Al-Rafidain Dental Journal

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Treatment Modalities of Apexogenesis: An Overview

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Article information

Received: 28 December 2022
Accepted:25 May 2023
Available online:1 October 2024

Keywords
Open apex
Apexogenesis
Calcium hydroxide
MTA
Biodentine
CEM
PRF
NHA

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Abstract

Permanent teeth with incomplete root formation subjected to pulp exposure due to caries or trauma, this cause interruption of root development and leave it with an open apex. Apexogenesis aims to preserve teeth vitality while allowing complete root formation and apical closure. Many materials had been used for this. This review article was conducted to highlight the indications, advantages, and limitations of different materials used for apexogenesis.

طرق علاج التولد الذروي: نظرة عامة.

الملخص

الاسنان الدائمية ذات التكوين الجذري غير المكتمل، معرضة لانكشاف اللب بسبب التسوس او الصدمة، وهذا يسبب توقف نمو الجذور وتركه بقمة مفتوحة . تهدف عملية تكون الذروة للحفاظ على حيوية السن مع السماح باكتمال الجذر وانغلاق ذروته . العديد من المواد تم استخدامها لذالك . أجريت هذه المقالة لتسليط الضوء على المؤشرات والمزايا والقيود الخاصة بالمواد المختلفة المستخدمة في عملية تكوين الذروة.

DOI:10.33899/RDENJ.2024.137277.1182,

INTRODUCTION

Pulp exposure due to caries or trauma is a common clinical condition, enamel and dentine are the outer shell that protects the pulp any breach of this outer shell makes the pulp vulnerable to being colonized by microorganisms which leads to stimulating pulp inflammatory response[1].

Young or immature permanent teeth is the term used to describe permanent teeth which have incomplete development of their roots, pulp exposure and degeneration of immature permanent teeth stop the process of root formation with the resulting persistent open apex teeth [2].

The apical foramen is formed by Hertwig's epithelial root sheath. Three years after tooth eruption is the approximate time required for complete root formation and apical closure [3]. Interruption of root development renders the root with an open apex and the canal fails to gain it is conical tapering and is referred to as a blunderbuss canal' 'means that the canal is wider towards the apex than the cervical area'' or non-blunderbuss "cylindrical shaped'' which is broad and parallel [4].

The vitality of the pulp should be preserved otherwise absence of root development might lead to teeth fragility [3]. In general, the best treatment option for carious or traumatized vital open apex teeth at the exposure time is vital pulp therapy (VPT) which includes pulp capping, and partial or full pulpotomy, this line of treatment helps immature teeth to preserve it is a vitality, complete root development, and apical closure with the resulting greater structural integrity and stronger root structure [5].

According to the American Association of Pediatric Dentistry (AAPD) abiogenesis is defined as the procedure that stimulates normal root development and apical closure of pulpily exposed vital young permanent teeth [6].

One of the minimally invasive procedures recommended by the American Association of Pediatric Dentistry to manage immature permanent teeth with pulp exposure to achieve abiogenesis is the'' pulpotomy'' in which the inflamed pulp tissue in the pulp chamber is excised and the remaining underlying healthy tissue is dressed with appropriate dental material to preserve pulp vitality [7]. Based on Cvek's pulpotomy, the level of pulp amputation is depended on whether the exposure site is small so a superficial pulpotomy of only 1–2 mm is indicated while multiple or large exposure sites need deep pulpotomy to the root canal orifice or the level of cementoenamel junction in the anterior teeth [8].

According to Megha in 2020 and Gupta in 2021 apexogenesis is indicated for immature permanent teeth with coronal pulp damage and healthy radicular pulp, no abscess formation, no abnormal response to thermal stimuli, absence of sensitivity to percussion, normal radiographic appearance, no excessive haemorrhage after coronal pulp amputation and no foul odor from the involved tooth.

The approximate time of apexogenesis is about 1-2 years, the pulp vitality, root development, and apical maturation should be followed at a 3-month recall interval, if the pulp becomes necrotic or there is any evidence of internal resorption, pulp extirpation, and apexification therapy should be carried out. dystrophic calcification of the pulp is the main risk of apexogenesis [6 & 8].

Several studies have assessed the factors that influence the success of apexogenesis treatment which include proper diagnosis through clinical and radiographic examination [9], Hertwig's epithelial root sheath condition, and pulp inflammation severity as root development needs healthy pulp and it is recorded that all the pulp become necrotic after one month of pulp exposure [10], proper isolation using a rubber dam, disinfection of the exposure site, obtaining pulpal hemostasis, accurate selection of pulp covering agent and skills of the dentist [11].

