

Vital Pulp Therapy an Insight Over the Available Literature and Future Expectations

 Samer Nagui HANNA,  Ruth PEREZ ALFAYATE,  James PRICHARD

ABSTRACT

Vital pulp therapy (VPT) defined as “treatment which aims at preserving and maintaining the pulp tissue that has been compromised but not destroyed by extensive dental caries, dental trauma, and restorative procedures or for iatrogenic reasons”; offers some beneficial advantages over the conventional root canal treatment such as protective resistance for mastication forces or to prevent the loss of environmental changes sensation ability, which can lead to unnoticeable progression of caries and later fracture. A wide range of materials are suggested in the literature to be used as pulp capping protective dressing materials that varies from ready-made synthetic materials to biological based scaffolds and composites. The aim of the present review is to provide a full understanding of currently used materials to clinicians in order to help in their decision-making process delivering the best available evidence-based treatments to their patients. An extensive search for recent available data regarding direct pulp capping materials and potential suggestions for future use have been made. Newly developed biological based scaffolds showed promising results in dentine regeneration therefore strengthening the tooth structure and overcoming potential drawbacks of use of currently available recommended materials.

Keywords: Biomaterials based scaffolds, direct pulp capping, indirect pulp capping, tricalcium silicate materials, vital pulp therapy

HIGHLIGHTS

- Vital Pulp Therapy (VPT) is considered one of the main regenerative fields in endodontics.
- Success & Failure rate varies greatly upon the accuracy of the diagnosis and the material used for pulp capping.
- Materials introduced varies from synthetic materials such as calcium Hydroxide and tri-calcium silicate material to biomaterials scaffolds.
- Nowadays, biomaterials and composite scaffolds are of great interest in the field of regenerative endodontics and being investigated for potential future use.
- This review provides the reader with insights and latest updates over the VPT materials and potential interests in research areas within the future.

INTRODUCTION

Vital pulp therapy (VPT) has been defined as treatment which aims at preserving and maintaining the pulp tissue that has been compromised but not destroyed by extensive dental caries, dental trauma, and restorative procedures or for iatrogenic reasons (1). Zhang and Yelick used another definition which added, “Stimulating the remaining pulp tissue to regenerate the dental pulp complex” to the previous definition (2). Clinically vital pulp therapy includes two main groups, indirect pulp capping and direct pulp capping (3). The European Society of Endodontology quality guidelines for endodontic treatment 2006, states that indi-

rect pulp capping is a procedure in which a protective cement or dressing placed over a thin layer of remaining sound or slightly softened dentine which if removed, it might expose the pulp. Direct pulp capping defined as: at the site of pulpal exposure, the pulp is covered with a protective dressing or base, which aims at protecting the pulp from additional injuries and permits healing and repair (4). Clinical management steps of deep carious lesions are summarized and presented in (Fig. 1) to ease and guide the clinicians during their daily clinical work.

Recently, a new pulpitis diagnosis classification has been suggested by Wolters et al., 2018. The authors suggested that within the diagnosed irreversible pulpitis cases, un-inflamed pulp tissue

Please cite this article as: Hanna SN, Perez Alfayate R, Prichard J. Vital Pulp Therapy an Insight Over the Available Literature and Future Expectations. *Eur Endod J* 2020; 1: 46-53

From the Department of Endodontic (S.N.H.I. ✉ samernagui@hotmail.com, J.P.) College of Medicine and Dental School, UK; Department of Endodontic (R.P.A.), Universidad Europea De Madrid, Spain

