https://doi.org/10.48047/AFJBS.6.16.2024.1538-1556

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

To Evaluate the Efficacy of Various Bioactive Materials in Pulpal Regeneration Treatment for Permanent Dentition in Pediatric Patients - A Systematic Review

Ghazal Khan[1], Khumara Roghani[2*], Shawana[3], Junaid Ahmed[4], Shehzad Fahad[5], Aimen Dawood[6]

[1]Senior Lecturer, Department of Dental Material, Women Dental Section, Abbottabad, Pakistan
[2*]Lecturer, Department of Dental Material, Khyber College of Dentistry, Peshawar, Pakistan
[3]Research Assistant (ORIC KMU Peshawar), Khyber Medical University, Pakistan
[4]Senior Lecturer, Dental Materials, Frontier Medical and Dental College, Abbottabad, Pakistan
[5]Assistant Professor Department of Dental Materials, Avicenna Medical and Dental College, Lahore, Pakistan
[6]Department of Dental Materials, IBMS, KMU, Peshawar, Pakistan

***Corresponding author:** Khumara Roghani
Lecturer, Department of Dental Material, Khyber College of Dentistry, Peshawar, Pakistan
Email: khumarroghani@gmail.com

Volume 6, Issue 16, Dec 2024

Received: 28 Nov 2024

Accepted: 12 Dec 2024

Published: 16 Dec 2024

doi:10.48047/AFJBS.6.16.2024.1538-1556

ABSTRACT

Background and Objectives

The current systematic review aimed to evaluate the efficacy of various bioactive materials in pulpal regeneration treatment for immature permanent dentition (6-18 years of age), according to the American Association of Endodontists (AAE) criteria.

Materials and Methods

The study protocol was registered on PROSPERO and adhered to the PRISMA guidelines. The research question was based on PICO format and an electronic search was carried out on MEDLINE/PubMed, and Cochrane databases till Oct 2024.Manual search using Google Scholar was also conducted to retrieve any additional article. A total of 22 studies that met the pre-defined inclusion criteria were then finalized for review.

Results

According to data retrieved from present review, the commonly used bioactive materials were calcium hydroxide ($Ca(OH)_2$), mineral trioxide aggregate (MTA), platelet-rich plasma (PRP), and platelet-rich fibrin (PRF). The final restorative materials used were glass ionomer cement and composite resin. Clinical success was reported in over 90% of cases, with consistent radiographic evidence of increased dentin thickness, closure of apical foramen, and periapical healing.

Conclusion

The review findings support the regenerative potential of biomaterials in endodontic treatment of permanent immature teeth, hence improving the overall prognosis. However, further studies are needed, through well-designed, multi-centre RCTs, that can help in the validation of these findings and standardization of treatment protocols.

Keywords:

Bioactive materials, pulp regeneration, pulp revascularization, regenerative endodontics

INTRODUCTION

Immature permanent teeth with necrotic pulp pose distinctive clinical challenges (1). These teeth are more susceptible to fracture due to incomplete root structure and thin dentinal walls, making it difficult to carry out root canal treatment (2). Regenerative endodontic therapy (RET) is a biologically driven technique to manage immature permanent teeth with necrotic pulp. It promotes dentinal wall thickening, periapical healing, and root maturation hence regenerating the pulp-dentin complex (3). Whereas traditional methods such as apexification intend to arrest root completion, RET encourages uninterrupted growth, minimizing the risk of fracture thereby improving the overall longevity & prognosis. It uses scaffolds, stem cells, and growth factors, to regenerate the tooth tissues thereby restoring the vitality (4).

The key factors that determine the success of RET is the scaffold material used (5). A natural scaffold for cell growth is achieved by inducing bleeding in the root canal. This revascularization aims to restore blood flow to the pulpal canal, enhancing cell proliferation and tissue healing (6). Studies have highlighted that survival rates exceeding 93% and success rates above 80% for regenerative endodontic treatment (RET), highlighting its efficacy in comparison with the conventional methods (7). Since the formation of a stable clot is the prerequisite for the success of RET, it can't be reliably predicted in all

cases, leading to the consideration of other scaffolds such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) (2).

Platelet-rich plasma (PRP)is rich in growth factors, formed by the processing of blood with anticoagulants. It enhances cell proliferation and tissue regeneration (8). platelet-rich fibrin (PRF) is a second-generation platelet concentrate. It has the added advantages of easy preparation, being autologous, and having immune cells and cytokines that help resist infection and promote healing. No biochemical processing is required and there is a sustained release of growth factors as well (7).

Mineral trioxide aggregate (MTA) is a key biocompatible material being used for the creation of apical seal. Being hydrophilic, moisture control is not necessary (9). The clinical effectiveness is highly dependent on its thickness. Excessive thickness may halt. tissue growth. Despite this, its application has led to the formation of cementum-like tissue, seen radiographically (3).

This systematic review intends to evaluate the efficacy of various bioactive materials, including MTA, calcium hydroxide PRP, and PRF, for successful pulpal regeneration in immature permanent teeth. By in-depth analysis of existing evidence, this review strives to identify and ascertain the most effective materials and techniques, addressing gaps in the literature and providing the basis for optimized healthcare experiences for pediatric patients.

MATERIALS AND METHODS

The study protocol was developed before starting the literature search and was registered on PROSPERO under registration ID-CRD42024611422, focusing on the efficacy of various scaffolds and bioactive materials in the regeneration of pulpal tissues in immature permanent dentition.

The research question was designed in the PICO format and included

- P: Population was the pediatric subjects (6-18 years of age)
- I: Intervention was the use of bioactive materials and scaffolds for pulpal regeneration
- C: Comparison was no treatment
- O: Outcome is the pulpal regeneration success according to the American Association of Endodontists (AAE) criteria.

A detailed search was conducted by two independent reviewers (GK and KR) on two databases i.e. PubMed Medline and Cochrane. A Google search was also conducted to find any relevant articles.

Inclusion Criteria

- Articles available in the English language
- Articles from the last 10 years (up to Oct 2024).
- Studies that focused on pediatric patients who underwent pulpal regeneration treatment, aged 6-18 years
- Study designs included were case-control, case report, case series, randomized controlled trials, and clinical trials.

Exclusion Criteria

- Articles whose full text wasn't available or couldn't be retrieved.
- Studies that didn't involve the pulp regeneration treatment using bioactive materials.