The outcome of apexogenesis should be evaluated from both clinical and radiographic points of view. Clinically there should be neither sign of sinus tract nor symptoms of pain or tenderness to percussion, with a positive response of the treated tooth to pulp sensibility testing [12]. Continued root development in immature teeth, evidence of mineralized bridge formation, and no signs of apical periodontitis or internal resorption should be demonstrated radiographically [13].

The material used in abiogenesis

1. calcium hydroxide Ca $(OH)_2$

In the field of dentistry, calcium hydroxide was introduced as a biological dressing by Herman in 1921 [14]. For many decades Ca $(OH)_2$ which is known commercially as (dycal, calasept, or present as powder mixed with normal saline or mixed with chlorhexidine digluconate… etc) was regarded as a gold standard material for maintaining pulp tissue vitality, and the standard pulpotomy agent for immature permanent teeth that maintain the vitality of the radicular tissue until the completion of apexogenesis [15].

Hydroxyl ions released from $Ca(OH)_2$ in an aqueous environment are responsible for it is antimicrobial activity [16]. Hydroxyl ion's lethal effects on the bacterial cell are due to protein denaturation, injury to the cytoplasmic membrane of the bacteria, and DNA damage [17]. The process of preventing dissolution of the material components of dentine by neutralizing lactic acid from osteoclasts and activating phosphatases which play an essential role in hard tissue formation is due to alkaline pH induced by Ca $(OH)_2$ [18]. This high pH cause necrosis of the pulp tissue adjacent to Ca $(OH)_2$, with acute inflammatory changes in the underlying tissue. A new odontoblastic layer and a bridge of dentin are formed after four weeks [19].

Using Ca $(OH)_2$ is still controversial, despite its long history of it is used in different forms of VPT, this is

because of many imperfections and tunnel defects in the hard tissue bridge under Ca $(OH)_2$ that may permit microleakage and bacterial reinfection, root weakness from long term use of Ca $(OH)_2$ in abiogenesis makes the tooth susceptible to fracture, lack of long-term coronal seal and less effective against Candida albicans and Enterococcus faecalis (20). Therefore, the search continues for materials that are more biocompatible while stimulating continued dentin formation and apical closure of immature teeth.

2. Mineral Trioxide Aggregate (MTA)

MTA was approved for human use in 1998 by Food and Drug Administration (FDA) and in 1993 it was introduced in the dental literature [21]. MTA is a biocompatible and hydrophilic endodontic cement capable of stimulating repair, healing, and osteogenesis, it is regarded as one of the multifunctional materials in dentistry [22]. The basic components of MTA are fine hydrophilic particles of'' tricalcium silicate, tricalcium aluminate, tricalcium oxide, silicate oxide & bismuth oxide'' which hardens in the presence of humidity [23,24]. Powder hydration results in the formation of a colloidal gel with a pH of 10.2 and increased to 12.5 after 3 to 4 hours when it gets solidifies [25]. MTA is usually provided as pre-dosed powder and liquid that are mixed to obtain a putty-like homogeneous paste with about 3:1 as the recommended water/powder ratio [26]. Less than 4 minutes is the appropriate mixing time for MTA as if it is insertion is delayed this led to dehydration of the mixture so the mixing time of MTA is very important [27].

From a histological point of view, placement of MTA in direct contact with human tissue, can release Ca^{++} ions for cell proliferation, it is high pH creates an antibacterial environment that regulates cytokine production; therefore, MTA induces hard tissue-producing cell migration and differentiation to form hydroxyapatite [28]. On exposed pulpal tissue MTA, stimulate the release of growth factors which is important to attract and organize odontoblasts to deposit reparative dentine [29].

For vital pulp therapy, MTA is regarded as a new gold standard [30]. As a first choice for pulpotomy, MTA takes the place of Ca $(OH)_2$ due to its better performance in apexogenesis, biocompatibility, disinfection abilities, and absence of cytotoxicity [14].

ProRoot MTA was first commercially available MTA in 1999 in the form of grey-coloured powder due to the existence of ferrous oxide, later on, it had been found that the aesthetics were affected by this grey colour so, the composition was modified, and ferrous oxide was replaced by magnesium oxide and marketed in 2002 as white ProRoot MTA [31].

Discoloration potential, long setting time, and wet sand-like consistency that makes MTA handling difficult are the main drawbacks of MTA [32]. To enhance MTA clinical utilization and minimize these limitations, modifications in the

composition of MTA were performed MTA Angelus which was produced in 2001and exhibited decreased setting time due to the elimination of calcium sulfate from it is composition [33] Nano-white MTA (NW-MTA) with fast setting time which is about 6 minutes due to decrease the particle size which results in increasing the surface area [21]. Also to control the setting reaction Light cured based MTA was formulated, and Ortho MTA and Micro-Mega (MM) MTA were introduced to elaborate the drawbacks ([34]. The addition of sodium hypochlorite gel had been described to decrease MTA setting time by about (30-60%) [35].