Received 10 June 2019,
Accepted 29 September 2019

Published online: 01 March 2020
DOI 10.14744/eej.2019.44154

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



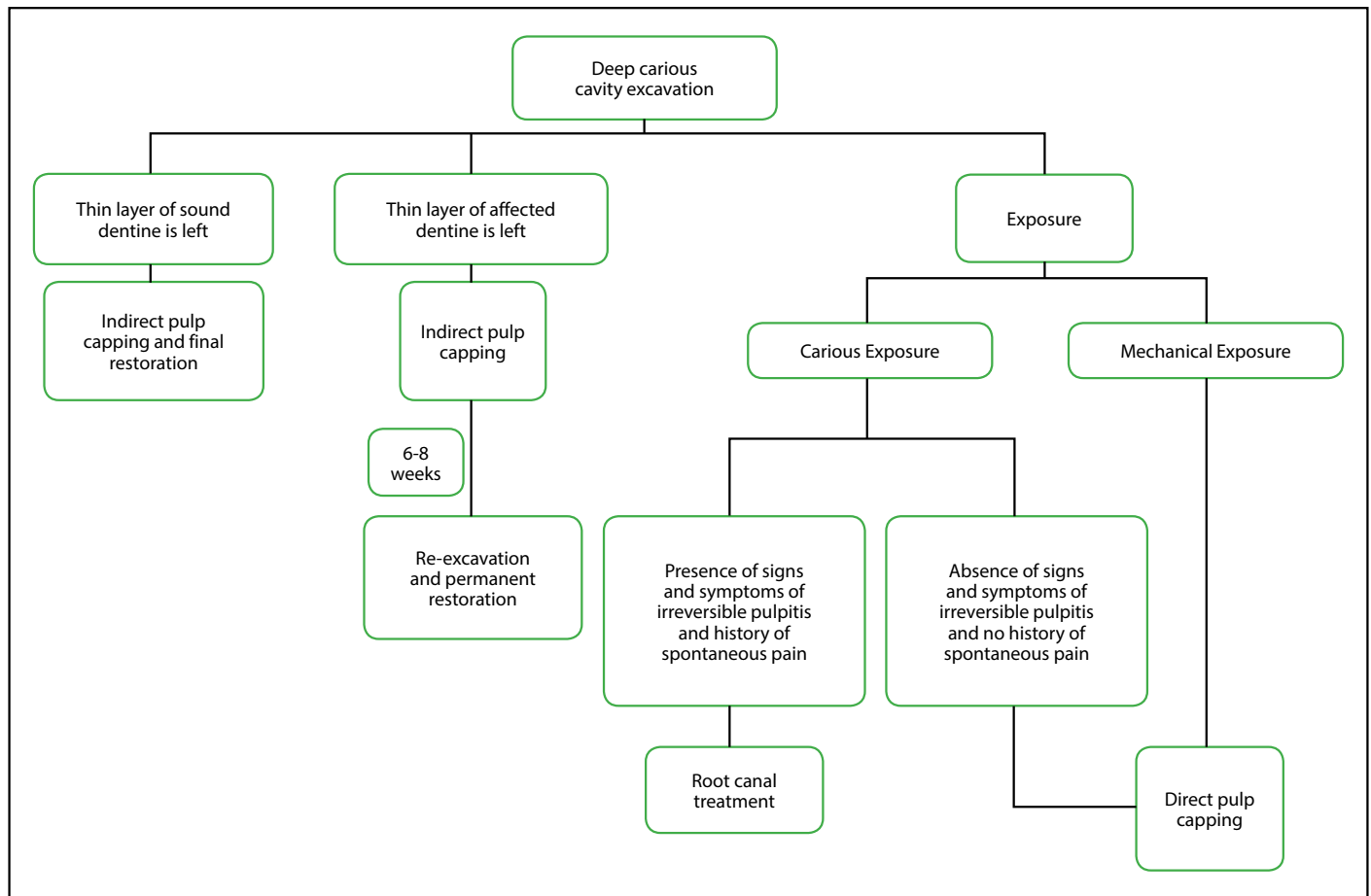


Figure 1. Deep carious excavation clinical scheme

could still be present. Therefore, in their paper, the authors proposed new terminology defining different conditions of pulpal inflammations. Initial pulpitis is proposed to describe heightened but not lengthened response to thermal pulp testing (cold) with no signs of spontaneous pain and no sensitivity to percussion. Mild pulpitis is described as heightened and lengthened response to thermal testing and sweets, slight sensitivity to percussion. Moderate pulpitis is prolonged and clear diagnostic signs of thermal pain and dull pain is also noted. Severe Pulpitis is lastly described as severe spontaneous and clear pain to thermal testing and severe to dull throbbing pain and tooth is extremely sensitive to touch and biting (5).

Regenerative endodontics is described as a biological procedure, which aims at growing tissues in order to heal or replace damaged or diseased tooth structures such as tooth dentine and dental pulp tissues (6). Therefore, the main objectives of regenerative endodontics are to regenerate pulp-like tissue, the pulp–dentine complex and replace damaged coronal dentine (7).

Vital pulp therapy offers great benefits over conventional root canal treatment (RCT). In cases with immature apices, preserving the vitality of the tooth is beneficial for the continuation of root development, enhancing the strength of the affected tooth (8). Another advantage offered by VPT over conventional RCT is better protective resistance against masticatory forces

(9). As summarized by the American Academy Of Pediatrics Dentistry (AAPD), good prognosis and long term retention of a permanent tooth requires favorable crown / root ratio, favorable dentine thickness and vitality which are offered by VPT after the tooth structure has been compromised by dental caries, trauma or other causes (10).

Vital pulp therapy history&success rates

The history of endodontics and pulp capping goes back in time to the 17th century (11). The first description of dental pulp tissue was explained by Pierre Fauchard (1678-1761) who also was the first author to describe the removal of pulp tissue in 1746 in his text book “Le chirurgien dentiste” (12). Later, in 1756, Phillip Pfaff was the first to use gold and lead for pulp capping (13). In 1821, Koecker theorized which, later in 1850; Codman confirmed that the aim of pulp capping was dentine bridge formation (14). During this era, the idea of pulp capping was mainly based on the belief that pulpal healing can only occur after being exposed to etching or cauterization (13). In the late 18th century, great advances were introduced into medicine and dentistry; examples of such advances are the introduction of dental radiographs in 1895, development of anesthesia by Horace Wells and William Morton (11). In the period of 1665–1683, Robert Hooke and Antoni van Leeuwenhoek discovered the existence of microscopic organisms using the simple microscope (15). Later, Pasteur and Lister described the role of microorganisms in the diseases (11). In 1921, Dätwyler conducted the

first clinical scientific study comparing different pulp capping materials and demonstrated that zinc oxide eugenol showed the best results (16). Since the introduction of calcium hydroxide as a root filling material by Hermann in 1920, and especially during the period from 1928 to 1930, several studies were conducted employing calcium hydroxide and concluded that it is a biocompatible material when used over vital pulp (17).

The success and failure rates of vital pulp therapy varied greatly in the literature due to different methodological considerations during the studies and advances in materials (18). Several factors were believed to affect the success rates such as the state of pulpal inflammation, presence of spontaneous pain before the treatment, whether the exposure was mechanical or carious, the size of the exposure, the age of the tooth, coronal restoration sealing and time of coronal restoration (1). In the study published by Honegger et al., 1979, 123 teeth which had direct pulp capping for an average period of 4 years were reviewed. They concluded that direct pulp capping had a failure rate of 17%. They also concluded that tooth age did not affect the outcome of the treatment, but rigorous aseptic procedures and sealing of dressing materials are prerequisites for success. They recommended that only accidentally exposed pulps without previous symptoms are liable to successful treatment by direct pulp capping with calcium hydroxide (19). In 1981, in another study by Baume and Holz, the authors agreed with the previous study that the failure rate increased if the pulp was diseased prior to treatment and that age has no influence. However, in their study, success rates varied from 80 % to 90 % depending on the skill level of the dentist performing the treatment (20).

More recently, Dammaschke et al., agreed with Baume and Holz and Honegger et al., that infected pulps or teeth that show spontaneous pain, demonstrated significantly lower success rates than teeth with no spontaneous pain. They also concluded that gender, jaw, and tooth type had no significant influence on the results; however regarding age, they showed that the highest rates of success were found in the age group 16-26 years old with a survival period of 14.7 years while the success rate was the lowest in the age group >60 years old with a survival period of 4.6 years (21).

There were no significant differences in the success rates between types of restorative material (amalgam, resin composite and gold restorations) however; teeth restored with glass ionomer cements demonstrated significantly lower success rates. Authors also concluded that the likelihood for a tooth to become necrotic was significantly higher the first 5 years after treatment and that if the tooth showed favorable outcomes in the first 5 years, it is very unlikely that it will show unfavorable outcomes in the longer term (18).

The overall success rates in cariously exposed pulps were shown to be 87.5%–95.4% which can similarly be compared with that of iatrogenic exposures ranging from 70%–98% (1).

