Comparative Analysis of Autologous Scaffold Formation Protocols in Regenerative Endodontic Therapy: A Systematic Review and Meta-Analysis

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ABSTRACT

Aims: To evaluate the protocols of autogenous scaffold formation in regenerative endodontic therapy, with a focus on their efficacy in functional recovery, continued root development, and periapical healing in necrotic permanent teeth with incomplete root formation, while also assessing the increase in root length, root thickness, and reduction of the apical foramen.

Study Design: This is a systematic review and meta-analysis assessing the performance of various protocols for autogenous scaffold formation.

Place and Duration of Study: The review was conducted using the Embase, PubMed, Web of Science, Scopus, Cochrane, and LILACS databases, covering articles published until June 2024.

Methodology: The research question was developed using the PICOT framework.Inclusion criteria focused on randomized clinical trials with a minimum six-month follow-up, protocols employing autogenous scaffolds, and control groups with at least ten participants. Paired and independent searches with no filters applied were performed using the registered Medical Subject Headings "(Regenerative Endodontics) AND (Endodontics) AND (Calcium Hydroxide) AND (Platelet-Rich Fibrin) AND (Blood Coagulation) AND (Tooth Injuries) AND (Dental Pulp) AND (Dental Pulp Diseases)" and its related entry terms, covering articles relevant to the study's theme with no language or time restrictions. From an initial pool of 3.321 articles, 11 studies met the inclusion criteria, and five were included in the meta-analysis.

Results: Experimental scaffolds (e.g., Platelet-Rich Plasma and Platelet Rich Fibrin) showed statistically significant improvements in Root Length Increase compared to blood clots ($P = 0.0006$). Blood clots outperformed in Apical Foramen Reduction ($P < 0.00001$), while Root Thickness Increase results were equivalent across groups. High heterogeneity among studies was observed.

Conclusion: Both traditional blood clots and experimental autogenous scaffolds showed efficacy in regenerative endodontics. While Platelet-Rich Plasma andPlatelet Rich Fibrin demonstrated better outcomes in root lengthening, blood clots provided superior apical healing.

Keywords: *Blood coagulation, calcium hydroxide, dental pulp, dental pulp diseases, endodontics, platelet-rich fibrin, regenerative endodontics, tooth injuries*

1. INTRODUCTION

The treatment of infected immature teeth has significantly advanced over the past two decades, offering patients more promising therapeutic outcomes, including the possibility of complete root development through the procedures advocated in regenerative endodontic therapy (Wikström et al., 2021; Diogenes et al., 2016; Cymerman & Nosrat, 2020).

Dental trauma is one of the primary causes of pulp necrosis in immature teeth. Epidemiological studies reveal that dental trauma occurs mainly in boys during childhood, potentially causing tissue damage to the dentine-pulp complex, such as pulp necrosis, fractures, luxations, intrusions, and avulsions (Lam, 2016; Wigler et al., 2013). Furthermore, it is also possible to treat these immature teeth at a later stage in adulthood. When root development is interrupted during childhood and not treated promptly, patients may seek treatment only much later (Joachim et al., 2018; Lin et al., 2014).

Necrotic immature teeth treatment with periodic changes of calcium hydroxide paste, and more recently in combination with an apical plug of mineral trioxide aggregate (MTA), has demonstrated a high success rate in the repair of apical lesions (Beslot-Neveu et al., 2011). However, it also shows a high incidence of root fractures due to the interruption of root formation and, consequently, the thin width of the root dentin (Andreasen et al., 2002).

The use of calcium hydroxide $(CaOH)_2$ pastes or pastes composed of combinations of antibiotics (tri-antibiotic paste: Minocycline/Amoxicillin/Clindamycin, Ciprofloxacin, and Metronidazole) for the treatment of immature teeth with pulp necrosis are the main intracanal medication options between sessions. Regarding the use of calcium hydroxide $(CaOH)_2$ paste, its action is highly effective within one week inside the root canal. Antibiotic pastes emerged in the early 2000s and were widely widespread in the following years (Trope, 2010), leading to new formulations and combinations (bi-antibiotic paste: Ciprofloxacin and Metronidazole) based on clinical findings and microbiological studies (Hargreaves et al., 2013; Maniglia-Ferreira et al., 2016; Báez et al., 2022).