MTA and Ca $(OH)_2$ were compared by El-Meligy 2006 and Özgür 2017. El-Meligy in 2006 (forty teeth in the Ca $(OH)_2$ group and forty teeth in the MTA group) reported the results in 3, 6, and 12-month follow up and Özgür in 2017 (fifteen teeth in the Ca $(OH)_2$ group and fifteen teeth in the MTA group) describes 6, 12, 18 and 24-month follow-up outcomes [36 & 37]. They found there was no statistically significant difference in either the clinical or radiographic success rate between MTA and Ca $(OH)_2$ at 6 months of follow-up and 12-month evaluation.

According to a huge randomized clinical trial achieved by Hilton *et al.* in 2013 over 2 years, the results showed that MTA had better performance compared with Ca (OH)2 [38].

Histologic evaluation after pulp capping demonstrated that MTA provides better long-term sealing, induces a thicker dentinal bridge formation at a faster rate, and reduces pulpal inflammation, hyperemia, and necrosis when compared to Ca $(OH)_2$ [39].

3. Calcium silicate-based cement (Biodentine)

Calcium silicate-based cement known as (dentine) is a bioactive type of bioceramic material that was specifically designed as a 'dentine replacement' material and became commercially available in 2009 [40]. Powder and liquid are the basic components of Biodentine [41]. Mainly, the powder is composed of (tricalcium silicates, dicalcium silicate, calcium carbonate), (zirconium oxide) as a radio-opacifier, and (iron oxide) as a filler, the liquid constituents include a water-reducing agent, calcium chloride as an accelerator agent, and water-soluble polymer[42].Biodentine is prepared according to the manufacturer's instruction to achieve a reproducible material with optimum properties, with a setting time being about 12 minutes due to the presence of a setting accelerator (Calcium chloride) [43].

Biocompatibility of Biodentine because it induces the expression of dentine sialoprotein and osteopontin and cell proliferation with significant regression of inflammatory reaction when placed in direct contact with the pulp tissue [44].

Following pulpotomy, Biodentine release Ca^{++} and increase the release of Transforming Growth Factor (TGF) - ß1 from the cells of the pulp which can ultimately stimulate angiogenesis, cell

differentiation, and mineralization of a tissue barrier in the dental pulp [45]. According to Adyanthaya *et al*. in 2021 Biodentine is regarded as a superior pulp capping material compared to MTA and calcium hydroxide because Biodentine can stimulate differentiation, proliferation, and migration of odontoblast and human pulp stem cells adhesion [46].

Biodentine has many advantages such as premium biocompatibility, low level of cytotoxicity, stimulating dentinal tags formation, thick dentinal bridge [42], the marginal adaptation of Biodentine does not affect by blood contamination [47], also Biodentine, the release of more silicon and Calcium ion than MTA [48]. Clinically Biodentine and MTA have the same applications, but; dentine has superior physical characteristics due to the pureness of tricalcium silicate, finer particle size, and use of zirconium oxide as a radio-opacifier [49], lack of tooth discoloration, fast setting time due to the presence of setting accelerator, better micromechanical anchorage and ease to handle [50].

According to Bakhtiar et al. in a 2017 histological examination and clinical trial, for in vivo study, tested Pro Root MTA, Biodentine and Theracal ($Ca(OH)_2$) showed that teeth were vital at eight weeks with all materials. But; there was significantly increased pulpal inflammation, tissue disorganization, and incomplete hard tissue bridge formation with Theracal ($Ca(OH)_2$) when compared to Biodentine and Pro Root MTA. In the same study similar results for Biodentine and Pro Root MTA (lack of inflammation and good tissue organization); however, complete dentinal bridge formation in all teeth showed in the Biodentine group while with Theracal ($Ca(OH)_2$) was (11%) and with Pro Root MTA (67%), respectively [51].

Another Randomised clinical trial tested $Ca(OH)_2$, Biodentine, and Pro Root MTA to stimulate the formation of reparative dentine. No significant difference between the materials, Biodentine had a 100% success rate with selected failures in $Ca(OH)_2$ and Pro Root MTA groups. Both Biodentine and Pro Root MTA maintain the vitality of the pulp. Even if not statistically significant MTA showed one case of failure [52].