Data Extraction

Data collection was independently performed on a predesigned proforma, proposed by two independent reviewers (GK and KR), and in case of disagreements, a third reviewer (SF) was involved, and potential conflict was resolved via dialogue. From the included studies, only data that met pre-defined inclusion criteria was retrieved and analyzed. The key findings are summarized in Table 1.

RISK OF BIAS ASSESSMENT:

It was carried out as follows:

For Randomized Controlled Trials, the Cochrane Rob 2 tool was used.

For Case Series/Case Reports: Joanna Briggs Institute (JBI) Critical Appraisal Checklists were followed.

The findings are summarized in Table 2.

Table 1: Clinical characteristics of the studies included in the review

STUDIES	POPULATION	TEETH CHARACTERISTICS	SIGN/SYMPTOMS	TREATMENT WITH RET	POST TREATMENT RESULTS
First Author: Gamze Topcuoglu (10) **Year**: 2016 **Journal**: Journal of Endodontics **Funding**: None reported	**Study Design**: Case report (3 cases) **Sample Size**: 3 patients **Gender Ratio**: 2 females, 1 male **Comorbidities**: None reported	**Tooth Position in the Arch**: Mandibular first molars **Stage of Root Development**: Immature roots with open apices	Negative responses to cold and electric pulp tests. No sensitivity to percussion or palpation. Radiographic examination indicated healthy periapical tissues.	**Number of Visits**: Single visit for all cases **Bioactive Material Used**: Platelet-rich plasma (PRP) and Bio dentine **Final Restorative Material**: Composite resin	**Follow-Up Duration**: 18 months **Clinical Success**: All teeth remained asymptomatic throughout the follow-up period. Negative responses to cold and electric pulp tests at follow-ups. **Periapical Healing**: Radiographic evidence showed thickening of canal walls and apical closure at the end of the follow-up period. **Additional Outcomes**: No complications reported. Physiologic mobility and normal probing depth around treated teeth.
First Author: Majed A. Almalki (11) **Year**: 2024 **Journal**: American Journal of Case Reports **Funding**: None declared	**Study Design**: Case report (1 case) **Sample Size**: 1 patient (female) **Gender Ratio**: 1 female **Comorbidities**: None reported	**Tooth Position in the Arch**: Right mandibular first molar **Stage of Root Development**: Immature roots with open apices	No symptoms reported. Negative responses to cold and electric pulp tests. No tenderness to percussion or palpation. Radiographic examination showed deep caries and apical radiolucency.	**Number of Visits**: Multi-visit (3 visits) **Bioactive Material Used**: Triple antibiotic paste (TAP) and Mineral Trioxide Aggregate (MTA) **Final Restorative Material**: Composite resin	**Follow-Up Duration**: 5 years **Clinical Success**: The tooth remained asymptomatic upon follow-up. Positive response to electric pulp test, negative response to cold test at the final visit. **Periapical Healing**: Radiographic examination revealed complete periapical healing, apical closure, increased root length, increased dentin thickness, and narrowed canal spaces. **Additional Outcomes**: No complications reported during the follow-up period.
First Author Hengameh Bakhtiar (12) **Year** 2017 **Journal** Journal of Endodontics (JOE) **Funding** Not declared	**Study Design** Case series **Sample size** (4 cases) **Gender ratio** 1 male: 3 females **Comorbidities** None reported	**Tooth position in the arch** maxillary central incisors. **Stage of root development** Teeth had immature roots with open apices.	All cases showed no response to cold pulp tests. All cases showed no response to electric pulp tests. Tenderness to percussion was noted in all cases. Pain on palpation was present in all cases. Swelling and sinus tract were observed in all cases. Periapical lesions were identified in all case	**Number of visits** The treatment involved multiple visits for follow-up assessments. **Bioactive material used** Bio dentine was used as the bioactive material. **Final restorative material** Injectable light cure glass ionomer cement was the final restorative material	**Follow-up Duration**: 18 months. **Clinical success** Vitality tests showed responsiveness in adjacent teeth. **Periapical healing** Apex closure was observed after 6 to 18 months. Root lengthening was not consistently evident in all cases. Root thickening occurred at 9 and 18 months. **Additional outcomes** Minimal discoloration was noted at the 18-month follow-up

First author Maria-Elpida Miltiadous (13) **Year** 2015 **Journal** Brazilian Dental Journal **Funding** Not declared	**Study Design** Case report **Sample size** One female only **Gender ratio** N/A **Comorbidities** None reported	**Tooth position in the arch** Maxillary right central incisor (tooth #11) **Stage of root development** Teeth had immature roots with open apices.	History of trauma, crown discoloration, moderate palpation pain, severe percussion pain, intraoral swelling, no mobility, radiographic evidence of open apex and thin dentinal walls, radiolucency around the apex	**Number of visits:** Two **Bioactive material used** Triple antibiotic paste (ciprofloxacin, metronidazole, amoxicillin), collagen membrane, mineral trioxide aggregate (MTA) **Final restorative material** Glass ionomer cement and composite resin	**Follow-ups**: 12, 24, and 36 months **Clinical Success**: Asymptomatic, no sensitivity to percussion or palpation, negative response to cold test **Periapical Healing**: Resolution of the periapical lesion, apical closure, no increase in root length or thickness of canal walls **Additional Outcomes**: Presence of a radiopaque mass in the vicinity of the root apex, no recurrence of swelling, functional tooth
First Author: Claudio Maniglia-Ferreira (14) **Year:** 2020 **Journal:** Brazilian Dental Journal **Funding:** None reported	**Study Design:** Case Report **Sample Size:** 1 patient **Gender Ratio:** Female **Comorbidities:** None reported	**Tooth Position in the Arch:** Permanent upper central incisors **Stage of Root Development:** Immature roots with thin dentinal walls and wide-open apices	Negative responses to pulp tests (cold stimuli) Swelling and tenderness to percussion and palpation Purulent secretion on access cavity preparation	**Number of Visits:** Three Blood clot used as a scaffold **Bioactive Material Used:** Double antibiotic paste (metronidazole/ciprofloxacin) Calcium hydroxide with 2% chlorhexidine gel Mineral trioxide aggregate (MTA) **Final Restorative Material:** Glass ionomer cement	**Follow-Up:** 12 years **Clinical Success:** Asymptomatic throughout the follow-up Negative responses to pulp tests after five years but maintained healthy periapical tissues **Periapical Healing:** Radiographs showed root development, apical closure, and calcifications CBCT revealed root defects and calcifications after 12 years **Additional Outcomes:** No complications; evidence of tissue invagination and increased root calcification
First Author: Saeed Asgary (15) **Year:** 2022 **Journal:** Journal of Clinical Pediatric Dentistry **Funding:** None reported	**Study Design:** Case Report **Size:** 1 patient **Gender Ratio:** Female **Comorbidities:** None reported	**Tooth Position in the Arch:** Permanent maxillary right central incisor **Stage of Root Development:** Immature root with an open apex	Negative responses to sensibility tests Tenderness to percussion and palpation Two large periapical lesions detected on CBCT Swelling on the palatal mucosa	**Number of Visits:** Two **Bioactive Material Used:** Modified triple antibiotic paste (penicillin G, metronidazole, ciprofloxacin) Calcium-enriched mixture (CEM) cement **Final Restorative Material:** Light-cured resin-bonded dental composite	**Follow-Up:** 2 years **Clinical Success:** Asymptomatic and functional tooth Resolution of swelling and symptoms after the first week **Periapical Healing:** Complete healing of endodontic lesions Evidence of dentinal bridge formation beneath CEM cement and apical maturation No response to sensibility tests **Additional Outcomes:** CEM cement was effective in promoting root development and healing
First Author: Loai Alsofi (16) **Year:** 2019 **Journal:** The Journal of	**Study Design:** Case Report **Sample Size:** 1 patient **Gender Ratio:** Female	**Tooth Position in the Arch:** Upper permanent central incisors (right and left)	Negative cold test responses for both central incisors No discoloration, tenderness to percussion, or palpation	**Number of Visits:** Single visit for revascularization, with follow-up over three years **Bioactive Material Used:** Mineral trioxide aggregate (MTA)	**Follow-Up:** 3 years **Clinical Success:** Initial root maturation and apical closure in the upper right central incisor