A recent randomized controlled trial conducted by Ali et al (2018) over deep caries with reversible pulpitis teeth; comparing the outcomes of self-limiting excavation protocol using

chemo mechanical Carisolv gel and dental microscope (self-limiting) versus selective removal to dentine using rotary burs, followed by MTA pulpal protection and Glass Ionomer (GI) final restoration. Results showed that after 12 months the probability of success rates was four times higher in cases of self-limiting technique rather than the conventional technique (22). This may indicate that shifting the caries removal from the conventional technique to the self-limiting technique in vital pulp therapy cases could increase success rates.

Few disadvantages and negative drawbacks of VPT were noted with some of the currently used materials. Using Calcium hydroxide were associated with some disadvantages such as inability to kill *Enterococcus faecalis* in the dentine (23), inability to adhere to dentine properly, dissolution over time and inability to provide microleakage seal over time (24). With the use of MTA, teeth discoloration were noted either with the use of grey or white MTA due to chemical interaction of bismuth oxide with dentine collagen (25). Also, it was noted that, on the long term evaluation of teeth underwent VPT, complete pulp space obliteration can be seen which render the root canal treatment more complex when needed in the future (26).

Vital pulp therapy materials

Since the 1920's, a wide range of materials have been suggested in the literature to be used as pulp capping protective dressing materials. Ideally, the pulp capping material should have the following properties (27):

- Stimulate reparative dentine formation
- Maintain pulpal vitality
- Be Bactericidal or bacteriostatic
- Adhere to dentine and other restorative materials
- Resist forces during placement of the final restoration and masticatory forces
- Release fluoride
- Be Sterile
- Be Radiopaque
- Provide bacteria tight seal

Examples of different pulp capping materials introduced in the literature are calcium hydroxide, glass ionomer, resin modified glass ionomer, Mineral Trioxide Aggregate (MTA) Biodentine, Bioceramics, Biological based scaffolds and composite (28).

Calcium hydroxide (CH)

Since its introduction into literature 1920 by Hermann, it was considered as the gold standard material for pulp capping (17). It is believed that the initial effect of calcium hydroxide is the development of superficial three layer necrosis resulted from the chemical injury caused by hydroxyl ions (29). Schröder also explained that the firm necrosis area is believed to be responsible for the irritation of the pulp and stimulating its defense mechanism and repair. The repair process begins with vascular and inflammatory cell migration and proliferation in order to eliminate the irritating agent this step is later followed by the

migration and proliferation of mesenchymal and endothelial pulp cells and the formation of collagen. Subsequently odontoblast differentiation occurs and the formation of tertiary dentine underneath the protective agent takes place (29).

CH has potent antibacterial properties, which were believed to be the main reason for using it successfully in pulp capping as it eliminates bacterial penetration and future injury to the pulp tissue (30).

Disadvantages of Calcium hydroxide include pulp surface inflammation and necrosis, the presence of tunnel defects in the newly formed tertiary dentine, which fails to provide an adequate seal against recurrent infections, high solubility in oral fluids and lack of adhesion (31).

Resin modified glass ionomer cement (RMGIC)

RMGICs are defined as "glass-ionomers that are modified by the inclusion of a resin monomer and set partly via an acid/base reaction and partly through photochemical polymerization" (32). The material was introduced in order to overcome the instability in the water balance seen in the previous generation of Glass Ionomers that set through an acid/base reaction only (33). RMGICs have been shown to be successful when used as a protective agent for thin sound dentine layers in deep cavities and in cases of indirect pulp capping (34). However, RMGICs exhibited poor results when placed in direct contact with pulpal tissue in cases of direct pulp capping (35). RMGICs were related to moderate to intense inflammatory responses in the dental pulp including a large necrotic zone and the absence of dentine bridge formation (36).

Mineral trioxide aggregate (MTA)

MTA was first introduced into literature in the 1990s as an experimental calcium silicate based material (37). MTA is a broadly used material used to seal pulpal cavities and external root surface communications (38). MTA is composed of Portland cement, which is mainly composed of tri-calcium and di-calcium silicate, and bismuth oxide as radiopacifier (39).

The commercialized forms of MTA introduced into the market were ProRoot® MTA and tooth coloured ProRoot® MTA, (Dentsply Tulsa Dental Specialties, Tulsa, OK, USA), and later, MTA Angelus® and MTA Bianco®, (Angelus, Londrina, Brazil).

MTA has been suggested as the material of choice in cases of pulp capping, pulpotomies, perforative root resorption defects, surgical root end filling (retrograde filling), root and pulp chamber perforations and in cases undergoing revascularization treatment (40). MTA has been reported to be a biocompatible material, which has inductive and conductive abilities for hard tissue formation (41). It is bactericidal, stimulates cementum-like hard tissue formation and bone regeneration (36).

Regarding MTA as a pulp capping material, it was concluded by Nair et al., after a randomized control study that MTA was clinically easier to use, resulted in less pulpal inflammation and had more predictable outcomes regarding hard tissue barrier formation when compared to calcium hydroxide (42). In a meta-analysis study, investigators reviewed 13 studies that had been conducted since 2003. 5 of the studies, involv-

ing 931 teeth, reported success rates between MTA and CH. While the other nine investigated the inflammatory response and dentine bridge formation differences between calcium Hydroxide and MTA. It was concluded from this meta-analysis that MTA had significantly superior success rates to CH. MTA specimens showed less pulpal inflammation in comparison to the CH specimens and that a higher percentage of calcified dentine bridge formation was noticed in the MTA capped groups (31).

Clinically, MTA had numerous drawbacks reported. Difficulty in handling together with a long setting time, high cost and potential discolouration to the tooth were reported (43).

Biodentine®

Biodentine (BD; Septodont, Saint- Maur-des-Fosses, France) is a newly developed material by Septodont. It is a calcium silicate-based Portland cement. It is a bioactive, biocompatible material and suitable for use in direct posterior restorations, furcal perforations, retrograde filling and pulp capping (44). Biodentine has positive effect on vital pulp cells and stimulates tertiary dentine formation and it has been shown that it is well tolerated by the pulp tissue when it is in direct contact (in cases of direct pulp capping) forming reparative dentine (45, 46).

Biodentine was shown to be faster in comparison to other materials such as MTA (47). The authors also concluded that the newly developed calcium silicate material presented enhanced mechanical properties and was able to form a good marginal seal. In a study conducted by Nowicka et al., comparing different pulpal response toward different pulp capping materials (MTA and Biodentine), they noted that placement of MTA was more time consuming and technically more difficult in comparison to Biodentine (44). They also concluded that Biodentine showed, similar efficacy in clinical setting, making it a viable substitute to MTA. A recent study evaluated the efficacy of Biodentine in a series of 15 case with follow up of 12 to 24 months, and authors concluded that all 15 cases were asymptomatic during follow up period therefore suggesting the use of Biodentine as vital pulp therapy material (48).