4. Calcium-enriched mixture (CEM) cement

Calcium-enriched mixture (CEM) cement was introduced to the field of dentistry as an endodontic cement with clinical applications similar to MTA but; CEM has different chemical composition than that of MTA [53]. When used as pulp capping materials both CEM cement and MTA have comparable biocompatibility [54]. Similar sealing ability of CEM and MTA, but CEM can provide an endogenous source of phosphate and calcium ions that hasten the formation of hydroxyapatite (HA) crystal as a second-seal, promote stem cell differentiation, and stimulate hard tissue formation (cementogenesis) [55]. The antimicrobial properties of CEM cement are due to the high alkaline pH of ~11, which is

comparable to Ca $(OH)_2$ and superior to the MTA antimicrobial effect [56]. The dentin bridge formed under CEM in different forms of VPT lacks any defects or irregularities so it is superior to that formed under Ca $(OH)_2$ and comparable with that in MTA [57]. The cytotoxic effect of CEM, MTA, and intermediate restorative material (IRM) was tested by Mozayeni *et al.* in 2012 and found that both MTA and CEM had insignificant and comparable cytotoxic potential and were significantly superior to IRM [58].

A rare case report of traumatic pulp exposure of an open apex maxillary incisor [59] and permanent molar with irreversible pulpitis and open apex [60] treated with CEM pulpotomy, clinical and radiographic examination demonstrated acceptable results which include pain relief, formation of dentine bridge under CEM, complete root formation and apical closure.

Nosrat *et al*. 2013 conducted a randomized clinical trial on 51 persons with immature permanent teeth having extensive dental decay and signs of symptomatic/asymptomatic pulpitis, the teeth were treated with CEM cement and MTA, and outcomes were reported at 6- and 12-months follow-up showed radiographical apical closure in 76.8% in CEM cement group and 73.8% in MTA group, and 100 % success rate clinically and radiographically [61].

5. Platelet-Rich Fibrin (PRF)

PRF is an autologous and bioactive product prepared by centrifuging a patient's whole blood, it contains high levels of functionally intact and nonactivated platelets within a fibrin matrix that over a few days releases a relatively constant concentration of growth factors [62]. PRF was first described by Choukroun et al. in 2001 [63]. When placed directly over the amputated pulp, PRF elicits minimal or nil inflammatory response because of it is biocompatibility and autologous nature [64]. PRF has a unique healing potential, in which healing of the pulp is achieved by moderating pulpal inflammation due to the release of healing cytokines [65].

Keswani *et al*. in 2014 used PRF for pulpotomy in immature permanent teeth and showed 88.8% success compared to 80.07% with using MTA [66].

A randomized controlled trial using MM-MTA (Micro Mega Mineral Trioxide Aggregate), Nano-hydroxyapatite (NHA), and PRF, reported clinically there was no significant difference among the tested materials, while radiographically there was statistically reduced tendency to pulp canal obliteration in the PRF group compared to MM-MTA and NHA groups [67]. Also, the study showed that apical closure in the PRF group at 6 months was incomplete (19.04%) while after 12 months there was complete apexogenesis in (60%) of cases this came following Keswani et al. [66] that showed (65.5%) complete apical closure at 12 months and (88.8%) at 24 months.

6. Nano-hydroxyapatite (NHA)

Nano-hydroxyapatite is a biocompatible and bioactive inorganic material with a

chemical composition ($Ca_{10}(PO_4)_3(OH)_2$) similar to the apatite crystals of human enamel [68]. In humans, NHA is used as a pulp capping agent [69], and in pigs used as pulpotomy and pulp capping material [70], these two studies reported that NHA could yield proper vascular and cellular response with complete tubular dentinal bridge formation.

Despite of different applications of NHA in dentistry, one study performed in 2022 is the first to estimate the employment of NHA as a pulpotomy material in the treatment of immature permanent molars in humans, the results showed equal clinical success and apical closure in NHA comparing to MM-MTA (Micro Mega Mineral Trioxide Aggregate) and PRF [67]. These results should be related to the ability of NHA to promote the migration of osteoblast cells, odontoblast-lime, and hard tissue regeneration [69 & 70]. The advantages of good handling properties of NHA compared to PRF preparation and handling, less expensive compared to MM-MTA made NAH used as a pulpotomy agent [71]. At 6 and 12 months follow up, obliteration of pulp canal was more pronounced in the nanohydroxyapatite (20%, 45%) and MM-MTA (15%, 35%) groups than the PRF (0%, 5%) group [67].

