Chapter 6

REGENERATIVE ENDODONTIC TREATMENT

Faruk ÖZTEKİN[1]

Regenerative endodontic treatment involves biological replacement of damaged, diseased or incomplete dentin-pulp complex cells, as long as possible, by maintaining their physiological functions with living cells of the same origin. The potential of regenerative dentistry is highly dependent on advances in biological therapy, which benefit from growth and differentiation factors that stimulate or accelerate natural biological regeneration. For this purpose, tissue engineering was used [1].

TISSUE ENGINEERING

Tissue engineering includes biological treatment strategies that aim to regain damaged or partially lost tissue in terms of structure, function and physiology[2].

Regenerative endodontic treatment is based on 3 basic principles of tissue engineering[3]:

1. Appropriate sources of stem / progenitor cells
2. Growth factors that can promote stem cell differentiation
3. Scaffolding suitable for regulation of cell differentiation

STEM CELLS

Stem cell is a non-specialized cell that has the ability to divide on its own and differentiate into various tissue cells. The most important feature of stem cells is their ability to renew themselves [4].

[1] Assistant Professor, Department of Endodontics, Faculty of Dentistry, Firat University, Elazig, TURKEY. foztekin@firat.edu.tr. ORCID iD: 0000-0002-5131-0063

The use of stem cells for regenerative purposes has become widespread in recent years. These cells have a wide range of potential uses in cardiology, including myocardial infarction, spinal cord injuries, and burn treatment in plastic surgery. In dentistry, it is aimed to maintain regeneration by preserving mesenchymal stem cells and dental pulp stem cells of apical papilla, which are left behind by regenerative endodontic treatment application [5].

TISSUE SCAFFOLD

The tissue scaffold determines the shape of the tissue to be regenerated by creating a three-dimensional structure and micro environment that mimics the extracellular matrix [1]. Since pulp stem cells must be organized in a three-dimensional structure and supported by vascularization; The use of biological tissue scaffolds consisting of porous polymers is needed [2].

Since tissue scaffolds are imitation of the extracellular matrix, growth factors to help differentiate stem cells and proliferate; Nutrients for their nutrition and development should also contain antibiotics to prevent bacterial growth [6]. Tissue scaffolds should be able to selectively bind to cells, localize them and be resorbed [7].

There are three types of tissue scaffolding used. These are natural tissue scaffolds (collagen and glycosaminoglycan), synthetic tissue scaffolds (polylactic acid, polyglycolic acid, polylactic-co glycolic acid), mineral tissue scaffolds (hydroxyapatite and calcium phosphate). Natural tissue scaffolds are mostly used in regenerative endodontics [8].

GROWTH FACTORS

The third component of tissue engineering is growth factors. Growth factors affect the cellular activities of all dental pulp cells, including progenitor / stem cells, including migration, proliferation, differentiation and apoptosis [9]. It is accepted that many growth factors and extracellular matrix protein, which are usually expressed and secreted during primary and secondary dentinogenesis, play a role in dental repair and dentine regeneration [10].

NEW TISSUE FORMATION MECHANISM

Regenerative endodontics procedures are based entirely on cellular reactions. After the bleeding in the root canal, stem cells from the apical papilla act quickly [11]. These cells need to differentiate, multiply and produce dentin in order to regenerate the pulp tissue [12]. The formation of new tissues formed in the root apex and canal cavity has been tried to be explained with different mechanisms [13]. One of these is the possibility that the few pulp cells that remain alive at the apical end of the root canal form a new matrix and differentiate into odontoblasts that will allow the root to grow and thicken [14]. However, it is stated that stem cells or bone marrow in the apical papilla may also be effective in the root development mechanism. In addition, it is thought that stem cells originating from periodontal ligament and dental pulp stem cells may play a role in the root development [15].

With regenerative endodontic treatment, it is aimed to maintain revascularization of the remaining apical papilla by protecting mesenchymal stem cells and dental pulp stem cells [16]. Growth factors released from dentin can chemically attract stem cells in the periapical region or remaining healthy pulp tissue. After the cell selection, these cells settle, attach, multiply, differentiate and eventually form new tissue [17]. In studies, blood has been used as a tissue scaffold because it contains different growth factors that will help new tissues to grow [18]. The blood clot can provide differentiation and growth due to the growth factors it contains. It can also stimulate the maturation of fibroblasts, odontoblasts, and cementoblasts, and has an important role in regeneration [19]. Intracanal bleeding that can be used as a tissue scaffold or platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) taken from the patient its use is considered to have a positive effect on the outcome of regenerative endodontic therapy [20].