Contemporary Dental Practice **Funding:** None reported	**Comorbidities:** None reported	**Stage of Root Development:** Immature roots with open apices and thin walls	Diagnosed with necrotic pulp and normal apical tissues	**Final Restorative Material:** Bonded resin restorations	Development of periapical radiolucency after three years, requiring conventional root canal treatment **Periapical Healing:** Resolution of periapical radiolucency after root canal treatment Continuous root growth in the left central incisor's apical fragment embedded in bone **Additional Outcomes:** Demonstrated the potential of single-visit revascularization to achieve root maturation
First Author: Jing Lu (17) **Year**: 2020 **Journal**: Journal of Endodontics **Funding**: None reported	**Study Design**: Case report **Sample Size**: 1 female **Gender Ratio**: 1 female **Comorbidities**: None reported	**Tooth Position in the Arch**: Maxillary central incisors **Stage of Root Development**: Immature roots with open apices	Tooth #9 had a sinus tract, was tender to percussion and palpation, and did not respond to pulp sensibility tests. Tooth #8 initially responded to pulp sensibility tests but became nonresponsive after 12 months post-treatment.	**Number of Visits**: two **Bioactive Material Used**: Calcium hydroxide, and Mineral Trioxide Aggregate (MTA) **Final Restorative Material**: Glass ionomer cement and composite resin	**Follow-Up Duration**: Tooth #9 followed for 30 months. Tooth #8 followed for 18 months. **Clinical Success**: Both teeth were asymptomatic post-treatment. **Periapical Healing**: Tooth #9 showed resolution of the periapical lesion, arrest of external root resorption (ERR), and repair of root perforation at follow-ups. Tooth #8 developed a periapical lesion post-treatment but was treated with regenerative endodontic procedures later. **Additional Outcomes**: Both teeth demonstrated canal obliteration by hard tissue formation at the final follow-ups.
First Author: Herbert L Ray Jr (18) **Year**: 2015 **Journal**: Dental Traumatology **Funding**: Not specified	**Study Design**: Case report **Sample Size**: 1 patient (11-year-old male) **Gender Ratio**: Not applicable (single patient) **Comorbidities**: None reported	**Tooth Position in the Arch**: Permanent maxillary left central incisor (tooth #9) **Stage of Root Development**: Incomplete root development with an open apex	History of sports-related trauma, non-responsive to cold testing, insensitive to percussion, tender to palpation, Class II mobility, deep pockets, intruded 3 mm, luxated buccally, periapical radiolucency, thin dentinal walls, incomplete root development, external root resorption	**Number of Visits:** Two **Bioactive Material Used:** Platelet-rich fibrin (PRF) **Final Restorative Material:** Composite resin restoration	**Follow-ups**: 12, 24, and 36 months **Clinical Success**: Negative to cold testing, positive to EPT testing at 24 and 36 months, no abnormal pocketing or probing depths **Periapical Healing**: Radiographic evidence of root length increase, intact lamina dura, osseous healing **Additional Outcomes**: Continued root growth, thickening of root dentinal walls, narrowing of root canal space, closure of root apex after 12 months
First Author: N B Nagaveni (19) **Year**: 2016 **Journal**: Journal of Clinical Pediatric Dentistry	**Study Design**: Case report **Sample Size**: 1 patient (11-year-old boy) **Gender Ratio**: Not applicable (single patient)	**Tooth Position in the Arch**: Right maxillary central incisor **Stage of Root Development**: Incompletely formed root with thin dentinal	The crown exhibited discoloration, indicating non-vitality and necrosis of the tooth. The tooth was tender to percussion and did not respond to cold and electric pulp tests.	**Number of Visits**: Two **Bioactive Material Used**: Platelet-rich fibrin (PRF) **Final Restorative Material**: Glass Ionomer Cement (GIC)	**Follow-ups**: 1, 3, 6, 9, and 12 months **Clinical Success**: Positive response to cold and electric pulp tests, no sensitivity to percussion and palpation tests, normal pocket probing depths **Periapical Healing**:

Funding: Not specified	**Comorbidities**: None reported	walls and wide open apex	Periodontal probing depth was within normal limits. Diagnosed as pulp necrosis with symptomatic apical periodontitis.		Radiographic evidence of root elongation, root end closure, continued thickening of the root dentinal walls, obliteration of root canal space, and normal peri radicular anatomy **Additional Outcomes**: Continued root growth, thickening of root dentinal walls, narrowing of root canal space, and closure of root apex after 12 months
First Author: G S Sachdeva (20) **Year**: 2014 **Journal**: International Endodontic Journal **Funding**: Not specified	**Study Design**: Case report **Sample Size**: 1 patient (16-year-old male) **Gender Ratio**: Not applicable (single patient) **Comorbidities**: None reported	**Tooth Position in the Arch**: Maxillary left lateral incisor (tooth 22) **Stage of Root Development**: Incompletely developed root with an open apex	History of trauma, discolored crown, tenderness to percussion and palpation, draining sinus tract, no response to thermal and electric pulp tests, large radiolucency associated with the open apex	**Number of Visits**: two visits **Bioactive Material Used**: Platelet-rich plasma (PRP) **Final Restorative Material**: Glass ionomer cement and composite resin	**Follow-ups**: 3, 6, 12, 24, and 36 months **Clinical Success**: Asymptomatic, no sensitivity to percussion or palpation, delayed positive response to electric pulp testing **Periapical Healing**: Resolution of the periapical lesion, increased thickening of the root walls, further root development, continued apical closure **Additional Outcomes**: Continued root growth, thickening of root dentinal walls, narrowing of root canal space, closure of root apex after 12 months
First Author: Raji Viola Solomon (21) **Year**: 2015 **Journal**: Indian Journal of Dental Research **Funding**: Not specified	**Study Design**: Case report **Sample Size**: 1 patient (15-year-old male) **Gender Ratio**: Not applicable (single patient) **Comorbidities**: None reported	**Tooth Position in the Arch**: Maxillary right central incisor (tooth #11) **Stage of Root Development**: Incomplete root development with an open apex	History of trauma, discolored crown, tenderness to palpation, negative pulp sensitivity tests, large periapical radiolucency	**Number of Visits**:Two **Bioactive Material Used**: Platelet-rich fibrin (PRF) **Final Restorative Material**: Glass ionomer cement (GIC) and composite resin	**Follow-ups**: 1 week, 1 month, 3 months, 6 months, 1 year, and 18 months **Clinical Success**: Asymptomatic, no sensitivity to percussion or palpation **Periapical Healing**: Complete regression of the periapical lesion, initiation of root end closure **Additional Outcomes**: Continued root growth, thickening of root dentinal walls, narrowing of root canal space, closure of root apex after 18 months
First Author Hazim Mohamed Rizk (22) **Year**2020 **Journal** Saudi Dental Journal **Funding** Not specified	**Study Design** Double-blinded randomized controlled trial **Sample Size** 25 **Gender Ratio** 13 males:12 females **Comorbidities** None specified	**Tooth Position in the Arch** Maxillary central incisors **Stage of Root Development** Incomplete root development with an open apex	Pain, mobility, swelling, sinus/fistula	**Number of Visits:** 2 **Bioactive Material Used** Platelet Rich Plasma (PRP) and Platelet Rich Fibrin (PRF) **Final Restorative Material** glass ionomer, composite	**Follow-ups** Every 3 months for one year **Clinical Success** 100% survival rate of teeth during the 12-month follow-up period **Periapical Healing** Marginal increase in radiographic root length and width, periapical bone density, and decrease in apical diameter **Additional Outcomes** PRF displayed higher crown discoloration compared to PRP

First author Rasha Adel Ragab (20) **Year** 2019 **Journal** The Journal of Clinical Pediatric Dentistry **Funding** Not specified	**Study Design** Double blinded Parallel Randomized Controlled Trial (RCT) **Sample size** 22 **Gender ratio** 15 males :7 females **Comorbidities** None specified	**Tooth position in the arch** Maxillary anterior teeth **Stage of root development** Incomplete root development with an open apex	Pain, swelling, apical periodontitis, abscess, fistula, discoloration	**Number of visits:** Two **Bioactive material used** Platelet rich fibrin (PRF) **Final restorative material** Glass ionomer cement	**Follow ups:** 6 months and 1 year **Clinical success** Most cases showed clinical success with continued root development **Periapical healing** Radiographic evidence of periapical healing in most cases **Additional outcomes** Formation of calcific bridges (cervical and/or apical)
First author Tugba Bezgin (23) **Year** 2015 **Journal** Journal of Endodontics **Funding** Not specified	**Study Design** Randomized Controlled Trial (RCT) **Sample size**20 teeth in 18 children **Gender ratio** 8 girls, 10 boys **Comorbidities** Not specified	**Tooth position in the arch** Maxillary incisors and premolars **Stage of root development** Incomplete root development with an open apex	Pain, swelling, fistula, sensitivity to percussion, apical abscesses	**Number of visits:**2 **Bioactive material used** Platelet-rich Plasma (PRP) **Final restorative material** White Mineral Trioxide Aggregate (MTA), Glass Ionomer Cement, Composite Resin	**Follow-ups** Every 3 months for 18 months **Clinical success** Most cases showed clinical success with continued root development **Periapical healing** Radiographic evidence of periapical healing in most cases **Additional outcomes** Formation of calcific bridges, pulp canal obliteration in some cases
First author Mohamed A Asal (24) **Year**2024 **Journal** The Journal of Contemporary Dental Practice **Funding** Not specified	**Study Design** Randomized Clinical Trial (RCT), Single blinded **Sample size** 24-children **Gender ratio** 8 males, 16 females **Comorbidities** Not specified	**Tooth position in the arch** Upper central incisors **Stage of root development** Incomplete root development with an open apex	Pain, swelling, sinus tract, percussion tenderness, tenderness to palpation	**Number of visits:** 2 **Bioactive material used** Platelet-rich Fibrin (PRF), Treated Dentin Matrix (TDM) **Final restorative material** Mineral Trioxide Aggregate (MTA), Resin-modified Glass Ionomer, Composite Restoration	**Follow-ups** Every 3 months for 15 months **Clinical success** 100% clinical success in both groups **Periapical healing** Significant reduction in lesion size in both groups, with PRF showing better outcomes **Additional outcomes** Significant increase in root length and radiographic root area (RRA) in both groups, with PRF showing better outcomes
First author Burc Pekpinarli (25) **Year** 2024 **Journal** Journal of Applied Oral Science **Funding** Ege University Scientific Research Project Fund (Project number 18-DIS-002)	**Study Design** Randomized Clinical Trial (RCT) **Sample size** 20 patients **Gender ratio** 9 females, 11 males **Comorbidities** Not specified	**Tooth position in the arch** Mandibular first molars **Stage of root development** Incomplete root development with an open apex	Pain, swelling, apical periodontitis, abscess, fistula, discoloration	**Number of visits :**2 **Bioactive material used** Calcium hydroxide (Ca(OH)2), Double antibiotic paste (DAP) **Final restorative material** Mineral Trioxide Aggregate (MTA), Resin-modified Glass Ionomer, Composite Restoration	**Follow-ups** 12 months **Clinical success** Significant increase in root length, root width, and radiographic root area (RRA) in both groups, with Ca(OH)2 showing better outcomes **Periapical healing** Radiographic evidence of periapical healing in most cases **Additional outcomes** Significant increase in MMP-8 levels in both groups, with Ca(OH)2 showing better outcomes in root length increase