Role of Laser in apexogenesis

Lasers have many dental applications such as cavity preparation, surgical procedures, and disinfection, etc., one of the applications related to this review is pulpotomy which needs soft tissue lasers with a wavelength that is absorbed by dental pulp and poorly penetrated through dental hard tissues thus diode lasers suitable for this application [72]. When used in pulpotomies, laser coagulate and decontaminate the affected and exposed pulp tissue thus maintaining pulp vitality [73]. In immature permanent teeth lasers stimulate the maturation of radicular pulp and enhance the development of the radicular dentinal walls [74]. Khatoon *et al*. in 2019 reported a case of an immature permanent molar with irreversible pulpitis treated with Er, Cr: YSGG laser followed by placement of MTA over the amputated pulpal tissue, after 17 months follow up there were no symptoms, complete root formation, and dentin bridge under MTA visible radiographically.

Another case report of traumatized immature maxillary lateral incisor treated by using a diode laser to amputate the pulp and achieve haemostasis under standard aseptic conditions then nano-ionomer cement was applied over the amputated pulpal tissue, follow up of 10 months with 1, 3, 6 and 10 months recall visit showed normal response to electric pulp testing and complete root formation and apical closure radiographically [75].

CONCLUSION

Several materials have been used in apexogenesis, each has it is own advantages and limitations. From our point of view biodentine and PRF has the superiority.

However, further studies indicated to assess of the effects of these materials in depth.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication and/or funding of this manuscript.

REFERENCES

1. Careddu R, & Duncan HF. How does the pulpal response to Biodentine and ProRoot mineral trioxide aggregate compare in the laboratory and clinic? *British Dental Journal*. 2018; 225(8): 743-749.
2. Namour M, & Theys S. Pulp revascularization of immature permanent teeth: a review of the literature and a proposal of a new clinical protocol. *The Scientific World J*. 2014;737503.
3. Megha R, Mary NSGP, Karthick A, & Vivekanandhan P. Diagnosis and Treatment Modalities of Open Apex–A Review. *Indian Journal of Forensic Medicine & Toxicology*. 2020; 14(4): 1380-1384.
4. Jain JK, Ajagannanavar SL, Jayasheel A, Bali PK, Jain CJ. Management of a fractured nonvital tooth with an open apex using mineral trioxide aggregate as an apical plug. *Int J Oral Health Sci*. 2017; 7: 44-7.
5. Potgieter N, Selvan B, & Van der Vyver PJ. Apexogenesis treatment with mineral trioxide aggregate: long-term follow-up of two cases. *South African Dental Journal*.2018; 73(2): 78-82.
6. Gupta R, Tomer AK, Cecilia LL. Challenges and Treatment Strategies of Open Apex. *IOSR Journal of Dental and Medical Sciences*. 2021; 20(3): 20-24.
7. Cushley S, Duncan HF, Lappin MJ, Tomson PL, Lundy FT, Cooper P, Clarke M, El Karim IA. Pulpotomy for mature carious teeth with symptoms of irreversible pulpitis: a systematic review. *Journal of Dentistry*. 2019; (1)88: 103158.
8. Winters J, Cameron AC, Widmer RP. Pulp therapy for primary and immature permanent teeth. InHandbook of Pediatric Dentistry. 2013; (pp. 103-122).
9. Shabahang S. Treatment options: apexogenesis and apexification. *Pediatric dentistry*. 2013;35(2):125-8.
10. Moradi S, Naghavi N, Roohani E, & Mohtasham N. Relationship between duration of pulp exposure and success rate of apexogenesis. *Iranian Endodontic Journal*. 2006; 1(4): 145.
11. Asgary S, & Ahmadyar M. Vital pulp therapy using calcium-enriched mixture: An evidence-based review. *Journal of conservative dentistry*. 2013; 16(2): 92.
12. Vidal K, Martin G, Lozano O, Salas M, Trigueros J, Aguilar G. Apical closure in apexification: a review and case report of apexification treatment of an immature permanent tooth with Biodentine. *Journal of endodontics*. 2016 ;42(5):730-4.
13. European Society of Endodontology. Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. *International endodontic journal*. 2006; 39(12):921-30.

