), pp. 1–12.

Kunert, M. and Lukomska-Szymanska, M. (2020). Bio-Inductive Materials in Direct and Indirect Pulp Capping - A Review Article. *Materials*, 13(5).

Koutroulis, A. *et al.* (2019). The role of calcium ion release on biocompatibility and antimicrobial properties of hydraulic cements. *Scientific Reports*, 9(1).

Laurent, P., Camps, J. and About, I. (2012). Biodentine TM induces TGF-β1 release from human pulp cells and early dental pulp mineralization. *International Endodontic Journal*, 45(5), pp. 439–448.

Le Van, C. et al. (2020). Acemannan induces rapid early osseous defect healing after apical surgery: A 12-month follow-up of a randomized controlled trial. Journal of Dental Sciences, 15(3), pp. 302–309.

Linsuwanont, P. *et al.* (2017). Treatment Outcomes of Mineral Trioxide Aggregate Pulpotomy in Vital Permanent Teeth with Carious Pulp Exposure: The Retrospective Study. *Journal of Endodontics*, 43(2), pp. 225–230.

Llena, C. *et al.* (2020). Follow-up of patients subjected to direct and indirect pulp capping of young permanent teeth. A retrospective study. *Clinical and Experimental Dental Research*.

López-García, S. *et al.* (2019). In vitro evaluation of the biological effects of ACTIVA kids BioACTIVE restorative, ionolux, and riva light cure on human dental pulp stem cells. *Materials*, 12(22).

Long, Y. *et al.* (2017). Evaluation of Pulp Response to Novel Bioactive Glass Pulp Capping Materials. *Journal of Endodontics*, 43(10), pp. 1647–1650.

Malkondu, Ö., Kazandağ, M. K. and Kazazoğlu, E. (2014). A review on biodentine, a contemporary dentine replacement and repair material. *BioMed Research International*, 2014.

Martens, L., Rajasekharan, S. and Cauwels, R. (2015). Pulp management after traumatic injuries with a tricalcium silicate-based cement (Biodentine™): a report of two cases, up to 48 months follow-up. *European Archives of Paediatric Dentistry*, 16(6), pp. 491–496.

Martínez Lalis, R. *et al.* (2009). Rat subcutaneous tissue response to modified Portland cement, a new mineral trioxide aggregate. *Brazilian Dental Journal*, 20(2), pp. 112–117.

Mitchell, P. J. C. *et al.* (1999). Osteoblast biocompatibility of mineral trioxide aggregate. *Biomaterials*, 20(2), pp. 167–173.

Morotomi, T., Washio, A. and Kitamura, C. (2019). Current and future options for dental pulp therapy. *Japanese Dental Science Review*, 55(1), pp. 5–11.

Nolla, C. A. (1960). The development of the permanent teeth. *Journal of dentistry for children*, Fourth Qua, pp. 254–266.

Nowicka, A. et al. (2013). Response of human dental pulp capped with biodentine and mineral trioxide aggregate. Journal of Endodontics, 39(6), pp. 743–747.

Park, S. J. *et al.* (2014). Odontogenic effect of a fast-setting pozzolan-based pulp capping material. *Journal of Endodontics*, 40(8), pp. 1124–1131.

Parinyaprom, N. *et al.* (2018). Outcomes of Direct Pulp Capping by Using Either ProRoot Mineral Trioxide Aggregate or Biodentine in Permanent Teeth with Carious Pulp Exposure in 6- to 18-Year-Old Patients: A Randomized Controlled Trial. *Journal of Endodontics*, 44(3), pp. 341–348.

Parirokh, M., Torabinejad, M. and Dummer, P. (2018). Mineral trioxide aggregate and other bioactive endodontic cements: an updated overview - part I: vital pulp therapy. *International Endodontic Journal*, 51(2), pp. 177–205.

Patel, E. *et al.* (2020). Oroactive dental biomaterials and their use in endodontic therapy. *Journal of Biomedical Materials Research - Part B Applied Biomaterials*, 108(1), pp. 201–212.

Patterson, S. S. (1958). The endodontic management of the young permanent tooth. *J. Dent. Child*, 25, pp. 215–223.

Paula, A. B. *et al.* (2020). Evaluation of dentinogenesis inducer biomaterials: An in vivo study. *Journal of Applied Oral Science*, 28.