The material is prepared using an amalgamator for 30 seconds and later carried by an amalgam carrier or root canal Messing gun and applied to the cavity (Biodentine product information leaflet 2009).

In a recent prospective randomized clinical trial, assessing the difference outcome of MTA compared to Biodentine used in vital pulp therapy cases, no statistical difference between both materials were noted. Average success rate of both materials was 93.3% at 6 months follow up, 96.2% at 1 year, 100% at two years and lastly 93.8% at the 3 years follow up. Those results favours the use of both tricalcium silicate material in direct and indirect pulp capping (49).

BioCeramics

Recently, Bioceramics were introduced to the market as IRoot BP Plus (Innovative Bioceramics, Vancouver, Canada) also labelled as EndoSequence Root Repair Material Putty (ERRM) (Brasseler, Savannah, GA, USA) and as TotalFill RRM Putty (FKG, La-Chaux-de-Fonds, Switzerland). IRoot BP is a newly devel-

oped calcium silicate-based bioactive ceramic with main composition being Tri-calcium silicate, bi-calcium silicate and calcium phosphate (50). Endosequence root repair material showed antibacterial properties similar to MTA when compared with CH against the main cariogenic bacteria Salivary Streptococci Mutans (SM) and Lactobacilli (51).

iRoot BP Plus was shown to have good biocompatibility with pulp tissue and induced the formation of a reparative dentine bridge; hence, it can be used as a pulp capping material in vital pulp therapy cases (52). iRoot BP Plus used with human dental pulp cells in-vitro, was shown to induce mineralization and induce odontoblastic differentiation associated with gene expression (53). The effect of ERRM on differentiation of dental pulp cells (DPC) was compared with ProRoot® MTA. The percentage of viable DPCs, proliferation rates and secretion of Vascular Endothelial Growth Factor (VEGF) were shown to be similar when grown on both materials (54). The authors concluded that ERRM could be considered as a suitable alternative to other pulp capping materials.

Biomaterials based scaffolds

Scaffolds play a very important role in tissue engineering. Choosing an appropriate scaffold is considered a crucial step (55). Scaffolds introduced for pulp tissue regeneration varies from natural scaffolds such as Collagen, Glycoaminoglycan, Chitosan, Alginate and Agarose; to synthetic scaffold such as Hydroxyapatite/ tri-calcium phosphate, Polyacetic acid, Polycaprolactone and Self-assembling peptide hydrogels (56).

Polysaccharides

Alginate

Alginate is described as being an anionic linear polysaccharide. It is comprised of repeating (1,4)-linked b-D-mannuronic sequences (M-blocks) and a-L-guluronic acid sequences (G-blocks) inter-spersed with MG sequences (MG-blocks) (57). Alginate was used in regenerative dentistry. The study showed that HDPCs in alginate scaffolds actively differentiated into odontoblast-like cells and induced calcification that mimicked dentine which support the usage of alginate as a scaffold (58). Alginate advantages consist of biocompatibility and non-immunogenicity; however, it also has some drawbacks including poor cell adhesion, low mechanical strength, and low degradability (59).

Chitosan

Chitosan is a deacetylated derivative of chitin and is composed of glucosamine and N-acetyl glucosamine (57). The chitin is naturally present in the exoskeleton of the marine crustaceans such as shrimps and crabs, as well as insects and the cell walls of fungi (60). As a scaffold in dental pulp regeneration, 3D chitosan scaffold was seen to be supporting the differentiation of DPSCs due to suitability for nerve cell attachment (61). Contradicting those results, Kim et al., compared chitosan with different other natural scaffolds and concluded that collagen and gelatin supported the HDPCs growth better (62). Due to its poor solubility, caused by its presence of amino groups and its high crystallinity, chitosan modifications needs to be done in order to increase its potential use in regenerative dentistry (63).

Extracellular matrix

Hyaluronic acid

Hyaluronic acid is a Linear polysaccharide abundant in cartilage ECM and consists of two alternating units, b-1,4-D-glucuronic acid and b-1,3-N acetyl-D-glucosamine (64). Because of the height molecular weight of the hyaluronic acid, when dissolved in water, its viscoelasticity increases making it easier to be used as an injectable scaffold (65). Depending on the molecular weight of the acid, the later can act as inhibitor of the proliferation, migration and angiogenesis of the endothelial cells in cases of high molecular weight. While in cases of low molecular weight, hyaluronic acid promotes the proliferation and cell attachment of the endothelial cell (66). Favourable properties are linked to the hyaluronic acid scaffolds such as bioactivity, biocompatibility, biodegradability and acting as a growth factors reservoir; however, its disadvantages include structural complexity, low mechanical strength and possible immunogenicity (67).

Collagen

Collagen is considered one of the most abundant components in extracellular matrices. It has been used in tissue engineering, drug delivery and reconstructive surgeries in dentistry and orthopedics (56). Most abundant types of collagen used in tissue engineering, is the collagen type I and allogenic collagen such as the bovine collagen which is proven to have excellent biocompatibility and bioactivity (68). Collagen intrinsic mechanical properties were proven sufficient for its usage in dental regeneration and its properties can be enhanced when used in hybrid form scaffolds (63). Further to this, in another study by Alsanea et al. 2011, differentiation of DPSC within collagen scaffolds into highly vascularized and organized matrix of odontoblastic like cells (69).

Proteins and peptides

Fibrin

Platelet-rich fibrin (PRF) which is considered as a second generation platelet concentrate, is a type of natural biological fiber scaffold (61). PRF is known to be rich in platelets, leukocytes and various growth factors that play an important and essential role in promoting cell proliferation and differentiation (70). PRF also contains osteogenic cytokines and fiber holders. The osteogenic cytokines and fiber holders act as three dimensional centrifugal mesh and form a near-natural polymer that captures the migrating cells and induce the release of platelet derived growth factors (71).

In the study conducted by Huang et al. 2010, authors tested the ability of the PRF to stimulate the proliferation and differentiation of deciduous and permanent dental pulp cells (DPCs). Authors concluded that PRF can be used successfully as natural scaffold for DPCs successfully inducing their proliferation and differentiation (72).