14. Padhee G, Mohanty S. Mineral Trioxide Aggregate v/s Calcium Hydroxide: A Review Article. *Indian Journal of Forensic Medicine & Toxicology*. 2020 ;14(4).
15. Ishwarya R, Arangannal P, Jeevarathan J, Vijayakumar M, Aarthi J, Amudha S. Application of mta and biodentine in pediatric endodontics: A review. *Eur J Mol Clin Med*. 2020;7(2):6509-15.
16. Beslot-Neveu A, Bonte E, Baune B, Serreau R, Aissat F, Quinquis L, Grabar S, Lasfargues JJ. Mineral trioxyde aggregate versus calcium hydroxide in apexification of non-vital immature teeth: Study protocol for a randomized controlled trial. Trials. 2011;12(1):1-8.
17. Nishanthi R, Ravindran V. Role of calcium hydroxide in dentistry: A review. *International Journal of Pharmaceutical Research*. 2020;12(2):2822-7.
18. El-Khodary HM, El-Ashiry EA, El-Shehaby FA, Nassar HA. Comparative study of CH and MTA used in apexogenesis for young first permanent molars. *Current Science International*. 2014;3(2):150-8.
19. Anjaneyulu K, Nivedhitha MS. Influence of calcium hydroxide on the post-treatment pain in Endodontics: A systematic review. *Journal of Conservative Dentistry: JCD*. 2014;17(3):200.
20. Chen Y, Chen X, Zhang Y, Zhou F, Deng J, Zou J, Wang Y. Materials for pulpotomy in immature permanent teeth: a systematic review and meta-analysis. *BMC Oral Health*. 2019;19(1):1-9.
21. Zafar K, Jamal S, Ghafoor R. Bio-active cements-Mineral Trioxide Aggregate based calcium silicate materials: a narrative review. *The Journal of the Pakistan Medical Association*. 2020;70(3):497.
22. Lin YT, Lin YT. Success rates of mineral trioxide aggregate, ferric sulfate, and sodium hypochlorite pulpotomies: A prospective 24-month study. *Journal of the Formosan Medical Association*. 2020 ;119(6):1080-5.
23. Tu MG, Sun KT, Wang TH, He YZ, Hsia SM, Tsai BH, Shih YH, Shieh TM. Effects of mineral trioxide aggregate and bioceramics on macrophage differentiation and polarization in vitro. *Journal of the Formosan Medical Association.* 2019;118(10):1458-65.
24. Lopes MB, Soares VC, Fagundes FH, Gonini-Junior A, Kaneshima RH, Guiraldo RD, Diz-Filho E, Berger SB, Felizardo KR, Santos ML. Analysis of molecular changes induced by mineral trioxide aggregate on sPLA2. *Brazilian dental journal*. 2019; 30:453-8.
25. Zarra T, Lambrianidis T, Vasiliadis L, Gogos C. Effect of curing conditions on physical and chemical properties of MTA. *Int Endod J* .2018;51(11):1279–1291.
26. Prakash V, Darsini J H, Karthick A, Venkatesh A. Mineral Trioxide Aggregate (MTA)–an overview. *European Journal of Molecular & Clinical Medicine*. 2020; 7(3): 2115-20.
27. Moretti AB, Sakai VT, Oliveira TM, et al. The effectiveness of mineral trioxide aggregate, calcium hydroxide and formocresol for pulpotomies in primary teeth. *Int Endod J*. 2008;41(7):547-555.

28. Cervino G, Laino L, D'Amico C, Russo D, Nucci L, Amoroso G, Gorassini F, Tepedino M, Terranova A, Gambino D, Mastroieni R. Mineral trioxide aggregate applications in endodontics: A review. *European journal of dentistry*. 2020;14(04):683-91.
29. Potgieter N, Selvan B, van der Vyver PJ. Apexogenesis treatment with mineral trioxide aggregate: long-term follow-up of two cases. *South African Dental Journal*. 2018 Mar 1;73(2):78-82.
30. Haapasalo M, Parhar M, Huang X, et al. Clinical use of bioceramic materials. *Endod. Topics*. 2015;32(1):97-117
31. Dutta A, Saunders WP. Calcium silicate materials in endodontics. *Dental Update*. 2014;41(8):708-22.
32. Tawil PZ, Duggan DJ, Galicia JC. Mineral trioxide aggregate (MTA): its history, composition, and clinical applications. *Compendium of continuing education in dentistry (Jamesburg, NJ: 1995)*. 2015 Apr 1;36(4):247-52.
33. Camilleri J. The physical properties of accelerated Portland cement for endodontic use. *Int Endod J* .2008;41:151-7
34. Gandolfi MG, Taddei P, Siboni F, Modena E, Ciapetti G, Prati C. Development of the foremost light-curable calcium-silicate MTA cement as root-end in oral surgery. Chemical-physical properties, bioactivity and biological behavior. *Dent Mater*. 2011;27: 134-57
35. Kogan P, He J, Glickman GN, Watanabe I. The effects of various additives on setting properties of MTA. *J Endod*. 2006; 32:569-72.
36. El-Meligy OA, Avery DR. Comparison of mineral trioxide aggregate and calcium hydroxide as pulpotomy agents in young permanent teeth (apexogenesis). *Pediatr Dent*. 2006; 28:399–404.
37. Özgür B, Uysal S, Güngör HC. Partial Pulpotomy in immature permanent molars after carious exposures using different hemorrhage control and capping materials. *Pediatr Dent*. 2017; 39:364–70.
38. Hilton T, Ferracane J, Mancl L. Comparison of CaOH with MTA for direct pulp capping: A pbrn randomized clinical trial. *J. Dent. Res*. 2013;92(7):16-22.
39. Shahnaz N, Ajaz M, Khalid A, Riyaz F. MTA PULPOTOMY ASSOCIATED APEXOGENESIS OF HUMAN PERMANENT MOLAR WITH IRREVERSIBLE PULPITIS: A CASE REPORT. *International Journal of Dental and Health Sciences*. 2015;2(05).
40. Khoshkhounejad M, Shokouhinejad N, Pirmoazen S. Regenerative endodontic treatment: Report of two cases with different clinical management and outcomes. *J Dent (Tehran)* .2015;12:460-8.
41. About I. Biodentine: from biochemical and bioactive properties to clinical applications. *Giornale Italiano di Endodonzia*. 2016;30(2):81-8.
42. Sanjari K, Ebrahimi Zadeh H. Minimally Invasive Management of a Dental Trauma: Two Years of Follow-up in Biodentine-Induced Maturogenesis.