Advantages of Regenerative Endodontic Treatment

Regenerative Endodontic Treatment is an inexpensive biotechnology where current hand tools and drugs can be used. In addition, the technique of application of treatment is simpler than traditional methods. As the infection is under control, there is no need for re-sessions as in apexification with calcium hydroxide. As the tooth regains its vitality, root development continues and the lateral dentin walls are strengthened due to the new dentin / hard tissue accumulation [8].

Disadvantages of Regenerative Endodontic Treatment

The disadvantages of regenerative endodontic therapy are the case reports showing that the blood clot provides regeneration of the pulp tissue; the source of the regenerated tissue has not yet been determined [21].

Regenerative Endodontic Treatment Methods

Methods being developed in regenerative endodontics; Revascularization of the root canal, stem cell therapy, scaffold implant, pulp implant, injectable tissue scaffold applications, three-dimensional cell software and gene therapy [1].

Revascularization

The term revascularization is used to reconstitute vascularization in the pulp cavity after traumatic injury [22]. In this technique, regeneration of tissues such as dentin, cementum, periodontal ligament, bone, that is, the regeneration of pulp rather than vascularization in the canal cavity. Regeneration of the pulp restores the functional properties of the tooth while providing, immature continues root development in teeth, prevents the formation of apical periodontitis and eliminates the formed periodontitis [13]. In this method, it is aimed to completely disinfect the necrotic root canal and to create a fibrin matrix by forming a blood clot. The open end of the root of the immature tooth allows new tissues to form in the pulp chamber [23].

Stem Cell Therapy

The easiest way to obtain cells with regeneration potential in dentistry is to inject the stem cells into the canal after the apexes are opened and the root canal is disinfected. Adult stem cells can be obtained from various tissues such as skin, cheek mucosa, adipose and bone tissue [24].

The advantages of adult stem cell therapy are that the autogenous stem cells are easy to manufacture and administer and have the potential to stimulate new pulp regeneration. The disadvantages are that the cells survival time and rates are low. When it is desired to create a new and functional pulp tissue, it is not possible to achieve high success only by injecting stem cells into the pulp chamber without scaffolding and bioactive signal molecules [19].

Pulp Implantation

After the pulp tissue is prepared in laboratory conditions, transplanting it into a shaped and disinfected root canal system is called a pulp implantation method [19]. The pulp tissue reproduced in culture medium is grown in vitro in a biodegradable polymer nanofiber layer or into the root canal system on the extracellular matrix protein layer such as collagen-1 or fibronectin [25].

Tissue Scaffolds Implantation

Pulp stem cells should be supported with a three-dimensional structure that will support cell organization and blood supply. This can be achieved with a tissue scaffold with a porous polymer structure where pulp stem cells can be buried [26]. A suitable scaffold should ensure cell growth and differentiation, cell adhesion should be increased and should provide a three-dimensional physical, chemical and biological environment suitable for cell migration [19].

The content of the tissue scaffold; The growth factors that ensure the proliferation, differentiation and rapid tissue formation of the stem cell, the foods that ensure the survival and growth of the cell and antibiotics that prevent the growth of bacteria in the root canal. The tissue scaffold should be able to be resorbed by the surrounding tissues without requiring new surgical practice. It should have a high porosity and a sufficient pore width suitably to allow cell nutrition and diffusion [27].

Injectable Tissue Scaffolds

Since pulp, which is a tissue engineering product in root canal systems, does not require structural support, soft three-dimensional scaffolding matrices have been brought to the agenda. The most important example, hydrogel, is an injectable tissue scaffold applied by syringe [28]. Hydrogels; It is an injectable tissue scaffold that can be applied with a syringe, it is non-invasive and can be easily applied to the root canal system.