Sharma and Mittal (73); compared different types of natural and artificial scaffolds in regenerative endodontics, specifically in inducing apexogenesis in necrotic immature permanent teeth. Within the four different scaffolds used, blood clot, PRF, collagen and PLGA; PRF exhibited the best results for all tested parameters. Authors interpreted this success to the strong and flexible properties the PRF have and to the richness

with growth factors required for cellular proliferation, differentiation and angiogenesis.

Also when the regenerative properties of the PRF were tested when used as pulp capping material in canines, authors concluded that using the PRF as pulp capping material supplies growth factors and potential network showing promising results for regeneration of the pulp (74).

Self assembling peptide nanofibers

Peptides are known to be short amino acids sequences of protein that have potential biological activities (56). As peptides can be manufactured as solid peptides synthesis, it add great benefits to the scaffold as of the customization of the biological, physical and chemical properties (75). Self-assembling peptide are modified peptides molecules that are self-assembled into fibrillary structures that its use have been suggested in the field of regenerative endodontics (56).

Self-assembling peptides matrix were shown to offer great advantages such as, structurally, a true mimic of the extracellular matrix due to their nanoscale dimensions (66).

In a study conducted Yoshima et al. (76), studying the quality of Puramatrix (self-assembling peptide nanomaterial) combined with dog mesenchymal stem cells (dMSCs) and/or platelet-rich plasma (PRP) in the regenerative healing of bone defects. All Puramatrix groups showed significant better results than the control groups.

Assessing the compatibility of the dental pulp stem cells (DPSCs) growth and differentiation with the Puramatrix, Cavalcanti et al. (77), who concluded that healthy DPSC survived and proliferated for at least three weeks in culture which supported the recommendation of using self-assembling peptides hydrogel as injectable scaffolds.

Composite Scaffolds

Growth factors (GF) are groups of proteins, which bind into cell receptors and induce cellular proliferation and differentiation (6). GF can also be described as extracellular signals, governing the morphogenesis and organogenesis during the epithelial and mesenchymal interactions (78).

Growth factors are considered one of the main three corner stones of tissue engineering and any regenerative procedure (79). GF are also considered key factors for tissue wound healing by regulating the immune function, proliferation and differentiation of cells (80).

Several growth factors have been demonstrated as potential therapeutic agents for hard tissue regeneration (81). There are different types, origins and functions that differentiate growth factors. Some are used to increase stem cell numbers such as the platelet derived growth factors (PDGF), fibroblasts growth factors (FGF), colony stimulating factors (CSF) and epidermal growth factors (EGF) (78, 82).

Others used to modulate and control the humoral and the cellular immune responses such as Interleukin 12 and Insulin-like Growth Factor 1 (IGF1) especially in activation and survival of antigen specific T cells (83). While others are crucial regulators

of vasculogenesis, angiogenesis and lymph-angiogenesis such as vascular endothelial growth factors (VEGF) (84).

Mixing Growth factors with pulp capping materials

The use of a scaffold releasing growth factor as a pulp capping material has been reported for dentine/pulp repair (85). It was shown to have superior results enhancing reparative dentinogenesis (86). In addition, Dobie et al., (87) concluded from that TGF- β 1 when incorporated in alginate hydrogel scaffold induced odontoblast-like cellular differentiation and up-regulated their matrix secretion in the human dentine pulp complex (87). In addition the formation of a reparative dentine bridge in rat molars when Fibroblast Growth Factor-2 (FGF-2) was incorporated in gelatin hydrogel and placed over exposed pulp was noted.

Mixing GF with tri-calcium phosphate materials was shown to enhance bone regeneration when placed in a bony defect after periapical surgery (88). The authors also noted that the GF added to the tri-calcium phosphate, helped regenerating vital tissues with necrotic pulp and periapical lesions, which indicates great advantages of adding GF to biomaterials.

When the effect of MTA alone and MTA mixed with fibroblast growth factors-2 (FGF-2) was compared in vitro, on human dental pulp cells behaviour, it was concluded that MTA and FGF-2 group significantly enhanced human dental pulp cells proliferation and osteogenic differentiation (89). In addition, the combination of both MTA and GH promoted cell adhesion, growth, differentiation and angiogenesis via the activation of bone morphogenic proteins and Mitogen-Activated Protein Kinase (MAPK) pathway (90).

CONCLUSIONS

Due to the emerging need for regenerative dentistry, concentration on the development of the ideal scaffold is needed. Different materials have been introduced in literature in order to seal and induce tertiary dentine regeneration. Newer introduced materials aim at sealing the exposure site while induce odontogenesis therefore increasing the vital pulp therapy success rates. Newer materials ranges from different synthetic materials such as bioceramics to the new biological proposed scaffolds. However, the most important governing factor in the success rate of VPT is the correct diagnosis of reversibility of pulpal inflammation and the extent of pulp infection. Also implementing new techniques in caries excavation for VPT cases could improve success rates of such cases. More research and studies are set to be exploring all-natural options for biological scaffolds and promising results are emerging. Also, more research areas should be explored in easier more confirmed ways of diagnosis of pulpal condition.

Disclosures

Conflict of interest: No conflict of interests within this study.

Ethics Committee Approval: As no Patient involvement in this study, no ethical approvals were mandatory.

Peer-review: Externally peer-reviewed.

Financial Disclosure: Self-funded.

Authorship contributions: Concept – S.N.H.I., J.P., R.P.A.; Design – S.N.H.I., J.P., R.P.A.; Supervision – S.N.H.I., J.P., R.P.A.; Funding – S.N.H.I.; Materials – S.N.H.I.; Data

collection &/or processing – S.N.H.I.; Analysis and/or interpretation – S.N.H.I.; Literature search – S.N.H.I.; Writing – S.N.H.I.; Critical Review – S.N.H.I., J.P., R.P.A.