Raddall, G., Mello, I. and Leung, B. M. (2019). Biomaterials and Scaffold Design Strategies for Regenerative Endodontic Therapy. *Frontiers in Bioengineering and Biotechnology*, 7.

Rechenberg, D. K., Galicia, J. C. and Peters, O. A. (2016). Biological markers for pulpal inflammation: A systematic review. *PLOS ONE*, 11(11).

Rodríguez Gutiérrez, G. *et al.* (2005). El hidróxido de calcio: su uso clínico en la endodoncia actual. *Revista Archivo Médico de Camagüey*, 9(3), pp. 143–152.

Roberts, H. W. et al. (2008). Mineral trioxide aggregate material use in endodontic treatment: A review of the literature. Dental Materials, 24(2), pp. 149–164.

Sabbagh, S., Sarraf Shirazi, A. and Eghbal, M. J. (2016). Vital pulp therapy of a symptomatic immature permanent molar with long-term success. *Iranian Endodontic Journal*, 11(4), pp. 347–349.

Sarkar, N. K. et al. (2005). Physicochemical basis of the biologic properties of mineral trioxide aggregate. Journal of Endodontics, 31(2), pp. 97–100.

Scheerer, S. Q., Steiman, H. R. and Cohen, J. (2001). A comparative evaluation of three root-end filling materials: An in vitro leakage study using Prevotella nigrescens. Journal of Endodontics, 27(1), pp. 40–42.

Saghiri, M. A. *et al.* (2016). Effect of biomaterials on angiogenesis during vital pulp therapy. *Dental Materials Journal*, 35(5), pp. 701–709.

Seltzer, S.; Bender, I. y Nazimor, H. (1957). Differential diagnosis of pulp conditions. *Oral Surgery, Oral Medicine, Oral Pathology*, Vol. 19, Isuue 3; pp. 383-391.

Shaffer, W.; Hine, M.; Levy, B. y Tomich, C. (1988). *Tratado de Patología Bucal*. Cuarta edición. México: Interamericana S.A., Cap. 8.

Sheth, P. P., Lolayekar, N. V. and Hegde, A. M. (2020). Use of Biodentine^{TM} for Vital Pulp Therapy in Children: Three Case Reports. *Indian Journal of Public Health Research & Development*.

Sharma, A. *et al.* (2020). Evaluation of indirect pulp capping using pozzolan-based cement (ENDOCEM-Zr®) and mineral trioxide aggregate - A randomized controlled trial. *Journal of Conservative Dentistry*, 23(2), pp. 152–157.

Sheng, X. Y. *et al.* (2016). Mineral formation on dentin induced by nano-bioactive glass. *Chinese Chemical Letters*, 27(9), pp. 1509–1514.

Songsiripradubboon, S. et al. (2017). Stimulation of Dentin Regeneration by Using Acemannan in Teeth with Lipopolysaccharide-induced Pulp Inflammation. Journal of Endodontics, 43(7), pp. 1097–1103.

Simón, J.; Walton, R.; Pashley, D.; Dowden, W. y Bakland, L. (1996). Patosis Pulpar, Capítulo 7. En: Ingle, J. y Bakland, L. *Endodoncia*. Cuarta edición. México: McGraw-Hill Interamericana.

Tabarsi, B. *et al.* (2010). A comparative study of dental pulp response to several pulpotomy agents. *International Endodontic Journal*, 43(7), pp. 565–571.

Tziafa, C. *et al.* (2014). Dentinogenic responses after direct pulp capping of miniature swine teeth with Biodentine. *Journal of Endodontics*, 40(12), pp. 1967–1971.

Tziafas, D. *et al.* (2001). Dentin regeneration in vital pulp therapy: design principles. *Advances in dental research*, 15, pp. 96–100.

Teicher, C. *et al.* (2019). La reparación de la pulpa dental. Materiales y alternativas de tratamiento: revisión de la información bibliográfica. *Rev. Asoc. Odontol. Argent*, pp. 110–115.

Torabinejad, M. y Walton, R. (1999). Biologìa de la pulpa y tejidos periapicales. En: *Endodoncia. Principios y Práctica Clínica*, Editorial Interamericana, pp. 8–29.

