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REVIEW ARTICLE

Healing process of Pulp Regeneration using Bioactive Materials: a review

Masoumeh Hassani Tabatabayi [1], Bahareh Aghamohammadi Ameghani [2*], Azin Tavakoli [3]
1- Associate Professor of Restorative department, Dental School of Tehran University of Medical Sciences
2- Resident of Restorative department, Dental School of Tehran University of Medical Sciences
3- Associate Professor of Surgical department of Veterinary Medicine, Islamic Azad University, Garmsar, Iran
* Corresponding author: Bahareh Aghamohammadi Ameghani

ABSTRACT
Vital pulp therapy includes direct and indirect pulp-cap- ping, pulpotomy and therapy that minimize pulpal injury by protecting the pulp from the toxic effects of chemical, bacterial, mechanical or thermal insult. Therefore, vital pulp therapy is aimed at treating reversible pulpal injures by sealing the pulp and stimulating the formation of tertiary dentinal formation. A number of materials have historically been used for retrograde fillings and perforation repair, such as amalgam, zinc-oxide-eugenol cements, composite resin, and glass-ionomer cements. Unfortunately, none of these materials have been able to satisfy the total requirements of an ideal material. Because of wide range of interest for natural materials, this paper attempts to review the healing process of pulp regeneration using bioactive materials. So, this review article attempts to define current, predictable patterns of fracture and managements based on patient. An electronic search has been conducted, during 2016, via PubMed and Medline database English literature.
Keywords: *MTA, PRF, Healing process, Pulp regeneration*

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INTRODUCTION

The vitality of the dentine-pulp complex is fundamental to the health of tooth and is a priority for targeting clinical management strategies. Preserving the pulp is important in the treatment of carious exposures in young permanent teeth or in the complex root canal systems of primary molars [37]. Exposures may result from caries, iatrogenic mishaps or traumatic injuries [10]. Several case series have suggested pulpotomy as a viable treatment for pulp exposures with pulpitis; the rationale being the healing potential of the remaining radicular tissue and the biocompatibility of pulpotomy agents [31]. Understandably, this material should demonstrate the ability to form a seal with dental tissues while also exhibiting biocompatible behavior with the tissues [31, 29]. A number of materials have historically been used for retrograde fillings and perforation repair, such as amalgam, zinc-oxide-eugenol cements, composite resin, and glass-ionomer cements. Unfortunately, none of these materials have been able to satisfy the total requirements of an ideal material [5]. The emergence of regenerative medicine has prompted of dental pulp and dentin regeneration. It was considered that pulp/dentin regeneration is preferable to pulpectomy/gutta-percha obturation from the perspective of preserving tooth longevity [7]. This review article attempts to define current, predictable patterns of fracture and managements based on patient. An electronic search has been conducted, during 2016, via PubMed and Medline database English literature. Peer-reviewed articles were targeted following key-words have been used: "MTA", "PRF", "Healing process", "Pulp regeneration". Available full-text articles were read. Related articles were also scrutinized. Hand search was also driven.

MATERIAL AND METHODS

The keywords used for the literature search for this review was peer-reviewed articles following key-words: MTA × PRF × healing process × pulp regeneration. Available full-text articles were read. Related articles were also scrutinized. Hand search was also driven. The search was carried out using Biological Abstracts, Chemical Abstracts, and the data bank of the PubMed and Medline database updated to 2016. The references found in the search were then studied in detail.

WHAT IS THE MTA?

Mineral trioxide aggregate (MTA) is a biomaterial that has been investigated for endodontic applications since the early1990s [48]. MTA was first described in the dental scientific literature in 1993 and was given approval for endodontic use by the U.S. Food and Drug Administration in 1998 [31]. As it will soon follow, MTA materials are derived from a Portland cement parent compound: it is interesting that no information has been published regarding to any investigations that led to the precise delineation of the present MTA materials [46]. Because existing materials did not have these ''ideal'' characteristics, MTA was developed and recommended for pulp capping, pulpotomy, apical barrier formation in teeth with necrotic pulps and open apexes, repair of root perforations, root-end filling, and root canal filling [17].