The aim of using these pastes is to enhance the elimination of endodontic infection, subsequently stimulating the formation of a blood clot within the pulp cavity. This clot promotes the development of new tissue with genetic memory capable of continuing root formation (Diogenes et al., 2014). The clot must be protected, and an apical barrier applied over it to anchor a coronal restorative material. MTA performs this function effectively, as it has physical, chemical, and biological properties suited to these requirements (Lee et al., 2015; Bücher et al., 2016).

This set of procedures forms the foundation of regenerative endodontic therapy (RET), grounded in the following tissue engineering principles: (i) the formation of a scaffold (supporting the organisation, proliferation, differentiation, and vascularisation—blood clot or Platelet Rich Fibrin); (ii) the presence of undifferentiated stem cells; and (iii) the presence of growth factors that stimulate the multiplication and differentiation of stem cells (Diogenes et al., 2017; Kharchi et al., 2020; Scelza et al., 2021; Cerqueira-Neto et al., 2021; Siddiqui et al., 2021).

Platelet-Rich Fibrin (PRF) is a fibrin-rich membrane achieved through the centrifugation of blood collected from the patient themselves, representing the second generation of platelet concentrate. While the blood clot serves as a good matrix, studies have demonstrated that it is poor in growth factors, unlike Platelet-Rich Plasma (PRP), which is rich in these factors, despite showing high concentrations for various growth factors (Shivashankar et al., 2017).It is primarily composed of membranes rich in platelets fibers, growth factors, and cytokines. PRF has the ability to promote repair and induce hard tissue development through the activation of growth factors such as PDGF and TGF-B1, for periods of up to two weeks (Dohan et al., 2019; He et al., 2009). Furthermore, it stimulates cellular differentiation and proliferation, facilitating angiogenesis, cell growth, and tissue formation (Dohan et al., 2019).

The short- and long-term outcomes when comparing treatments using blood clot stimulation and PRF/PRP are similar. Yoshpe et al. (2020) and Ulusoy et al. (2019) state that apical closure occurred in 73.9% of cases, and positive sensitivity test responses were confirmed in nearly 90% of cases when using one of these techniques. However, other authors, such as Kandemir et al. (2020), argue that PRF has advantages over PRP and blood clot stimulation, as PRF eliminates the use of anticoagulants, thrombin, calcium chloride activation, and the two-step centrifugation process.

The protocols employed for necrotic teeth with incomplete root development treatment vary regarding techniques, as well as advantages and disadvantages, leading to uncertainty and hesitation among professionals in selecting the appropriate step-by-step approach.

Therefore, this systematic review and meta-analysis aim to evaluate protocols for the formation of autogenous scaffolds at a clinical level for necrotic permanent teeth with incomplete root development endodontic regeneration, aiming for functional recovery, continued root formation and thickness, and periapical healing.Also, the purpose of this study is to investigate whether PRF/PRP show differences in clinical outcomes when compared to clot stimulation. The null hypothesis tested posits that there is no significant difference in clinical outcomes between the control group (clot) and the experimental groups (PRF/PRP).

2. MATERIAL AND METHODS

Research protocol registration

The protocol of this review was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols Statement (PRISMA)and submitted to and registered on the PROSPERO platform, receiving the identification code CRD42024594834.

Research information and strategy

The research question was constructed using the PICOT strategy, where P refers to Population, I to Intervention, C to Control, O to Outcomes/Primary Outcome, and T to Study Type (PICOT). In this context, the following criteria were applied: Population: patients with permanent teeth exhibiting incomplete root development; Intervention: protocols for autogenous scaffold formation in regenerative endodontic procedures; Control: different protocols of autogenous scaffold formation; Primary Outcome: efficacy in functional recovery, continued root formation, and periapical healing; Study Type: randomized clinical trials.