Three Dimensional Cell Smear

In this technique; Theoretically, a special device is used to reconstruct the pulp tissue and distribute the cell layers into the hydrogel, and then the resulting structure is surgically implanted. The advantage of this method is that different cells are located exactly in place. The three-dimensional cell spreading technique can fully mimic natural pulp tissue [19].

Gene Therapy

Gene therapy; is a treatment that defines gene transplantation for somatic cells to express growth factors, morphogens, transcription factors and extracellular matrix molecules [29]. The goal of gene therapy is to ensure that the body produces the substance it needs in a healthy way, rather than delivering the necessary chemical from outside the body [19]. As a result of studies, it has been found that gene therapy cannot progress as part of endodontic therapy and some unwanted health problems may occur during gene therapy [30].

IN-CANAL DRUGS USED IN REGENERATIVE ENDODONTIC TREATMENT

Calcium Hydroxide

Calcium hydroxide is a dental material used in many fields such as direct and indirect pulp coatings, amputation, root canal treatments, repair of iatrogenic root perforations, apexification, treatment of resorbations and root fractures. Successful results were obtained for many years with the use of this material presented to dentistry by Hermann in the 1920s [31].

Calcium hydroxide shows its main effect by decomposing to Ca + 2 and OH- ions. The high alkaline nature of calcium hydroxide is associated with its hydroxyl ions and their release into the medium, and these highly reactive free radicals form the basis of the bactericidal property of calcium hydroxide [32].

Calcium hydroxide; It is frequently used in endodontics due to its easy manipulation, alkaline pH, antibacterial effect and hence accelerating recovery [31]. In resorptive defects converts local environmental factors to ideal conditions for recovery [32]. It neutralizes acid products and activates alkaline phosphatase, contributing to hard tissue formation [33]. It is preferred for intra-canal disinfection due to its hydroscopic feature and anti-inflammatory effect [34].

Calcium hydroxide is ineffective in eliminating Enterococcus faecalis (E.faecalis), which is the most important bacterium in treatment resistant infections, although it is a commonly used canal because of its antimicrobial efficacy and biocompatibility feature against endodontic pathogens [31].

Antibiotic Pastes

Systemic antibiotic administration is based on patient compliance with dose regimens followed by absorption through the gastrointestinal tract and distribution through the circulatory system to bring the drug to the infected area. Therefore, the infected area needs a normal blood supply; this does not apply to teeth with necrotic pulp and teeth without pulp tissue. Therefore, local application of antibiotics in the root canal system may be a more effective method of drug delivery [35]. More effective concentrations are obtained than those found in the systemic circulation after oral administration with local antibiotic applications [36].

Metronidazole, which is an effective antibiotic for anaerobes, has been chosen as the intra-canal drug because it constitutes the compulsory anaerobes as the majority of bacteria infecting the root canal system. In teeth with periradicular infection, metronidazole alone cannot eliminate all bacteria due to the variety of bacteria in the root canals. Therefore, it is used in combination with ciprofloxacin and minocycline [37]. Due to the color change caused by minocycline in teeth, some authors recommend modifying this antibiotic and using cefaclor instead of TAP or eliminating minocycline [14].

Disadvantages of antibiotic pastes used inside the canal, such as color change, cytotoxicity, sensitization, development of resistance and difficulty in removing from the root canal should be taken into account . In order to eliminate or reduce these disadvantages, it has been proposed to use antibiotic pastes at lower concentrations [38].

CALCIUM SILICATE BASED CEMENTS USED IN REGENERATIVE ENDODONTIC TREATMENT

Mineral Trioxide Aggregate (MTA)

MTA was first described by Lee, Monsef and Torabinejad in 1993 [39]. It was stated that MTA has a good sealing property, offers an excellent prognosis in the long term, is relatively easy to manipulate and promotes tissue regeneration as well as high biocompatibility [40].

Chemical Composition

MTA consists of tricalcium silicate, tricalcium aluminate, tricalcium oxide, silicate oxide and bismuth oxide [41]. The most important structural difference with Portland cement is that it does not contain potassium and its structure contains bismuth oxide [40]. Bismuth oxide was added to the material to improve its structural properties and provide radiopacity.

Tulsa Dental (Dentsply, USA) launched the white MTA preparations on the market in 2002, since the first MTA was gray in color, causing unwanted color changes in the front teeth. White and gray MTA differ in iron, aluminum and magnesium oxide contents [40].