First author Hazim Mohamed Rizk(26) **Year** 2019 **Journal** International Journal of Clinical Pediatric Dentistry **Funding** Not specified	**Study Design** Split Mouth Double-blinded Randomized Controlled Trial **Sample size** 13 patients **Gender ratio** 7 males, 6 females **Comorbidities** Not specified	**Tooth position in the arch** Maxillary central incisors **Stage of root development** Incomplete root development with an open apex	Pain, mobility, swelling, sinus/fistula	**Number of visits :**2 **Bioactive material used** Platelet-rich Plasma (PRP), Blood Clot **Final restorative material** Mineral Trioxide Aggregate (MTA), Glass Ionomer, Composite	**Followups** 3, 6, 9, and 12 months **Clinical success** 100% success rate in both groups **Periapical healing** Significant increase in radiographic root length, width, periapical bone density, and decrease in apical diameter in PRP group compared to blood clot group **Additional outcomes** PRP group showed less crown discoloration compared to the other group
First author Hazim Mohamed rizk (27) **Year**2020 **Journal** International Journal of Clinical Pediatric Dentistry **Funding** Not specified	**Study Design** Split-mouth Double-blind Randomized Controlled Trial **Sample size**13 patients **Gender ratio** 7 males, 6 females **Comorbidities** Not specified	**Tooth position in the arch** Maxillary central incisors **Stage of root development** Incomplete root development with an open apex	Pain, mobility, swelling, sinus/fistula	**Number of visits:**2 **Bioactive material used** Platelet-rich Fibrin (PRF), Blood Clot (BC) **Final restorative material** Mineral Trioxide Aggregate (MTA), Glass Ionomer, Composite	**Follow-ups** 3, 6, 9, and 12 months **Clinical success** 100% success rate in both groups **Periapical healing** Significant increase in radiographic root length, width, periapical bone density, and decrease in apical diameter in PRF group compared to BC group **Additional outcomes** PRF group showed less crown discoloration compared to BC group
First author Yanfei Zhang (28) **Year** 2024 **Journal** Journal of Clinical Pediatric Dentistry **Funding** Health Science and Technology Project of Shaoxing (2022KY059), Science and Technology Foundation Public Welfare Project of Shaoxing (2022A14035)	**Study Design** Randomized Controlled Trial (RCT), Single blinded **Sample size**56 patients (7-16 years old) **Gender ratio** 25 males, 31 females **Comorbidities** Not specified	**Tooth position in the arch** Mandibular premolars **Stage of root development** Incomplete root development with an open apex	Pain, swelling, apical periodontitis, abscess, fistula, discoloration	**Number of visits:** 2 **Bioactive material used** Concentrated Growth Factor (CGF), Blood Clot (BLC) **Final restorative material** Resin-modified Glass Ionomer Cement (RMGIC)	**Follow-ups** 6 months and 12 months **Clinical success** 92.59% clinical success in both groups **Periapical healing** Significant increase in root length and radiographic root area (RRA) in CGF group compared to BLC group **Additional outcomes** CGF group showed better radiographic outcomes and periapical healing
First author Ahmad Abdel Hamid Elheeny (29) **Year**	**Study Design** Randomized Controlled Trial (RCT) **Sample size**	**Tooth position in the arch** Mature incisors	Periapical radiolucency, chronic apical abscess, asymptomatic apical periodontitis	**Number of visits:**2 **Bioactive material** Clot (BC) **Final restorative material**	**Followups** 6 months and 12 months **Clinical success**93.9% in REPs group, 97% in NS-RCR group **Periapical healing**

2024 **Journal** Scientific Reports **Funding** None	66 mature incisors in adolescents **Gender ratio** 49 males,17 females **Comorbidities** Not specified	**Stage of root development** Mature teeth		Biodentine, Resin-modified Glass Ionomer, Composite Resin	Comparable reduction in periapical radiolucency in both groups **Additional outcomes** Positive pulp sensibility in 54.54% of REPs group after 12 months
First author Ahmed Shawky ElSheshtawy (30) **Year** 2020 **Journal** International Endodontic Journal **Funding** None specified	**Study Design** Randomized Controlled Trial (RCT) **Sample size** 26 patients **Gender ratio** 15 males,11 females **Comorbidities** Not specified	**Tooth position in the arch** Permanent anterior teeth **Stage of root development** Incomplete root development with an open apex	Necrotic pulps, periapical radiolucency, swelling/sinus tract	**Number of visits:** 2 **Bioactive material used** Platelet-rich Plasma (PRP), Blood Clot (BLC) **Final restorative material** Mineral Trioxide Aggregate (MTA), Reinforced Glass Ionomer, Resin Composite	**Follow-ups** 3, 6, 9, and 12 months **Clinical success** Comparable clinical and radiographic outcomes for PRP and BLC **Periapical healing** Significant reduction in periapical area diameter (PAD) for both groups **Additional outcomes** Increase in root length, root dentinal thickness, and radiographic root area (RRA) for both groups

Table 2(a)Risk of bias assessment for randomized controlled trials

	Rizk et al 2019	**Ragab et al 2019**	**BezginEt al 2015**	**Asal et al 2024**	**Pekpinarli et al 2024**	**Rizk et al 2020**	**Rizk et al 2020**	**Zhang et al 2024**	**Elheeny et al 2024**	**Elsheshtawy et al 2020**
Randomization process (item 1) 1.1	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
1.2	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
1.3	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Effect of assignment to intervention (item 2.a) 2.1	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.2	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK
2.3	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.4	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.5	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.6	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK

2.7	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Effect of adhering to intervention (item 2.b) 2.1	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.2	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK	HIGH RISK
2.3	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.4	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.5	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
2.6	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Missing outcome data (item 3) 3.1	SOME CONCERNS	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	SOME CONCERNS
3.2	SOME CONCERN	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	SOME CONCERN
3.3	SOME CONCERN	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	SOME CONCERN
3.4	SOME CONCERN	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	SOME CONCERN
Measurement of the outcome (item 4) 4.1	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
4.2	LOW RISK	LOW RISK	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	HIGH RISK	HIGH RISK	HIGH RISK
4.3	LOW RISK	LOW RISK	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	HIGH RISK	HIGH RISK	HIGH RISK
4.4	LOW RISK	LOW RISK	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	HIGH RISK	HIGH RISK	HIGH RISK
4.5	LOW RISK	LOW RISK	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	HIGH RISK	HIGH RISK	HIGH RISK
Selection of the reported studies (item 5) 5.1	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
5.2	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
5.3	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Overall risk of bias	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**SOME CONCERNS**

Table 2(b) : Risk of bias assessment for case reports.