Paired and independent searches were conducted in the bibliographic databases Embase, PubMed, Web of Science, Scopus, Cochrane, and LILACS, restricting the search to Latin-Roman alphabet languages. Original randomized clinical studies published until June 2024 were identified and selected using the following descriptors registered in the Medical Subject Headings (MeSH): "Regenerative Endodontics; Endodontics; Calcium Hydroxide, Platelet-Rich Fibrin, Blood Coagulation, Tooth Injuries, Dental Pulp, Dental Pulp Diseases," combined using the Boolean operator "AND." The search algorithms and strategies are available in Appendix 1.

Data collection was conducted using keywords to search for randomized clinical trial articles that address the main clinical protocols in regenerative endodontics, their advantages and disadvantages, and the characteristics of the materials used in the procedures, highlighting their roles in the treatment. References identified in the articles through these keywords in the databases were selected based on their relevance and contribution to the present study, and they were individually evaluated by two independent researchers according to the information presented.

Eligibility criteria

Randomized clinical trials published in Latin-Roman alphabet languages were included, provided they met the following criteria: control groups with at least 10 participants, a minimum follow-up period of 6 months per patient after treatment, and regenerative endodontic therapy protocols involving continued root formation, increased root thickness, apical foramen closure, and the formation of autogenous scaffolds. Studies published in non-Latin-Roman alphabet languages, systematic reviews and meta-analyses, as well as histological, in vitro, case reports, pre-journal studies, letters to the editor, book chapters, conference proceedings, and animal studies were excluded. Additionally, protocols involving apical plugs without root formation, studies including individuals with allergies to medications or materials necessary for the procedures, pregnant or lactating women, patients with medical conditions or on medications affecting healing or blood coagulation, patients with severe coronal defects, non-restorable teeth, root fractures, or resorptions, and randomized clinical trials without a minimum follow-up of 6 months were also excluded.

Study selection

The studies were initially screened by title and abstract. Subsequently, the pre-selected studies were analyzed in full text and definitively selected based on the application of inclusion and exclusion criteria (Figure 1).