REFERENCES

- Ghoddusi J, Forghani M, Parisay I. New approaches in vital pulp therapy in permanent teeth. *Iran Endod J* 2014; 9(1):15–22.
- Zhang W, Yelick PC. Vital pulp therapy-current progress of dental pulp regeneration and revascularization. *Int J Dent* 2010; 2010:856087. [CrossRef]
- American Association of Endodontists. Guide to Clinical Endodontics. 4th ed. Available at: <http://sje.mx/wp-content/uploads/04guide-to-clinical-endo.pdf>. Accessed Sep 30, 2019.
- European Society of Endodontology. Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. *Int Endod J* 2006; 39(12):921–30. [CrossRef]
- Wolters WJ, Duncan HF, Tomson PL, Karim IE, McKenna G, Dorri M, et al. Minimally invasive endodontics: a new diagnostic system for assessing pulpitis and subsequent treatment needs. *Int Endod J* 2017; 50(9):825–9.
- Murray PE, Garcia-Godoy F, Hargreaves KM. Regenerative endodontics: a review of current status and a call for action. *J Endod* 2007; 33(4):377–90.
- Kumar H, Kavitha A, Jayaprada J, Shetty SR. Regenerative Endodontics. *Indian J Dent Adv* 2010; 2(2):203–9.
- Ward J. Vital pulp therapy in cariously exposed permanent teeth and its limitations. *Aust Endod J* 2002; 28(1):29–37. [CrossRef]
- Caplan DJ, Cai J, Yin G, White BA. Root canal filled versus non-root canal filled teeth: a retrospective comparison of survival times. *J Public Health Dent* 2005; 65(2):90–6. [CrossRef]
- American Academy on Pediatric Dentistry Clinical Affairs Committee-Pulp Therapy subcommittee; American Academy on Pediatric Dentistry Council on Clinical Affairs. Guideline on pulp therapy for primary and young permanent teeth. *Pediatr Dent* 2008-2009; 30(7 Suppl):170–4.
- Castellucci A. A Brief History of Endodontics. In: *Endodontie*. Vol 1. Il Tri-dente; 2002. p. 2–5.
- Bresciani S. La scoperta della polpa dentale. *Odontoiatria & dintorni* 1993; 1:7–9.
- Dammaschke T. The history of direct pulp capping. *J Hist Dent* 2008; 56(1):9–23.
- Koch CRE, Thorpe BL. History of dental surgery. Chicago: The National Art Publishing Company; 1909.
- Gest H. The discovery of microorganisms by Robert Hooke and Antoni Van Leeuwenhoek, fellows of the Royal Society. *Notes Rec R Soc Lond* 2004; 58(2):187–201. [CrossRef]
- Fuks AB, Peretz B. Pediatric Endodontics - Current Concepts in Pulp Therapy for Primary and Young Permanent Teeth. 1st ed. Switzerland: Springer International Publishing; 2016.
- Hermann BW: Kalziumhydroxid als Mittel zum Behandeln und Füllen von Zahnwurzelkanälen. Dissertation. Würzburg; 1920.
- Dammaschke T. A new bioactive cement for direct. *Int Dent - African Ed* 2010; 2(2):2–7.
- Honegger D, Holz J, Baume LJ. Long-term clinical supervision of direct pulp capping (performed by the students of the School of Dentistry, Geneva). [Article in French]. *SSO Schweiz Monatsschr Zahnheilkd* 1979; 89(10):1020–41.
- Baume LJ, Holz J. Long term clinical assessment of direct pulp capping. *Int Dent J* 1981; 31(4):251–60.
- Dammaschke T, Leidinger J, Schäfer E. Long-term evaluation of direct pulp capping-treatment outcomes over an average period of 6.1 years. *Clin Oral Investig* 2010; 14(5):559–67. [CrossRef]
- Ali AH, Koller G, Foschi F, Andiappan M, Bruce KD, Banerjee A, et al. Self-Limiting versus Conventional Caries Removal: A Randomized Clinical Trial. *J Dent Res* 2018; 97(11):1207–13. [CrossRef]
- Sirén EK, Haapasalo MP, Waltimo TM, Ørstavik D. In vitro antibacterial effect of calcium hydroxide combined with chlorhexidine or iodine potassium iodide on *Enterococcus faecalis*. *Eur J Oral Sci* 2004; 112(4):326–31.
- Akhlaghi N, Khademi A. Outcomes of vital pulp therapy in permanent teeth with different medicaments based on review of the literature. *Dent Res J (Isfahan)* 2015; 12(5):406–17. [CrossRef]
- Marciano MA, Costa RM, Camilleri J, Mondelli RF, Guimarães BM, Duarte MA. Assessment of color stability of white mineral trioxide aggregate angelus and bismuth oxide in contact with tooth structure. *J Endod* 2014; 40(8):1235–40. [CrossRef]
- Algahtani F. Vital Pulp Therapy Challenges and Promises in Permanent Teeth. *Mod Res Dent* 2019; 3(4):1–4. [CrossRef]
- Cohen BD, Combe EC. Development of new adhesive pulp capping materials. *Dent Update* 1994; 21(2):57–62.
- Qureshi A, E S, Nandakumar, Pratap Kumar, Sambashivarao. Recent advances in pulp capping materials: an overview. *J Clin Diagn Res* 2014; 8(1):316–21. [CrossRef]