	DOMAIN 1	DOMAIN 2	DOMAIN 3	DOMAIN 4	DOMAIN 5	DOMAIN 6	DOMAIN 7	DOMAIN 8	OVERALL RISK
Topçuoğlu et al 2016	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Malki et al 2024	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Elpida et al 2015	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Ferreira et al 2020	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Asgary et al 2022	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Loai Alsof 2019	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Lu et al 2020	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Nagaveni et al 2016	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Ray et al 2015	YES	YES	YES	YES	YES	NO	NO	NO	MODERATE
Sachdeva et al 2014	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Solomon et al 2015	YES	YES	YES	YES	YES	YES	YES	YES	LOW

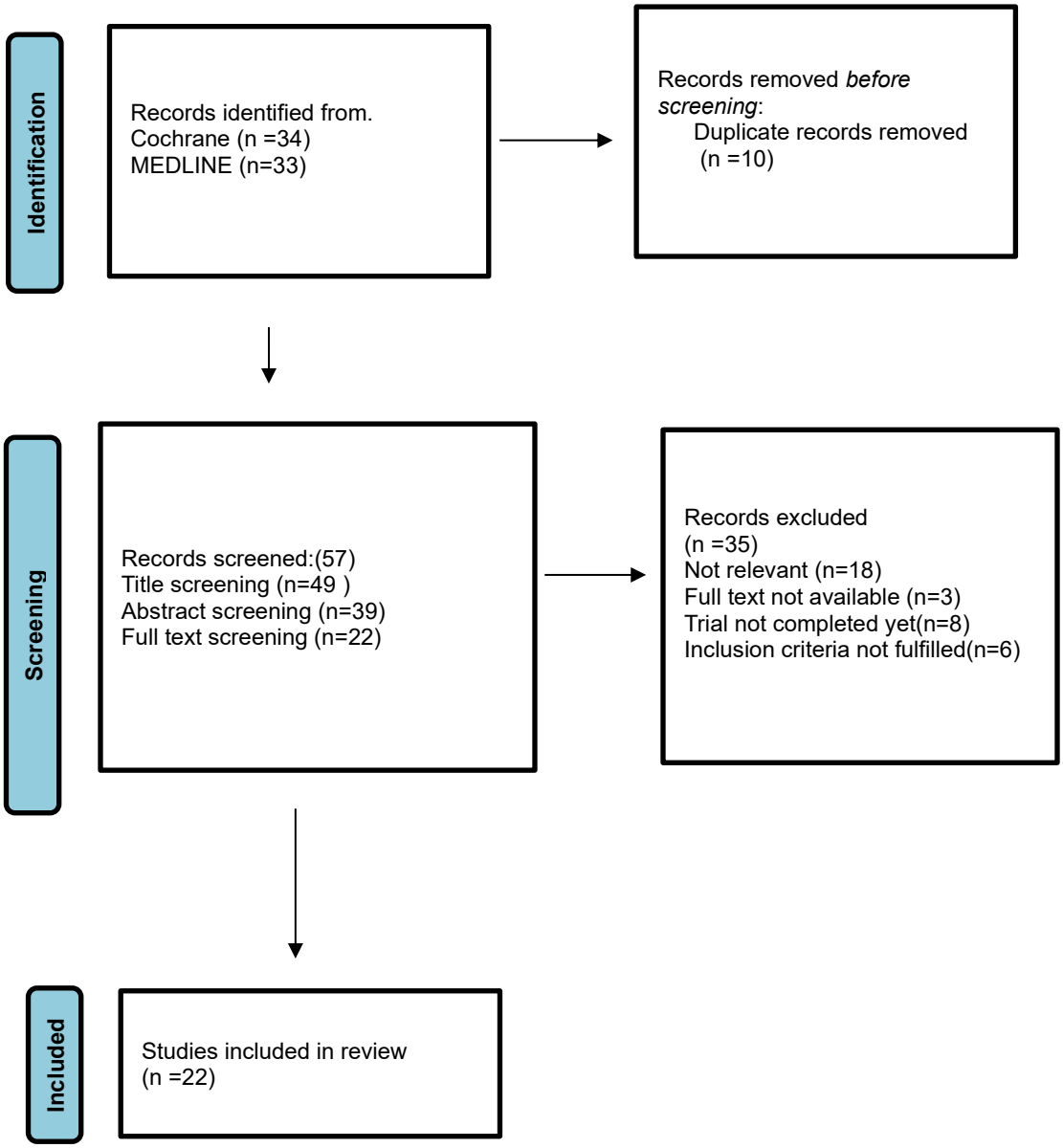
table 2(c): Risk of bias assessment for case series

	DOMAIN 1	DOMAIN 2	DOMAIN 3	DOMAIN 4	DOMAIN 5	DOMAIN 6	DOMAIN 7	DOMAIN 8	DOMAIN 9	DOMAIN 10	OVERALL RISK
Bakhtiar et al 2016	NO	YES	YES	NO	NO	YES	YES	YES	NO	YES	LOW

RESULTS

The electronic search was completed on 22nd November,2024. A total of 67 articles were retrieved, and 10 duplicates were removed. 57 articles were title screened. After title screening, 49 articles were selected for abstract screening. 39 articles were found suitable for full-text screening. After full-text screening, 22 articles that met the predefined inclusion criteria were found fit for further analysis in the current systematic review. The manual search using Google Scholar didn't retrieve any additional articles. The search strategy is summarized in the Prisma flow diagram (Fig 1).

Figure 1: Flow chart of the search strategy



DESCRIPTIVE ANALYSIS

This systematic review extracted 22 studies aimed at pulpal regeneration treatments, using bioactive materials, for permanent dentition in pediatric subjects. There was heterogeneity in the study designs including case reports, case series, and randomized controlled trials (RCTs). The commonly used bioactive materials were calcium hydroxide ($Ca(OH)_2$), mineral trioxide aggregate (MTA), platelet-rich plasma (PRP), and platelet-rich fibrin (PRF). The final restorative materials used were glass ionomer cement and composite resin. Clinical success was reported in over 90% of cases, with consistent radiographic evidence of increased dentin thickness, closure of apical foramen, and periapical healing. For simple cases, the single visit was opted whereas for complex cases with significant periapical lesions multi-visit treatment protocol was followed. Follow-up durations ranged from 6 months to 12 years, exhibiting clinical and radiographic success in most cases.