The desired consistency of MTA is achieved by mixing 3 parts of powder and 1 part of liquid. Mixing can be done on paper or glass with a metal or plastic spatula. Adding more or less water during its preparation causes a decrease in the final hardness of the material. After the mixture, the MTA carrier is placed in the desired place and condensed with a moist cotton pellet. Since irrigation after MTA placement may cause material to flow away, all irrigation procedures must be completed before MTA placement [42].

Clinical Use and Physical Properties

Due to its properties such as biocompatibility and bacterial sealing, MTA is seen as an ideal material for the protection, repair and maintenance of pulp and therefore it is used in many dental treatments in pediatric dentistry.

Clinical uses of MTA [42];

- As a pulp coating material,
- As an amputation material,
- As repair material for the repair of furcation and root perforations,
- In the treatment of apexification, in order to ensure apical occlusion,
- Repairing the resorption zones in the root,
- As retrograde filler
- As repair material in root fractures

Physical properties of MTA;

1) Compressive Strength: MTA shows the lowest resistance to compressive forces in the first 24 hours compared to amalgam, IRM (Intermediate Restorative Material) and Super-EBA. However, after 21 days, the pressure was reported to increase to 67.3 megapascals (MPa), and its resistance was comparable to IRM and Super-EBA, but significantly lower than amalgam [40].
2) Radiopacity: The average radiopacity for MTA is reported to be equivalent to 7.17 mm thick aluminum. Although this value is lower than IRM, Super EBA, amalgam and gutta percha, it is sufficient to be easily seen radiographically [43].
3) Marginal Adaptation and Sealing Ability: This feature is critical in retrograde filling, perforation repair, pulp coating and pulpotomy procedures. Bates et al. [44] found MTA more successful than other retrograde filling materials. Expansion of MTA during hardening may be the reason for its excellent sealing property [45].
4) Solubility: Fridland et al. [46] It was stated that as the powder / water ratio changes, its solubility changes, and the high powder / water ratio increases the smoothness and solubility of MTA. In addition, bismuth oxide added to MTA has been reported to decrease the solubility of MTA [40].
5) Biocompatibility: In Torabinejad and Kettering's [47](135) studies, it was found that MTA is not mutagenic and is very low cytotoxic compared to Super-EBA and IRM. MTA does not cause an inflammatory reaction in direct contact or causes minimal infection. It also has the effect of inducing tissue regeneration [48].
6) Tissue Regeneration: MTA provides regeneration in periodontal tissues and has osteoconductive and osteoinductive properties, thereby inducing the formation of dentin, cement, and hard tissue [40].

7) Antibacterial and antifungal properties: Contrary results were obtained from the studies on the antibacterial properties of MTA. These contradictory results are thought to depend on the type of MTA used and the powder / liquid ratio of MTA. It can be considered a good antibacterial agent, especially against E.faecalis and Streptococcus sanguis, thanks to its good sealing properties and preventing microleakage. In some studies, it has been reported that MTA has an antibacterial effect on some facultative bacteria while it is not effective on anaerobes [40].

Disadvantages of MTA

The biggest disadvantages of MTA are the long hardening time, the difficulty of application, the powder / liquid ratio being adjusted manually, the same ratio cannot be obtained every time, the potential of coloration especially in the front teeth, the presence of toxic elements in its component, the high cost and the difficult to disassemble after insertion. In addition, the necessity of placing damp cotton after the use of MTA prevents the use of a single session [40]. One of the disadvantages is poor chemical bonding to dentine [49].

Biodentine

Biodentine is a calcium silicate based material produced in 2009 with the slogan ‘instead of dentin [50].

Composition and Hardening Reaction

Biodentine powder part consists of tricalcium silicate (main component), calcium carbonate (filler), zirconium oxide (radiopacity provider), dicalcium silicate, calcium oxide, iron oxide. The liquid part consists of a water-soluble polymer (water reducing agent) and calcium chloride. Although tricalcium silicate is a common substance in both MTA and Biodentine, it consists of the monoclinical form of MTA and triclinic form of Biodentine [51]. The hardening time of Biodentine is 12 minutes and thus, it provides restoration and becomes intraorally functional in a single session. This allows for use in pediatric dentistry.