Archives of Trauma Research. 2020;9(2):93-8.

43. Kaur M, Singh H, Dhillon J S, Batra M, Saini M. MTA versus Biodentine: Review of Literature with a Comparative Analysis. *J Clinical and Diagnostic Research*. 2017;11(8): 1-5.
44. Barczak K, Palczewska-Komsa M, Sikora M, Buczkowska-Radlińska J. Biodentine™–use in dentistry. Literature review. *Pomeranian Journal of Life Sciences*. 2020;66(2).
45. Torabinejad M, Parirokh M, Dummer PMH. Mineral trioxide aggregate and other bioactive endodontic cements: an updated overview-part II: other clinical applications and complications. *Int Endod J*. 2018;51(3):284-317.
46. Adyanthaya A, Prathyusha P, Risana K, Sivaraman A, Nazreen AK, Aloysious R, Sangeetha CR, Nair SS. Biodentine Total Pulpotomy as an Effective Alternative to Conventional Endodontic Therapy for Young Permanent Teeth--A Study from Calicut, India. *Journal of Evolution of Medical and Dental Sciences*. 2021;10(21):1593-8.
47. Bolhari B, Ashofteh Yazdi K, Sharifi F, Pirmoazen S. Comparative scanning electron microscopic study of the marginal adaptation of four root-end filling materials in presence and absence of blood. *J Dent (Tehran)*. 2015; 12:226-34
48. Gandolfi MG, Van Landuyt K, Taddei P, Modena E, Van Meerbeek B, Prati C. Environmental scanning electron microscopy connected with energy dispersive X ray analysis and Raman techniques to study ProRoot mineral trioxide aggregate and calcium silicate cements in wet conditions and in real time. *J Endod*. 2010; 36:851 7.
49. Rajasekharan S, Martens LC, Cauwels RGEC,Anthonappa RP, Verbeeck RMH. Biodentine™ material characteristics and clinical applications: a 3year literature review and update. *Eur Arch Paediatr Dent* .2018;19:122.
50. Alvarado ML, Lozano AS, Garza HV, Jau RA. Terrazas EM, Cepeda SE, Solis-Soto JM. Biodentine: Characteristics and applications today. *International Journal of Applied Dental Sciences*. 2021;7(3), Part C.
51. Bakhtiar H, Nekoofar MH, Aminishakib P, Abedi F, Moosavi FN, Esnaashari E, Azizi A, Esmailian S, Ellini MR, Mesgarzadeh V, Sezavar M. Human pulp responses to partial pulpotomy treatment with TheraCal as compared with Biodentine and ProRoot MTA: a clinical trial. *Journal of endodontics*. 2017;43(11):1786-91.
52. Brizuela C, Ormeño A, Cabrera C et al. Direct pulp capping with calcium hydroxide, Mineral Trioxide Aggregate, and Biodentine in permanent young teeth with caries: A randomized clinical trial. *J Endod*. 2017; 43: 1776–1780.
53. Asgary S, Shahabi S, Jafarzadeh T, Amini S, Kheirieh S. The properties of a new endodontic material. *J Endod*. 2008; 34:990-3
54. Asgary S, Eghbal MJ, Parirokh M, Ghanavati F, Rahimi H. A comparative study of histologic response to different

pulp capping materials and a novel endodontic cement. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2008;106(4):609-14.