- Schröder U. Effects of calcium hydroxide-containing pulp-capping agents on pulp cell migration, proliferation, and differentiation. *J Dent Res* 1985; 64 Spec No:541–8. [CrossRef]
- Poggio C, Arciola CR, Beltrami R, Monaco A, Dagna A, Lombardini M, et al. Cytocompatibility and antibacterial properties of capping materials. *ScientificWorldJournal* 2014; 2014:181945. [CrossRef]
- Li Z, Cao L, Fan M, Xu Q. Direct Pulp Capping with Calcium Hydroxide or Mineral Trioxide Aggregate: A Meta-analysis. *J Endod* 2015; 41(9):1412–7.
- Mitra S. Curing reactions of glass ionomer materials. In: Hunt PR, editor. *Glass Ionomers: The next generation*. Proceeding of the 2nd International Symposium on Glass Ionomers. Pennsylvania: International Symposium in Dentistry, PC; 1994; 13–22.
- Mount GJ, Papageorgiou E. Some curing properties of light activated glass ionomer cement. *Aust Dent J* 1992; 37:309–10.
- Costa CA, Giro EM, do Nascimento AB, Teixeira HM, Hebling J. Short-term evaluation of the pulpo-dentin complex response to a resin-modified glass-ionomer cement and a bonding agent applied in deep cavities. *Dent Mater* 2003; 19(8):739–46. [CrossRef]
- Cui C, Zhou X, Chen X, Fan M, Bian Z, Chen Z. The adverse effect of self-etching adhesive systems on dental pulp after direct pulp capping. *Quintessence Int* 2009; 40(6):e26–34.
- do Nascimento AB, Fontana UF, Teixeira HM, Costa CA. Biocompatibility of a resin-modified glass-ionomer cement applied as pulp capping in human teeth. *Am J Dent* 2000; 13(1):28–34.
- Torabinejad M, Watson TF, Pitt Ford TR. Sealing ability of a mineral trioxide aggregate when used as a root end filling material. *J Endod* 1993; 19(12):591–5. [CrossRef]
- Tanomaru M, Viapiana R, Guerreiro J. From MTA to New Biomaterials Based on Calcium Silicate. *Odovtos Int J Dent Sci* 2016; 18(1):18–22.
- Camilleri J, Montesin FE, Brady K, Sweeney R, Curtis RV, Ford TR. The constitution of mineral trioxide aggregate. *Dent Mater* 2005; 21(4):297–303. [CrossRef]
- Casella G, Ferlito S. The use of mineral trioxide aggregate in endodontics. *Minerva Stomatol* 2006; 55(3):123–43.
- Hakki SS, Bozkurt SB, Hakki EE, Belli S. Effects of mineral trioxide aggregate on cell survival, gene expression associated with mineralized tissues, and biomineralization of cementoblasts. *J Endod* 2009; 35(4):513–9.
- Nair PN, Duncan HF, Pitt Ford TR, Luder HU. Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with Mineral Trioxide Aggregate: a randomized controlled trial. 2008. *Int Endod J* 2009; 42(5):422–44. [CrossRef]
- Parirokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review--Part I: chemical, physical, and antibacterial properties. *J Endod* 2010; 36(1):16–27. [CrossRef]
- Nowicka A, Lipski M, Parafiniuk M, Sporniak-Tutak K, Lichota D, Kosierkiewicz A, et al. Response of human dental pulp capped with bio-dentine and mineral trioxide aggregate. *J Endod* 2013; 39(6):743–7.
- Shayegan A, Jyrysta C, Atash R, Petein M, Abbeele AV. Biodentine used as a pulp-capping agent in primary pig teeth. *Pediatr Dent* 2012; 34(7):e202–8.
- Laurent P, Camps J, About I. Biodentine(TM) induces TGF-β1 release from human pulp cells and early dental pulp mineralization. *Int Endod J* 2012; 45(5):439–48. [CrossRef]
- Bachoo IK, Seymour D, Brunton P. A biocompatible and bioactive replacement for dentine: is this a reality? The properties and uses of a novel calcium-based cement. *Br Dent J* 2013; 214(2):E5. [CrossRef]
- Dube K, Jain P, Rai A, Paul B. Preventive endodontics by direct pulp capping with restorative dentin substitute-biodentine: A series of fifteen cases. *Indian J Dent Res* 2018; 29(3):268–74. [CrossRef]
- Awawdeh L, Al-Qudah A, Hamouri H, Chakra RJ. Outcomes of Vital Pulp Therapy Using Mineral Trioxide Aggregate or Biodentine: A Prospective Randomized Clinical Trial. *J Endod* 2018; 44(11):1603–9. [CrossRef]
- Shi S, Bao ZF, Liu Y, Zhang DD, Chen X, Jiang LM, et al. Comparison of in vivo dental pulp responses to capping with iRoot BP Plus and mineral trioxide aggregate. *Int Endod J* 2016; 49(2):154–60. [CrossRef]
- Elshamy FM, Singh G, Elraih H, Gupta I, Idris FA. Antibacterial Effect of New Bioceramic Pulp Capping Material on the Main Cariogenic Bacteria. *J Contemp Dent Pract* 2016; 17(5):349–53. [CrossRef]