The MTA materials are a mixture of a refined Portland cement and bismuth oxide, and are reported to contain trace amounts of SiO_2, CaO, MgO, K_2SO_4, and Na_2SO_4 [22]. The major component, Portland cement, is a mixture of dicalcium silicate, tricalcium silicate, tricalcium aluminate, gypsum, and tetracalcium aluminoferrite [43]. Gypsum is an important determinant of setting time, as is tetracalcium aluminoferrate, although to a lesser extent. MTA products may contain approximately half the gypsum content of Portland cement, as well as smaller amounts of aluminum species, which provides a longer working time than Portland cement [14]. The MTA materials have been reported to solidify similar to other mineral cements, in which the anhydrous material dissolves, followed by the crystallization of hydrates in an interlocking mass [6]. The basic framework of the hydrated mass is formed by the interlocking of cubic and needle-like crystals in which the needle-like crystals form in sharply delineated thick bundles that fill the inter-grain space between the cubic crystals [9]. The effect of mixing MTA powder with different liquids and additives has shown that the choice of preparation liquid can have an effect on setting time and compressive strength [42]. Up to 2002, only one MTA material consisting of gray colored powder was available, and in that year white mineral trioxide aggregate (WMTA) was introduced as ProRoot MTA (Dentsply Endodontics, Tulsa, OK, USA) to address esthetic concerns [22]. After that time, two forms of MTA materials were categorized: the traditional gray MTA (GMTA) and WMTA. Scanning electron microscopy (SEM) and electron probe microanalysis characterized the differences between GMTA and WMTA and found that the major difference between GMTA and WMTA is in the concentrations of Al2O3, MgO, and FeO [21].

WHAT IS THE PLATELET-RICH FIBRIN?

In transfusion medicine, platelet concentrates were originally used for the treatment and prevention of haemorrhage due to severe thrombopenia, which is often caused by medullar aplasia, acute leukaemia or significant blood loss during long-lasting surgery. The standard platelet concentrate for transfusion has been named platelet-rich plasma (PRP) and classically contains 0.5×10^{11} platelets per unit [4]. The use of blood-derived products to seal wounds and stimulate healing started with the use of fibrin glues, which were first described 40 years ago and are constituted of concentrated fibrinogen (polymerization induced by thrombin and calcium) [36].

Platelet-rich fibrin (PRF) described by Choukroun *et al*. [11] is a second generation platelet concentrate which allows one to obtain fibrin membranes enriched with platelets and growth factors, after starting from an anticoagulant-free blood harvest without any artificial biochemical modification. The PRF clot forms a strong natural fibrin matrix, which concentrates almost all the platelets and growth factors of the blood harvest [16] and shows a complex architecture as a healing matrix, including mechanical properties no other platelet concentrate offers. The PRF can be considered as a natural fibrin-based biomaterial favorable to the development of a micro vascularization and able to guide cell migration into wound area. Its chief advantages include ease of preparation and lack of biochemical handling of blood, which makes this preparation strictly autologous [1].

MECHANISM OF ACTION OF MTA

The setting mechanism of WMTA has been examined using X-ray photoelectron spectroscopy that reported surface sulfur and potassium species increase 3-fold during the setting reaction. This suggested that MTA material setting time could be prolonged by the formation of a passivating trisulfate species

layer, which may serve to prevent further hydration and reaction [13]. This trisulfate species may serve a protective function, as it was reported that that WMTA flexural strength was significantly reduced when 2-mm thick layers were exposed to sterile saline moisture for more than 24h [15]. Calcium release from MTA materials diminishes slightly with time while MTA materials were reported to form a porous matrix characterized by internal capillaries and water channels in which increased liquid/powder ratio produced more porosity and increased solubility [14]. The GMTA solubility levels have been reported to be stable over time, but the usually reported pH of between 11 or 12 may slightly decrease [16]. The high pH level of MTA materials has led some to theorize that the biologic activity is due to the formation of calcium hydroxide. WMTA solubility, hardness, and radiopacity has been compared to two Portland cements reporting that WMTA was significantly less soluble, exhibited greater Vickers hardness, and was more radiopaque [18].