55. Kabbinale P, Chethena KC, Kuttappa MA. Role of calcium-enriched mixture in endodontics. *Archives of Medicine and Health Sciences*. 2015;3(1):80.
56. Asgary S, Kamrani FA. Antibacterial effects of five different root canal sealing materials. *J Oral Sci* .2008;50:469-74.
57. Tabarsi B, Parirokh M, Eghbal MJ, Haghdoost AA, Torabzadeh H, Asgary S. A comparative study of dental pulp response to several pulpotomy agents. *Int Endod J*. 2010; 43:565-71.
58. Mozayeni M, Salem Milani A, Alim Marvasti L, Asgary S. Cytotoxicity of new ceramic enriched mixture (CEM) compared with MTA and IRM. *Aust Endod J* .2012;38:70-5.
59. Nosrat A, Asgary S. Apexogenesis treatment with a new endodontic cement: A case report. *J Endod*. 2010; 36:912-4.
60. Nosrat A, Asgary S. Apexogenesis of a symptomatic molar with calcium enriched mixture. Int Endod J 2010; 43:940-4.
61. Nosrat A, Seifi A, Asgary S. Pulpotomy in caries-exposed immature permanent molars using calcium-enriched mixture cement or mineral trioxide aggregate: a randomized clinical trial. *International Journal of Paediatric Dentistry*. 2013;23(1):56-63.
62. Gunasekaran S, Sakthivel S, Shanthala BM, Babu G, Vijayan V. Clinical Application of Platelet-Rich Fibrin in Pediatric Dentistry. *Journal of Health and Allied Sciences NU*. 2021;12(3).
63. Choukroun J, Adda F, Schoeffler C, Vervelle AP. Une opportunité en paro-implantologie: le PRF. *Implantodontie*. 2001;42(55): e62.
64. Noor Mohamed R, Basha S, Al-Thomali Y. Efficacy of platelet concentrates in pulpotomy–a systematic review. *Platelets*. 2018 ;29(5):440-5.
65. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet rich plasma: a milieu of bioactive factors. *Arthroscopy*. 2012; 28:429–439.
66. Keswani D, Pandey RK, Ansari A, Gupta S. Comparative evaluation of platelet-rich fibrin and mineral trioxide aggregate as pulpotomy agents in permanent teeth with incomplete root development: a randomized controlled trial. *J Endod*. 2014; 40:599–605.
67. Eid A, Mancino D, Rekab MS, Haikel Y, Kharouf N. Effectiveness of Three Agents in Pulpotomy Treatment of Permanent Molars with Incomplete Root Development: A Randomized Controlled Trial. *InHealthcare*. 2022; 10(3): 431.
68. Bordea IR, Candrea S, Alexescu GT, Bran S, Băciuț M, Băciuț G, Lucaciu O, Dinu CM, Todea DA. Nano-hydroxyapatite use in dentistry: A systematic review. *Drug metabolism reviews*. 2020 ;52(2):319-32.
69. Swarup SJ, Rao A, Boaz K, Srikant N, Shenoy R. Pulpal response to nano hydroxyapatite, mineral trioxide aggregate and calcium hydroxide when used as a

direct pulp capping agent: an in vivo study. *Journal of Clinical Pediatric Dentistry*. 2014;38(3):201-6.

70. Shayegan A, Atash R, Petein M, Abbeele AV. Nanohydroxyapatite used as a pulpotomy and direct pulp capping agent in primary pig teeth. *Journal of Dentistry for Children*. 2010;77(2):77-83.
71. Landi E, Celotti G, Logroscino G, Tampieri A. Carbonated hydroxyapatite as bone substitute. *Journal of the European Ceramic Society*. 2003;23(15):2931-7.
72. Mathur VP, Dhillon JK, Kalra G. A new approach to facilitate apexogenesis using soft tissue diode laser. Contemporary Clinical Dentistry. 2014;5(1):106.
73. Olivi G, Genovese MD. Erbium chro- mium laser in pulp capping treatment. *J Oral Laser App*. 2006; 6:291-299
74. Furze HA, Furze ME. Pulpotomy with laser in primary and young permanent teeth. *J Oral Laser App*. 2006; 6:53-58.
75. Khatoon FT, Nguyen TN, Chen W. APEXOGENESIS OF AN IMMATURE PERMANENT MOLAR WITH THE USE OF Er, Cr: YSGG LASER AND MINERAL TRIOXIDE AGGREGATE. *The International Journal of Microdentistry*. 2019; 10(1): 10-3.