Physical and Mechanical Properties

Compressive strength is considered as one of the main physical properties of calcium silicate based cements.Biodentine-like products have a wide range of uses in vital pulp treatments. Accordingly, it is essential that it has a sufficient compressive strength against external forces [52]. Compared to other tricalcium silicate cements, Biodentine's higher compressive strength is attributed to the low water / cement ratio provided by the water-soluble polymer in the liquid part. Such as Biodentine's bending strength (34 MPa), elastic modulus (22,000 MPa) and Vickers hardness (60 HV) its physical properties are higher than MTA but show similar values to dentin. It has an inhibitory effect on Biodentine microorganisms with its high alkaline pH. In addition to alkaline pH, it provides disinfection in the area surrounding hard and soft tissues [53].

Biodentine maintains the vitality of the pulp and promotes the healing process. The effect of Biodentine on activation, differentiation and dentin regeneration of projection cells and Biodentine has been found to provide dentin regeneration by differentiating the progenitor cells to odontoblasts [53].

The micromechanical adhesion of Biodentine is caused by the alkaline effect during the hardening reaction. High pH leads to dissolution of organic tissues outside the dentinal tubules. The alkaline area between Biodentine and dental hard tissue creates an environment where Biodentine can enter the exposed dentin tubules. Thus, with the connection formed with countless tubules, a magnificent sealing is provided [50].

Clinical Use

Biodentine is a calcium silicate based material, and it draws great attention with its similarity to MTA and its applicability in cases where MTA is indicated. Biodentine endodontically root perforations, apexification, resorptive lesions and endodontic surgery; It is also a material that can be used as a retrograde filling material in addition to dentin in pulp coating [50].

Endosequence Root Repair Material (ERRM)

In order to overcome the disadvantages of MTA, new calcium silicate based cements have been introduced with similar basic components and biological effects [54]. ERRM (Brassaler, Savannah, USA) is a bioceramic material with paste and injector paste forms that are produced ready-to-use and do not need mixing. It can be used in root perforation repair, regenerative treatments, retrograde fillings [55].

According to the manufacturer, it consists of calcium silicate, monobasic calcium phosphate, zirconium oxide, tantalum oxide, propylene fillers and thickeners. High alkaline pH is partly responsible for its antibacterial property. Bioceramics refer to the combination of calcium silicate and calcium phosphate, valid for biomedical or dental use [56].The pH of the bioceramic materials during placement reaches 12.8. ERRM has a strength of 70-90 MPa. The material also has excellent radio opacity [55].

REFERENCES

1. Cvek M. Prognosis of luxated non-vital maxillary incisors treated with calcium hydroxide and filled with gutta-percha. A retrospective clinical study. Endod Dent Traumatol. 1992;8(2):45-55.
2. Diogenes A, Henry MA, Teixeira FB, et al. An update on clinical regenerative endodontics. Endodontic Topics. 2013;28(1):2-23.
3. Jeeruphan T, Jantarat J, Yanpiset K, et al. Mahidol study 1: comparison of radiographic and survival outcomes of immature teeth treated with either regenerative endodontic or apexification methods: a retrospective study. J Endod. 2012;38(10):1330-6.
4. Andreasen JO, Farik B, Munksgaard EC. Long-term calcium hydroxide as a root canal dressing may increase risk of root fracture. Dent Traumatol. 2002;18(3):134-7.
5. Galler KM. Clinical procedures for revitalization: current knowledge and considerations. Int Endod J. 2016;49(10):926-36.
6. Fouad AF, Verma P. Healing after regenerative procedures with and without pulpal infection. J Endod. 2014;40(4 Suppl):S58-64.