DISCUSSION

This systematic review highlights the innovative capacity of various bioactive materials in pulpal regeneration treatment for permanent teeth in pediatric patients. They have opened a new era to endodontics by their regenerative potential achieving remarkable clinical results, periapical healing, and root maturation. Amongst the reviewed materials, platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) have a slow release of concentrated growth factors that enhance angiogenesis, proliferation of stem cells, and tissue regeneration(31). These results are consistent with our review findings highlighting significant improvements in root length, dentinal wall thickness, and radiographic outcomes associated with these materials. Mineral trioxide aggregate (MTA) also reaffirmed its status as a cornerstone material in regenerative endodontics, credited for its biocompatibility, antimicrobial properties, and apical barrier formation (9), supporting the findings of our review.

Our study has highlighted the role of emerging materials such as concentrated growth factors (CGF) and treated dentin matrix (TDM). According to the findings, CGF was associated with superior root area development compared to traditional scaffolds like blood clots, while TDM contributed to accelerated healing and enhanced root maturation. The same findings are evident in the study by Yang et al (32).These innovations signify a shift toward biologically active and patient-specific regenerative solutions. The review also highlighted the clinical efficiency of single-visit protocols utilizing PRF or PRP, which reduce treatment burden while maintaining excellent outcomes, making them particularly suitable for less complex cases. Conversely, multi-visit protocols were indispensable in managing teeth with severe infections or extensive periapical pathology, in agreement with the findings from the existing literature (8,33)

Long-term follow-ups further validated the applications of these treatments. One of the included studies in this systematic review reported periapical healing and progressive root maturation over 12 years, verifying the potential of RET as a reliable and biocompatible alternative to traditional apexification treatment. The findings observed in all the studies were, the improvement in clinical signs and symptoms along with radiographic evidence of root maturation and periapical

healing, highlighting the significance of these materials in improving the overall longevity of immature necrotic dentition.

STRENGTHS AND LIMITATIONS

A major strength of this systematic review is the inclusion of widespread study designs, ranging from case reports to randomized controlled trials (RCTs), extracting information for diverse clinical applicability. Also, the long-term follow-up has further affirmed the sustainability of regenerative endodontics. Moreover, the evaluation of innovative materials like CGF and TDM adds profundity to the review, owing to its unequivocal role as a forward-looking analysis of regenerative endodontics.

However, there are certain limitations of this review. The widespread study design providing an in-depth analysis also has some disadvantages. The heterogeneity in study designs, sample sizes, and follow-up durations initiates variability that restricts the comparability of outcomes. Also, the data regarding systemic health was lacking, which could influence treatment outcomes. Another significant limitation is the inclusion of case reports and case series that included a few patients only, increasing susceptibility to publication bias. Lastly, there is little evidence in support of materials like CGF and TDM, making it necessary to carry out further research through well-designed, multi-center RCTs that can help in the validation of the findings and standardization of treatment protocols.

CONCLUSION

The review findings support the regenerative potential of biomaterials in endodontic treatment of permanent immature teeth, hence improving the overall prognosis. However, further studies are needed, through well-designed, multi-centre RCTs, that can help in the validation of these findings and standardization of treatment protocols.

REFERENCES

1. Çalışkan MK, Demirci GK, Güneri P. Regenerative endodontic therapy with platelet rich fibrin: Case series. Journal of Clinical Pediatric Dentistry. 2020;44(1):15–9.
2. Arikatla SK, Chalasani U, Mandava J, Yelisela RK. Interfacial adaptation and penetration depth of bioceramic endodontic sealers Background : Aim : Materials and Methods : Statistical Analysis Used : Results : Conclusions : 2018;21(4):373–7.
3. Caleza-Jiménez C, Ribas-Pérez D, Biedma-Perea M, Solano-Mendoza B, Mendoza-Mendoza A. Radiographic differences observed following apexification vs revascularization in necrotic immature molars and incisors: a follow-up study of 18 teeth. European Archives of Paediatric Dentistry [Internet]. 2022;23(3):381–9. Available from: https://doi.org/10.1007/s40368-022-00692-z
4. Banchs F, Trope M. Revascularization of immature permanent teeth with apical periodontitis: New treatment protocol? J Endod. 2004;30(4):196–200.
5. Harlamb SC. Management of incompletely developed teeth requiring root canal treatment. Aust Dent J. 2016;61:95–106.

6. Loroño G, Conde AJ, Estévez R, Brizuela C, Cisneros R, Alfayate RP. Regenerative Endodontic Procedure in an Immature Permanent Incisor with Internal Root Resorption: a Case Report. Journal of Dentistry (Iran). 2022;23(2):155–60.
7. Báez V, Corcos L, Morgillo F, Imperatrice L, Gualtieri AF. "Meta-analysis of regenerative endodontics outcomes with antibiotics pastes and calcium hydroxide. The apex of the iceberg." J Oral Biol Craniofac Res. 2022;12(1):90–8.
8. Shivashankar VY, Johns DA, Maroli RK, Sekar M, Chandrasekaran R, Karthikeyan S, et al. Comparison of the effect of PRP, PRF and induced bleeding in the revascularization of teeth with necrotic pulp and open apex: A triple blind randomized clinical trial. Journal of Clinical and Diagnostic Research. 2017;11(6):ZC34–9.
9. Tek GB, Keskin G. Use of Mineral Trioxide Aggregate with or without a Collagen Sponge as an Apical Plug in Teeth with Immature Apices. Journal of Clinical Pediatric Dentistry. 2021;45(3):165–70.
10. Topçuoğlu G, Topçuoğlu HS. Regenerative Endodontic Therapy in a Single Visit Using Platelet-rich Plasma and Biodentine in Necrotic and Asymptomatic Immature Molar Teeth: A Report of 3 Cases. J Endod. 2016;42(9):1344–6.
11. Almalki MA. Regenerative Endodontic Procedure on an Immature Necrotic Molar: A Case Report with a 5-Year Review. American Journal of Case Reports. 2024;25:1–8.
12. Bakhtiar H, Esmaeili S, Fakhr Tabatabayi S, Ellini MR, Nekoofar MH, Dummer PMH. Second-generation Platelet Concentrate (Platelet-rich Fibrin) as a Scaffold in Regenerative Endodontics: A Case Series. J Endod [Internet]. 2017;43(3):401–8. Available from: http://dx.doi.org/10.1016/j.joen.2016.10.016
13. Miltiadous MEA, Floratos SG. Regenerative endodontic treatment as a retreatment option for a tooth with open apex - A case report. Braz Dent J. 2015;26(5):552–6.
14. Gurgel ED, De F, Gomes A, Reis SA, Pappen FG. 12-Year Follow-Up of Regenerative Endodontic Treatment of I m m a t u r e Pe r m a n e n t U p p e r I n c i s o r s w i t h Ac u t e A b s c e s s. 2020;31(August 2007):680–4.
15. Asgary S, Parhizkar A, Samiei M. Management of an infected immature tooth with a talon cusp using regenerative endodontic treatment: A case report. Journal of Clinical Pediatric Dentistry. 2022;46(6):45–9.
16. Alsofi L. Regenerative endodontics for upper permanent central incisors after traumatic injury: Case report with a 3-year follow-up. Journal of Contemporary Dental Practice. 2019;20(8):974–7.
17. Lu J, Liu H, Lu Z, Kahler B, Lin LM. Regenerative Endodontic Procedures for Traumatized Immature Permanent Teeth with Severe External Root Resorption and Root Perforation. J Endod [Internet]. 2020;46(11):1610–5. Available from: https://doi.org/10.1016/j.joen.2020.07.022
18. Ray HL, Marcelino J, Braga R, Horwat R, Lisien M, Khaliq S. Long-term follow up of revascularization using platelet-rich fibrin. Dental Traumatology. 2016;32(1):80–4.