MECHANISM OF ACTION OF PRP

PRP works via the degranulation of the alpha granules in platelets, which contain the synthesized and pre-packed growth factors. The growth factors which are released from activated platelets were:

1. Platelet derived growth factor (PDGF)
2. Transforming growth factors β 1 and β 2 (TGF β 1& 2)
3. Vascular Endothelial Growth Factor (VEGF)
4. Platelet derived endothelial cell growth factor
5. Interleukin – 1 (IL-1)
6. Basic fibroblast growth factor (βFGF)
7. Platelet activating factor -4 (PAF-4)

The active secretion of these growth factors is initiated by the clotting process of blood and begins within 10 minutes after clotting. More than 95% of the presynthesized growth factors are secreted within 1 hour. Therefore, PRP must be developed in an anti-coagulated state and should be used on the graft, flap, or wound, within 10 minutes of clot initiation [34]. The secreted growth factors immediately bind to the external surface of cell membranes of cells in the graft, flap, or wound via transmembrane receptors. These transmembrane receptors in turn induce an activation of an endogenous internal signal protein, which causes the expression of (unlocks) a normal gene sequence of the cell such as cellular proliferation, matrix formation, osteoid production, collagen synthesis etc. thus PRP growth factors act through the stimulation of normal healing, just much faster [33].

PRF is in the form of a platelet gel and can be used in conjunction with bone grafts, which offers several advantages including promoting wound healing, bone growth and maturation, graft stabilization, wound sealing and hemostasis, and improving the handling properties of graft materials. PRF can also be used as a membrane. Clinical trials suggest that the combination of bone grafts and growth factors contained in PRP and PRF may be suitable to enhance bone density [12]. In an experimental trial, the growth factor content in PRP and PRF aliquots was measured using Elisa kits. The results suggest that the growth factor content (PDGF and TGF-β) was comparable in both. Another experimental study used osteoblast cell cultures to investigate the influence of PRP and PRF on proliferation and differentiation of osteoblasts. PRF has many advantages over PRP [27]. It eliminates the redundant process of adding anticoagulant as well as the need to neutralize it. The addition of bovine-derived thrombin to promote conversion of fibrinogen to fibrin in PRP is also eliminated. The conversion of fibrinogen into fibrin takes place slowly with small quantities of physiologically available thrombin present in the blood sample itself. Thus, a physiologic architecture that is very favorable to the healing process is obtained due to this slow polymerization process [20].

PULP REGENERATION BY PRF AND MTA

Enamel extracellular matrix has been related to important biologic functions in tooth development and successfully used in dentistry in the form of enamel matrix derivative (EMD) to incite natural cementogenesis to restore a fully functional periodontal ligament, cementum and alveolar bone in the treatment of intra bony defects in patients with severe and advanced periodontitis, through regeneration of the affected tissues [31]. Therefore, it is important to develop biocompatible treatments directed at maintaining pulp vitality and increasing tooth longevity. To increase the success rate, a critical need exists to develop new biologically based therapeutics that reduce pulp inflammation and promote the formation of dentine pulp tissues [49]. However, it was shown that the newly grown tissues into the root canal space have little similarity to normal pulp tissue but with more resemblance to cementum, periodontal ligament, or bone. The cause of this outcome is possibly related to the lack of stem cells derived from remaining vital pulp and apical papilla, which are destroyed by severe endodontic infection. Stem cells

responsible for newly regenerated tissues might be derived from several other sources, including systemic blood, local tissue such as bone [31]. Furthermore, whether these newly formed tissues can function like normal pulp and stabilize the tooth without giving rise to further infection or canal obliteration still. Iohara *et al* [25], they also found that transplantation of unfractionated total pulp cells into root canal showed less tissue formation followed by evidence of mineralization on day 90 compared with transplantation of $CD10^{5+}$ pulp cells and stromal cell–derived factor-1. Although DPSCs are the most direct cell source in dental pulp regeneration, a number of other cell sources including SCAPs\and bone marrow mesenchymal stem cells may also contribute to dental pulp regeneration [3]. This may be another reason why the transplantation of autologous DPSCs alone did not help dental pulp regeneration in the present study. Further studies are needed to identify the cell sources of the tissues formed in the canal space (ie, from periapical tissues or from the transplanted DPSCs). Growth factors and a suitable scaffold are also essential considerations in tissue regeneration. PRP contains several growth factors including transforming growth factor beta 1, platelet-derived growth factor, fibroblast growth factor, vascular endothelial growth factor, and epidermal growth factor that support cell growth [24].