7. Hoshino E, Kurihara-Ando N, Sato I, et al. In-vitro antibacterial susceptibility of bacteria taken from infected root dentine to a mixture of ciprofloxacin, metronidazole and minocycline. Int Endod J. 1996;29(2):125-30.
8. Petrino JA, Boda KK, Shambarger S, et al. Challenges in regenerative endodontics: a case series. J Endod. 2010;36(3):536-41.
9. Thomson A, Kahler B. Regenerative endodontics--biologically-based treatment for immature permanent teeth: a case report and review of the literature. Aust Dent J. 2010;55(4):446-52.
10. Topçuoğlu HS, Arslan H, Akçay M, et al. The effect of medicaments used in endodontic regeneration technique on the dislocation resistance of mineral trioxide aggregate to root canal dentin. J Endod. 2014;40(12):2041-4.
11. Nagas E, Cehreli ZC, Uyanik MO, et al. Effect of several intracanal medicaments on the push-out bond strength of ProRoot MTA and Biodentine. Int Endod J. 2016;49(2):184-8.
12. Pinkham J. Çocuk diş hekimliği: bebeklikten ergenliğe: Atlas Kitapçılık; 2009.
13. Fuks AB. Pulp therapy for the primary and young permanent dentitions. Dent Clin North Am. 2000;44(3):571-96, vii.
14. Chen X, Bao ZF, Liu Y, et al. Regenerative endodontic treatment of an immature permanent tooth at an early stage of root development: a case report. J Endod. 2013;39(5):719-22.
15. Flanagan TA. What can cause the pulps of immature, permanent teeth with open apices to become necrotic and what treatment options are available for these teeth. Aust Endod J. 2014;40(3):95-100.
16. Andreasen JO, Ravn JJ. Epidemiology of traumatic dental injuries to primary and permanent teeth in a Danish population sample. Int J Oral Surg. 1972;1(5):235-9.
17. Hargreaves KM, Diogenes A, Teixeira FB. Treatment options: biological basis of regenerative endodontic procedures. J Endod. 2013;39(3 Suppl):S30-43.
18. Sharma A. Dens evaginatus of anterior teeth (talon cusp) associated with other odontogenic anomalies. J Indian Soc Pedod Prev Dent. 2006;24 Suppl 1:S41-3.
19. 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.
20. Atala A. Tissue engineering, stem cells and cloning: current concepts and changing trends. Expert Opin Biol Ther. 2005;5(7):879-92.
21. Brivanlou AH, Gage FH, Jaenisch R, et al. Stem cells. Setting standards for human embryonic stem cells. Science. 2003;300(5621):913-6.
22. Tsukamoto Y, Fukutani S, Shin-Ike T, et al. Mineralized nodule formation by cultures of human dental pulp-derived fibroblasts. Arch Oral Biol. 1992;37(12):1045-55.
23. Buchaille R, Couble ML, Magloire H, et al. A substractive PCR-based cDNA library from human odontoblast cells: identification of novel genes expressed in tooth forming cells. Matrix Biol. 2000;19(5):421-30.

24. Kindler V. Postnatal stem cell survival: does the niche, a rare harbor where to resist the ebb tide of differentiation, also provide lineage-specific instructions? J Leukoc Biol. 2005;78(4):836-44.
25. Venugopal J, Ramakrishna S. Applications of polymer nanofibers in biomedicine and biotechnology. Appl Biochem Biotechnol. 2005;125(3):147-58.
26. Nakashima M, Akamine A. The application of tissue engineering to regeneration of pulp and dentin in endodontics. J Endod. 2005;31(10):711-8.
27. Sachlos E, Czernuszka JT. Making tissue engineering scaffolds work. Review: the application of solid freeform fabrication technology to the production of tissue engineering scaffolds. Eur Cell Mater. 2003;5:29-39; discussion -40.
28. Taylor MS, Daniels AU, Andriano KP, et al. Six bioabsorbable polymers: in vitro acute toxicity of accumulated degradation products. J Appl Biomater. 1994;5(2):151-7.
29. Bonadio J, Smiley E, Patil P, et al. Localized, direct plasmid gene delivery in vivo: prolonged therapy results in reproducible tissue regeneration. Nat Med. 1999;5(7):753-9.
30. Jüllig M, Zhang WV, Stott NS. Gene therapy in orthopaedic surgery: the current status. ANZ J Surg. 2004;74(1-2):46-54.
31. Siqueira JF, Jr., Lopes HP. Mechanisms of antimicrobial activity of calcium hydroxide: a critical review. Int Endod J. 1999;32(5):361-9.
32. Farhad A, Mohammadi Z. Calcium hydroxide: a review. Int Dent J. 2005;55(5):293-301.
33. Fava LR, Saunders WP. Calcium hydroxide pastes: classification and clinical indications. Int Endod J. 1999;32(4):257-82.
34. Çalışkan MK. Endodontide tanı ve tedaviler: Nobel Tıp Kitabevleri; 2006.
35. Taneja S, Kumari M, Parkash H. Nonsurgical healing of large periradicular lesions using a triple antibiotic paste: A case series. Contemp Clin Dent. 2010;1(1):31-5.
36. Berkhoff JA, Chen PB, Teixeira FB, et al. Evaluation of triple antibiotic paste removal by different irrigation procedures. J Endod. 2014;40(8):1172-7.
37. Sato I, Ando-Kurihara N, Kota K, et al. Sterilization of infected root-canal dentine by topical application of a mixture of ciprofloxacin, metronidazole and minocycline in situ. Int Endod J. 1996;29(2):118-24.
38. Ruparel NB, Teixeira FB, Ferraz CC, et al. Direct effect of intracanal medicaments on survival of stem cells of the apical papilla. J Endod. 2012;38(10):1372-5.
39. Lee SJ, Monsef M, Torabinejad M. Sealing ability of a mineral trioxide aggregate for repair of lateral root perforations. J Endod. 1993;19(11):541-4.
40. 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.
41. Torabinejad M, Hong CU, McDonald F, et al. Physical and chemical properties of a new root-end filling material. J Endod. 1995;21(7):349-53.