Tran, X. V. *et al.* (2019). Reparative mineralized tissue characterization after direct pulp capping with calcium-silicate-based cements. *Materials*, 12(13).

Trope, M.; Chivian, N. y Sigurdsson, A. (2016). Lesiones traumáticas, En: Cohen, S. y Burns, R. Vías de la pulpa. Onceava Ed.

Veleiro, C. (2010). Traumatismos dentales en niños y adolescentes. *Revista Latinoamericana de Ortodoncia y Odontopediatría.*

Villasana, A. (2002). Patología pulpar y su diagnóstico. *Salud Dental para Todos*, pp. 1–35.

Vu, T. T. *et al.* (2020). Acemannan used as an implantable biomaterial for vital pulp therapy of immature permanent teeth induced continued root formation. *Pharmaceutics*, 12(7), pp. 1–16.

Watson, T. F. et al. (2014). Present and future of glass-ionomers and calcium-silicate cements as bioactive materials in dentistry: Biophotonics-based interfacial analyses in health and disease. Dental Materials, 30(1), pp. 50–61.

APPENDIX

Table 2
Trends in the use of bioinductive materials for pulp therapy in immature permanent teeth

References	Type of Study	Dental Treatment	Materials	Seal	Calcified dentin bridge	Direct biological effect on pulp	Cost	Dentine substitute	Success
Abuelniel et al. (2020)	Randomized clinical trial	Pulpotomy in traumatized immature permanent teeth	MTA Biodentine™	Yes Yes	Present Present	Present Present	High High	No Yes	Significant Significant
American Academy of Pediatric Dentistry (2010/2011)	Systematic review	Pulp therapy in immature permanent teeth	Calcium hydroxide Glass ionomer cement MTA	No Yes Yes	More or less Present Present	Present Present Present	Low High High	No No No	Significant Moderate Significant
Awawdeh et al. (2018)	Randomized clinical trial	Direct pulp capping in immature permanent teeth with decay exposure	Biodentine™ MTA	Yes Yes	Present Present	Present Present	High High	Yes No	Significant Significant
Chang et al. (2014)	Basic research	Not applicable	Bioaggregate Micromega MTA ProRoot MTA Intermediate restorative material	Yes Yes Yes No	Present Present Present Not present	Present Present Present Present	High High High Low	No No No No	Significant Significant Significant Low
Chinadet et al. (2019)	Case study	Pulpotomy in young permanent molar	Biodentine ™	Yes	Present	Present	High	Yes	Significant
Cho et al. (2013)	Clinical trial	Direct pulp capping in teeth with pulp exposed	Calcium hydroxide MTA	No Yes	More or less Present	Present Present	Low High	No No	Moderate Significant
Cohenca et al. (2013)	Systematic review	Pulp therapy in young permanent teeth	Calcium hydroxide MTA Bioaggregate	No Yes Yes	More or less Present Present	Present Present Present	Low High High	No No No	Low Significant Significant
Dammaschke et al. (2010)	Clinical trial	Direct pulp capping	Calcium hydroxide	No	More or less	Present	Low	No	Significant (when definitive restauration was with amalgam or composite restoration) Low (when definitive restauration was with glass ionomer cement)

Table 2 (Continuation)