The descriptions of various bioactive molecules including growth factors lead to exciting alternative treatments of dentin-pulp complex. The usage of growth factors alone in regenerative treatment approaches tried to be developed imitating the physiological events of the body has been questioned [38]. Newly formed tissues in the canals could extend to the surface of MTA in some cases or occupy half of the canal space after 3 months. The growth of the tissue into the canal seemed not limited by the blood supply with an apical opening of 0.8 mm in diameter. When tissues engineered in the laboratory are implanted into the human body, only cells within 100–200 mm from the nearest capillary can attain sufficient diffusion of nutrients to survive. Thus, it was suggested that a voluminous tissue be prevascularized for achieving immediate and sufficient blood supply after implantation [23]. MTA is a good material for pulp capping and apexification, which can induce dental pulp cell differentiation and the secretion of mineralized tissue [38]. Cells in new vital tissues in the apical canal were more immature with larger and deeply stained nuclei. These cells pertain more potential for multilineage differentiation. Cementum-like tissue was along the internal root canal walls. In some cases, cementum-like tissue inside the root canal was connected with root surface cementum. The source of stem cells responsible for bone-like and cementum-like tissues is not clear, possibly from the periapical tissues [23].

CASE REPORTS

Most direct pulp capping investigations have compared MTA with calcium hydroxide (CH). Two studies found the presence of a calcified bridge in many pulp specimens capped with MTA after 1 week [39], whereas several other studies demonstrated calcified bridge formation after 2 weeks in all or most specimens [2]. It is compared CH and MTA as pulp capping agents on monkeys' teeth. Their results showed that the majority of pulps that were capped with MTA were free of inflammation, and all of them showed calcified bridge formation after 5 months. In contrast, the pulp of teeth that were capped with CH showed presence of inflammation and significantly less calcified bridge formation. In an investigation on dogs' teeth, Faraco *et al* [19] used MTA or Dycal as pulp capping agents and reported tubular hard tissue formation with no pulp inflammation beneath any MTA sample. In contrast, the majority of Dycal-capped pulps showed presence of inflammation, and only one third of the specimens exhibited calcified bridge formation. On the basis of these results, the researchers concluded that pulp capping with MTA produces significantly better results than with Dycal. In a study with dogs' teeth, Tziafas *et al* [48] showed osteodentin structure 2 weeks after pulp capping with MTA. They reported that bridge formation occurs under MTA in 2 stages. During the first 2 weeks, osteodentin matrix formation takes place, whereas after 3 weeks, a complete layer of reparative dentin is formed at the capping site. In a prospective case series study on 276 teeth with WMTA as a root-end filling material, Saunders [44] reported 88.8% clinical and radiographic success after 4–72 months. He concluded that using careful microsurgical techniques combined with MTA as a root-end filling material results in high success rates for endodontic surgery.

In a case series study, Pace *et al* [37] reported successful outcomes in 10 of 11 teeth with necrotic pulps and open apexes after application of MTA as an apical barrier after 24 months. In a prospective radiographic examination of 43 teeth with necrotic pulps and open apices, Simon *et al* [46] used either WMTA or GMTA as apical barriers and reported 81% success for these cases. The investigators in this study did not perform clinical evaluations of the cases, and they did not identify the success rates for each type of MTA. In another case series study, Sarris *et al* [43] used MTA as an apical plug in 17 incisors and followed them for a mean time of 12.53 ± 2.94 months. Of these, 94.1% were assessed as being successful clinically, whereas 76.5% were reported to be successful radiographically.

Lecovic *et al*. [30] implanted PRP with a bone allograft in periodontal defects. The authors reported that the bone healing in the PRP group was not different from results achieved with the combination of the allograft and guided tissue regeneration. Kim *et al*. [27] reported the first PRP study in an animal model. Using a histomorphometric analysis the authors found a higher percentage of bone contact on the surface of the dental implant in a group of particulate dentin– plaster of Paris and PRP compared to the control group [8]. These reports suggest a positive clinical role of PRP in bone regeneration, but the experiments raise the question whether the good clinical results are primarily based on an improved osseous regeneration or more likely due to the formation of a fibrin gel and the stimulation of the surrounding connective tissue leading to a faster and improved healing of soft tissues, reducing the rate of wound dehiscence and local infections.

CONCLUSION

Dental pulp capping is a treatment of vital teeth in order to maintain the integrity, morphology and function of the pulp. Direct pulp capping treatment indicated for perforation of the pulp because trauma, caries or restoration procedures. Materials used for pulp capping are calcium hydroxide, zinc oxide eugenol and resin-based materials. The use of these materials has a high failure rate. developed a material contain growth factors, present in platelet rich plasma (PRP) is a platelet-derived growth factor (PDGF), research results that PDGF in vitro plays an important role in the regeneration odontoblast cells, the dentinogenesis and pulp tissue regeneration.

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