42. Torabinejad M, Chivian N. Clinical applications of mineral trioxide aggregate. Journal of endodontics. 1999;25(3):197-205.
43. Ding SJ, Kao CT, Shie MY, et al. The physical and cytological properties of white MTA mixed with Na2HPO4 as an accelerant. J Endod. 2008;34(6):748-51.
44. Bates CF, Carnes DL, del Rio CE. Longitudinal sealing ability of mineral trioxide aggregate as a root-end filling material. J Endod. 1996;22(11):575-8.
45. Shipper G, Grossman ES, Botha AJ, et al. Marginal adaptation of mineral trioxide aggregate (MTA) compared with amalgam as a root-end filling material: a low-vacuum (LV) versus high-vacuum (HV) SEM study. Int Endod J. 2004;37(5):325-36.
46. Fridland M, Rosado R. Mineral trioxide aggregate (MTA) solubility and porosity with different water-to-powder ratios. J Endod. 2003;29(12):814-7.
47. Kettering JD, Torabinejad M. Investigation of mutagenicity of mineral trioxide aggregate and other commonly used root-end filling materials. J Endod. 1995;21(11):537-42.
48. Sumer M, Muglali M, Bodrumlu E, et al. Reactions of connective tissue to amalgam, intermediate restorative material, mineral trioxide aggregate, and mineral trioxide aggregate mixed with chlorhexidine. J Endod. 2006;32(11):1094-6.
49. Park JW, Hong SH, Kim JH, et al. X-Ray diffraction analysis of white ProRoot MTA and Diadent BioAggregate. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(1):155-8.
50. Malkondu Ö, Karapinar Kazandağ M, Kazazoğlu E. A review on biodentine, a contemporary dentine replacement and repair material. Biomed Res Int. 2014;2014:160951.
51. Camilleri J, Sorrentino F, Damidot D. Investigation of the hydration and bioactivity of radiopacified tricalcium silicate cement, Biodentine and MTA Angelus. Dent Mater. 2013;29(5):580-93.
52. Kayahan MB, Nekoofar MH, McCann A, et al. Effect of acid etching procedures on the compressive strength of 4 calcium silicate-based endodontic cements. J Endod. 2013;39(12):1646-8.
53. Rajasekharan S, Martens LC, Cauwels RG, et al. Biodentine™ material characteristics and clinical applications: a review of the literature. Eur Arch Paediatr Dent. 2014;15(3):147-58.
54. Moinzadeh AT, Aznar Portoles C, Schembri Wismayer P, et al. Bioactivity Potential of EndoSequence BC RRM Putty. J Endod. 2016;42(4):615-21.
55. Alanezi AZ, Jiang J, Safavi KE, et al. Cytotoxicity evaluation of endosequence root repair material. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(3):e122-5.
56. Savannah G. Bioceramic technology–The game changer in endodontics. Endodontic Practice. 2009:13.