19. Nagaveni NB, Pathak S, Poornima P, Joshi JS. Revascularization induced maturogenesis of non-vital immature permanent tooth using platelet-rich-fibrin: A case report. Journal of Clinical Pediatric Dentistry. 2016;40(1):26–30.
20. Adel Ragab R, El Lattif AEA, El Wahab El Dokky NA. Comparative study between revitalization of necrotic immature permanent anterior teeth with and without platelet rich fibrin: A randomized controlled trial. Journal of Clinical Pediatric Dentistry. 2019;43(2):78–85.
21. Solomon RV, Faizuddin U, Guniganti SS, Waghray S. Analysis of the rate of maturogenesis of a traumatized Cvek′s stage 3 anterior tooth treated with platelet-rich fibrin as a regenerative tool using three-dimensional cone-beam computed tomography: An original case report. Indian Journal of Dental Research. 2015;26(1):90–5.
22. Rizk HM, Salah Al-Deen MSM, Emam AA. Comparative evaluation of Platelet Rich Plasma (PRP) versus Platelet Rich Fibrin (PRF) scaffolds in regenerative endodontic treatment of immature necrotic permanent maxillary central incisors: A double blinded randomized controlled trial. Saudi Dental Journal [Internet]. 2020;32(5):224–31. Available from: https://doi.org/10.1016/j.sdentj.2019.09.002
23. Bezgin T, Yilmaz AD, Celik BN, Kolsuz ME, Sonmez H. Efficacy of platelet-rich plasma as a scaffold in regenerative endodontic treatment. J Endod [Internet]. 2015;41(1):36–44. Available from: http://dx.doi.org/10.1016/j.joen.2014.10.004
24. Asal MA, Elkalla IH, Awad SM, Elhawary YM, Alhosainy AY. Comparative Evaluation of Platelet-rich Fibrin and Treated Dentin Matrix in Regenerative Endodontic Treatment of Nonvital Immature Permanent Teeth: A Randomized Clinical Trial. J Contemp Dent Pract. 2024;25(6):563–74.
25. Pekpinarli B, Kaval ME, Cogulu D, Ilhan B, Sorsa T, Tervahartiala T, et al. The effect of calcium hydroxide and double antibiotic paste on radiographic outcomes and periapical MMP-8 levels in regenerative endodontic procedures: a randomized clinical trial. J Appl Oral Sci. 2024;32:e20240122.
26. Rizk HM, Al-Deen MSS, Emam AA. Regenerative Endodontic Treatment of Bilateral Necrotic Immature Permanent Maxillary Central Incisors with Platelet-rich Plasma versus Blood Clot: A Split Mouth Double-blinded Randomized Controlled Trial. Int J Clin Pediatr Dent. 2019;12(4):332–9.
27. Rizk HM, Salah Al-Deen MS, Emam AA. Pulp revascularization/revitalization of bilateral upper necrotic immature permanent central incisors with blood clot vs platelet-rich fibrin scaffolds—A split-mouth double-blind randomized controlled trial. Int J Clin Pediatr Dent. 2020;13(4):337–43.
28. Zhang Y, Sheng M. Clinical and radiographic evaluation of regenerative endodontic procedures (REPs) with or without concentrated growth factor (CGF) as scaffolds for non-vital immature mandibular premolars. Journal of Clinical Pediatric Dentistry. 2024;48(4):168–75.

29. Elheeny AAH, Hussien OSE, Abdelmotelb MA, ElMakawi YM, Wahba NKO. A 12-month randomized controlled trial to assess the efficacy of revitalization of retreated mature incisors with periapical radiolucency in adolescents. Sci Rep [Internet]. 2024;14(1):1–10. Available from: https://doi.org/10.1038/s41598-024-66305-5
30. ElSheshtawy AS, Nazzal H, El Shahawy OI, El Baz AA, Ismail SM, Kang J, et al. The effect of platelet-rich plasma as a scaffold in regeneration/revitalization endodontics of immature permanent teeth assessed using 2-dimensional radiographs and cone beam computed tomography: a randomized controlled trial. Vol. 53, International Endodontic Journal. 2020. 905–921 p.
31. Wikström A, Brundin M, Romani Vestman N, Rakhimova O, Tsilingaridis G. Endodontic pulp revitalization in traumatized necrotic immature permanent incisors: Early failures and long-term outcomes—A longitudinal cohort study. Int Endod J. 2022;55(6):630–45.
32. Yang F, Sheng K, Yu L, Wang J. Does the use of different scaffolds have an impact on the therapeutic efficacy of regenerative endodontic procedures? A systematic evaluation and meta-analysis. BMC Oral Health [Internet]. 2024;24(1):1–13. Available from: https://doi.org/10.1186/s12903-024-04064-5
33. Abdellatif D, Iandolo A, De Benedetto G, Giordano F, Mancino D, Euvrard E, et al. Pulp regeneration treatment using different bioactive materials in permanent teeth of pediatric subjects. Journal of Conservative Dentistry and Endodontics. 2024;27(5):458–84.