References	Type of Study	Dental Treatment	Materials	Seal	Calcified dentin bridge	Direct biological effect on pulp	Cost	Dentine substitute	Success
Gudkina et al. (2012)	Systematic review	Pulp therapy of immature permanent teeth with exposed pulp because of decay or trauma	Calcium hydroxide, MTA, Portland cement, Calcium Enriched Mixture Enamel Matrix Derivative	No Yes Yes Yes Yes (with Ca (OH) 2)	More or less Present Present Present Present	Present Present Present Present Present	Low High Low High High	No No No No No	Significant Significant Significant Significant Significant
Hegde et al. (2017)	Clinical trial	Direct pulp capping of carious teeth	MTA Biodentine™	Yes Yes	Present Present	Present Present	High High	No Yes	Significant Significant
Kavita et al. (2020)	Clinical trial	Direct pulp capping	Biodentine™	Yes	Present	Present	High	Yes	Significant
Kunert & Lukomska (2020)	Systematic review	Direct and indirect pulp capping	MTA ProRoot MTA, Angelus, RetroMTA, Biodentine, TheraCal LC, ACTIVE Bioactive	Yes Yes Yes Yes Yes Yes (after dentine bonding agent application)	Present Present Present Present Present Present	Present Present Present Present Present Present	High High High High Low Low	No No No Yes No No	Significant Significant Significant Significant Significant Significant
Linsuwanont et al. (2016)	Retrospective study	Pulpotomy of vital permanent teeth with carious vital exposure	MTA	Yes	Present	Present	High	No	Significant
Llena et al. (2020)	Retrospective study	Direct and indirect pulp capping	Calcium hydroxide Glass ionomer	No	More or less	Present	Low	No	Moderate
Martens et al. (2015)	Clinical trial	Apexogenesis in immature permanent teeth	Biodentine™	Yes	Present	Present	High	Yes	Significant
Morotomi et al. (2019)	Systematic review	Direct pulp capping, Vital pulp amputation, Treatment of non-vital teeth	Calcium hydroxide MTA Improved MTA/calcium silicates materials Glass-based cement	No Yes Yes Yes	More or less Present Present Present	Present Present Present Present	Low High High	No No No Yes	Moderate Significant More research needed Significant
Nowicka et al. (2013)	Clinical trial	Direct pulp capping	Biodentine™ MTA	Yes Yes	Present Present	Present Present	High High	Yes No	Significant Significant

Table 2 (Continuation)

References	Type of Study	Dental Treatment	Materials	Seal	Calcified dentin bridge	Direct biological effect on pulp	Cost	Dentine substitute	Success
Parinyaprom et al. (2017)	Clinical trial	Direct pulp capping of permanent teeth with carious pulp exposure	Biodentine™ MTA	Yes Yes	Present Present	Present Present	High High	Yes No	Significant Significant
Parirokh et al. (2018)	Systematic review	Direct and indirect pulp capping in young permanent teeth	MTA Calcium hydroxide CEM Biodentine	Yes Yes Yes Yes	Present Present Present Present	Present Present Present Present	High Low Variable High	No No Variable Yes	Significant Significant Significant
Patel et al. (2019)	Systematic review	Not applicable	MTA Bioceramics and other materials	Yes Yes	Present Present	Present Present	High Variable	No N/A	Significant Significant
Priyal et al. (2020)	Clinical trial	Direct pulp capping Indirect pulp capping	Biodentine™	Yes	Present	Present	High	Yes	Significant
Paula et al. (2019)	Experimental study	Direct pulp capping	Biodentine™ MTA	Yes Yes	Present Present	Present Present	High High	Yes No	Significant Significant
Raddall et al. (2019)	Systematic review	Regenerative endodontic therapy	Naturally-Derived Scaffolds (Hyaluronic acid) Synthetic Scaffolds (VitroGel 3D®) Potential scaffolds for future studies	Yes (with MTA filling) Yes (with MTA filling) N/A	Present Present N/A	Present Present N/A	High High N/A	N/A N/A N/A	More research needed More research needed More research needed
Sabbagh et al. (2016)	Clinical trial	Pulpotomy	Calcium-enriched mixture	Yes	Present	Present	High	No	Significant
Saghiri et al. (2016)	Systematic review	Regenerative endodontics	Calcium hydroxide MTA CEM Biodentine™ Glass ionomer resins and adhesive	Yes Yes Yes Yes Yes	Present Present Present Present More or less	Present Present Present Present Present	Low High High High High	No No No Yes No	Significant Significant Significant Significant Moderate
Sharma et al. (2020)	Randomized controlled trial	Indirect pulpar capping	ENDOCEM-Zr® MTA	Yes Yes	Present Present	Present Present	High High	No No	Significant Significant
Stephane et al. (2020	Clinical trial	Pulpotomy	MTA	Yes	Present	Present	High	No	Significant
Tziafa et al. (2014)	Clinical trial	Direct pulp capping	MTA Biodentine™	Yes Yes	Present Present	Present Present	High High	No Yes	Significant Significant
Vu et al. (2020)	Clinical trial	Direct pulp capping	MTA Acemannan (bioactive polysaccharides of Aloe vera)	Yes Yes	Present Present	Present Present	High Low	No No	Significant Significant

Source: Own elaboration (2021)