52. Liu S, Wang S, Dong Y. Evaluation of a bioceramic as a pulp capping agent in vitro and in vivo. *J Endod* 2015; 41(5):652–7. [\[CrossRef\]](#)
53. Zhang S, Yang X, Fan M. BioAggregate and iRoot BP Plus optimize the proliferation and mineralization ability of human dental pulp cells. *Int Endod J* 2013; 46(10):923–9. [\[CrossRef\]](#)
54. Machado J, Johnson JD, Paranjpe A. The Effects of Endosequence Root Repair Material on Differentiation of Dental Pulp Cells. *J Endod* 2016; 42(1):101–5. [\[CrossRef\]](#)
55. Trope M. Regenerative potential of dental pulp. *Pediatr Dent* 2008; 30(3):206–10. [\[CrossRef\]](#)
56. Moussa DG, Aparicio C. Present and future of tissue engineering scaffolds for dentin-pulp complex regeneration. *J Tissue Eng Regen Med* 2019; 13(1):58–75. [\[CrossRef\]](#)
57. Chang B, Ahuja N, Ma C, Liu X. Injectable scaffolds: Preparation and application in dental and craniofacial regeneration. *Mater Sci Eng R Rep* 2017; 111:1–26. [\[CrossRef\]](#)
58. Fujiwara S, Kumabe S, Iwai Y. Isolated rat dental pulp cell culture and transplantation with an alginate scaffold. *Okajimas Folia Anat Jpn* 2006; 83(1):15–24. [\[CrossRef\]](#)
59. Galois L, Hutasse S, Cortial D, Rousseau CF, Grossin L, Ronziere MC, et al. Bovine chondrocyte behaviour in three-dimensional type I collagen gel in terms of gel contraction, proliferation and gene expression. *Biomaterials* 2006; 27(1):79–90. [\[CrossRef\]](#)
60. Issa MM, Köping-Höggård M, Artursson P. Chitosan and the mucosal delivery of biotechnology drugs. *Drug Discov Today Technol* 2005; 2(1):1–6.
61. Feng X, Lu X, Huang D, Xing J, Feng G, Jin G, et al. 3D porous chitosan scaffolds suit survival and neural differentiation of dental pulp stem cells. *Cell Mol Neurobiol* 2014; 34(6):859–70. [\[CrossRef\]](#)
62. Kim SE, Park JH, Cho YW, Chung H, Jeong SY, Lee EB, et al. Porous chitosan scaffold containing microspheres loaded with transforming growth factor-beta1: implications for cartilage tissue engineering. *J Control Release* 2003; 91(3):365–74. [\[CrossRef\]](#)
63. Lee KY, Mooney DJ. Hydrogels for tissue engineering. *Chem Rev* 2001; 101(7):1869–79. [\[CrossRef\]](#)
64. Ouasti S, Donno R, Cellesi F, Sherratt MJ, Terenghi G, Tirelli N. Network connectivity, mechanical properties and cell adhesion for hyaluronic acid/PEG hydrogels. *Biomaterials* 2011; 32(27):6456–70. [\[CrossRef\]](#)
65. Gutowska A, Jeong B, Jasionowski M. Injectable gels for tissue engineering. *Anat Rec* 2001; 263:342–9. [\[CrossRef\]](#)
66. Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix elasticity directs stem cell lineage specification. *Cell* 2006; 126(4):677–89. [\[CrossRef\]](#)
67. Xu X, Jha AK, Duncan RL, Jia X. Heparin-decorated, hyaluronic acid-based hydrogel particles for the controlled release of bone morphogenetic protein 2. *Acta Biomater* 2011; 7(8):3050–9. [\[CrossRef\]](#)
68. Prescott RS, Alsanea R, Fayad MI, Johnson BR, Wenckus CS, Hao J, et al. In vivo generation of dental pulp-like tissue by using dental pulp stem cells, a collagen scaffold, and dentin matrix protein 1 after subcutaneous transplantation in mice. *J Endod* 2008; 34(4):421–6. [\[CrossRef\]](#)
69. Alsanea R, Ravindran S, Fayad MI, Johnson BR, Wenckus CS, Hao J, et al. Biomimetic approach to perforation repair using dental pulp stem cells and dentin matrix protein 1. *J Endod* 2011; 37(8):1092–7. [\[CrossRef\]](#)
70. Yu J, Zhao W, Lu J, Hao Y, Lv C, Cao C, et al. Platelet-rich brin as a scaffold in combination with either deciduous or permanent dental pulp cells for bone tissue engineering. *Int J Clin Exp Med* 2016; 9(8):15177–84.
71. Qian Y, Han Q, Chen W, Song J, Zhao X, Ouyang Y, et al. Platelet-Rich Plasma Derived Growth Factors Contribute to Stem Cell Differentiation in Musculoskeletal Regeneration. *Frontiers in Chemistry* 2017; 5:89.
72. Huang FM, Yang SF, Zhao JH, Chang YC. Platelet-rich fibrin increases proliferation and differentiation of human dental pulp cells. *J Endod* 2010; 36(10):1628–32. [\[CrossRef\]](#)
73. Sharma S, Mittal N. A comparative evaluation of natural and artificial scaffolds in regenerative endodontics: A clinical study. *Saudi Endod J* 2016; 6(1):9–15. [\[CrossRef\]](#)
74. Tabatabayi MH, Tavakoli A, Ameghani BA. Regenerative property of PRF used as capping material in pulpotomy in dogs. *Biomedical Research* 2017; 28(10):4634–9.
75. Collier JH, Segura T. Evolving the use of peptides as components of biomaterials. *Biomaterials* 2011; 32(18):4198–204. [\[CrossRef\]](#)
76. Yoshimi R, Yamada Y, Ito K, Nakamura S, Abe A, Nagasaka T, et al. Self-assembling peptide nanofiber scaffolds, platelet-rich plasma, and mesenchymal stem cells for injectable bone regeneration with tissue engineering. *J Craniofac Surg* 2009; 20(5):1523–30. [\[CrossRef\]](#)
77. Cavalcanti BN, Zeitlin BD, Nör JE. A hydrogel scaffold that maintains viability and supports differentiation of dental pulp stem cells. *Dent Clin North Am* 2013; 29(1):97–102. [\[CrossRef\]](#)
78. Saber SE. Tissue engineering in endodontics. *J Oral Sci* 2009; 51(4):495–507. [\[CrossRef\]](#)
79. Sedgley CM, Cherkas P, Chogle SMA, Geisler TM, Hargreaves KM, Paranjpe AK, Yamagishi VT-K. *Endodontics: colleagues for excellence*, vol. Spring. Chicago: American Association of Endodontists Foundation; 2013. Regenerative endodontics.
80. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev* 2003; 83(3):835–70. [\[CrossRef\]](#)
81. Marie PJ. Fibroblast growth factor signaling controlling bone formation: an update. *Gene* 2012; 498(1):1–4. [\[CrossRef\]](#)
82. Nakao K, Itoh M, Tomita Y, Tomooka Y, Tsuji T. FGF-2 potently induces both proliferation and DSP expression in collagen type I gel cultures of adult incisor immature pulp cells. *Biochem Biophys Res Commun* 2004; 325(3):1052–9. [\[CrossRef\]](#)
83. Alenzi FQ, Alenazi FA, Al-Kaabi Y, Salem ML. The use of growth factors to modulate the activities of antigen-specific CD8+ T cells in vitro. *J Med Life* 2011; 4(4):399–406.
84. Roy H, Bhardwaj S, Ylä-Herttua S. Biology of vascular endothelial growth factors. *FEBS Lett* 2006; 580(12):2879–87. [\[CrossRef\]](#)
85. Janebodin K, Horst OV, Osathanon T. Dental pulp responses to pulp capping materials and bioactive molecules. *CU Dent J* 2010; 33:229–48.
86. Lovschall H, Fejerskov O, Flyvbjerg A. Pulp-capping with recombinant human insulin-like growth factor I (rhIGF-I) in rat molars. *Adv Dent Res* 2001; 15:108–12. [\[CrossRef\]](#)
87. Dobie K, Smith G, Sloan AJ, Smith AJ. Effects of alginate hydrogels and TGF-beta 1 on human dental pulp repair in vitro. *Connect Tissue Res* 2002; 43(2-3):387–90. [\[CrossRef\]](#)
88. Jayalakshmi KB, Agarwal S, Singh MP, Vishwanath BT, Krishna A, Agrawal R. Platelet-Rich Fibrin with β -Tricalcium Phosphate-A Novel Approach for Bone Augmentation in Chronic Periapical Lesion: A Case Report. *Case Rep Dent* 2012; 2012:902858. [\[CrossRef\]](#)
89. Liu CH, Huang TH, Hung CJ, Lai WY, Kao CT, Shie MY. The synergistic effects of fibroblast growth factor-2 and mineral trioxide aggregate on an osteogenic accelerator in vitro. *Int Endod J* 2014; 47(9):843–53. [\[CrossRef\]](#)
90. Yun HM, Chang SW, Park KR, Herr L, Kim EC. Combined Effects of Growth Hormone and Mineral Trioxide Aggregate on Growth, Differentiation, and Angiogenesis in Human Dental Pulp Cells. *J Endod* 2016; 42(2):269–75. [\[CrossRef\]](#)