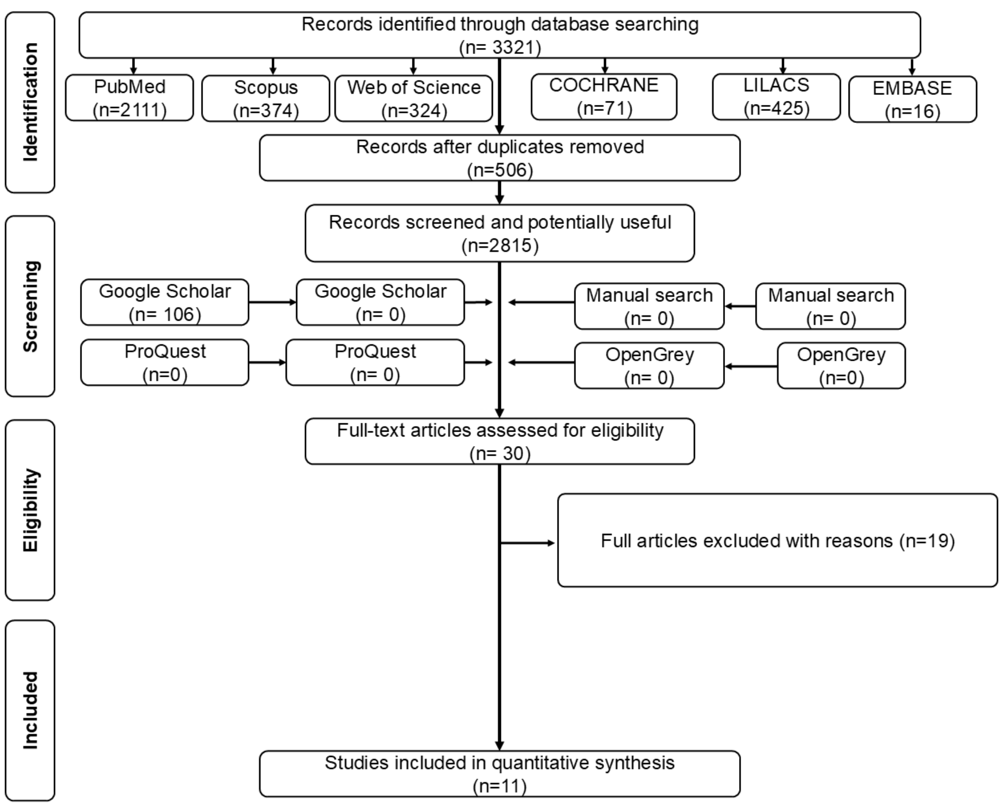


Figure 1. Flowchart of Filtered Studies

Data extraction

The included studies were tabulated in a spreadsheet using Microsoft Excel (version 2019, Microsoft Corp., Redmond, WA, USA), and were characterized by authorship, year of publication, location, patient age, type of tooth in the arch selected, intracanal medication and its intraradicular action period, sample size, the scaffold chosen for the experimental and control groups, material used for the cervical plug and final restoration, and the percentage of apical healing. Following the initial selection, articles presenting Blood Clot as the scaffold for the control group were selected. Among these, those providing quantitative data on the primary parameters evaluated—root length increase (RLI), root thickness increase (RTI), and apical foramen reduction (AFR)—over periods of 6 to 12 months, ≥ 12 months, and their respective p-values were chosen for the meta-analysis.

Bias risk assessment

The risk of bias in each of the studies definitively selected was assessed using the Risk of Bias 2 (RoB 2) protocol, conducted through the Review Manager 5.4 software. The following criteria were considered: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases.

Meta-analysis

The data were exported and quantitatively evaluated using the software Review Manager (version 5.4, The Cochrane Collaboration, Copenhagen) and R (version 4.3.2, R Core Team), where the meta-analysis was performed on some of the studies. Only studies that used blood clot as the comparative reference group (n = 5 – the exact number of studies included in the meta-analysis) were included at this stage, as it represents the current standard. This approach was necessary to ensure a more precise analysis of the experimental protocols evaluated. The main analysis was conducted using forest plots of two parameters (Root Length Increase and Apical Foramen Reduction). A random-effects model (95% Confidence Interval) was employed due to the methodological heterogeneity observed during the screening of the included studies, allowing for a better combined estimate. This was quantified and confirmed using the metrics Tau^2, Chi^2, and I^2.These tests help determine whether differences in results are due to chance or actual variations across studies, such as differences in populations, interventions, or methodologies. Tau^2 quantifies the variance between studies, Chi^2 tests the statistical significance of heterogeneity, and I^2 estimates the proportion of total variation caused by heterogeneity. This analysis is crucial for ensuring the robustness of conclusions and enabling a more reliable interpretation of the combined evidence.The risk of publication bias was assessed using Begg's and Egger's tests—rank and regression-based methods that check for correlation between study effect sizes and variances and identify funnel plot asymmetry, which may indicate potential publication bias

Final article development

Finally, this article was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature searching extension guidelines.

3. RESULTS

At the initial search, 3,321 articles were identified, and 506 duplicates were removed. The remaining 2,815 studies were screened through title and abstract, resulting in 30 articles selected for full-text analysis. A total of 19 studies were excluded for various reasons, including lack of access to the study, tomographic or review studies, having a small sample size, the absence of a control group, or deviations from the scope of this research, leaving 11 randomized controlled trials included for qualitative analysis. All included studies were randomized controlled trials with parallel designs, except for two studies, Rizk et al. (2019), and Rizk et al. (2020(2)), which used a split-mouth design (Table 1).

Table 1. Final Studies Selected for the Systematic Review

Study	Age Range (years)	Tooth Type	Medication/ Duration	Sample Size (n)	Experimental Group	Control Group	Cervical Plug + Final Restoration
Abo-Heikal et al; 2023	9-24	Maxillary Anterior Teeth	Calcium Hydroxide/2 weeks	12/12 n=24	i-PRF	PRP	MTA + Composite Resin
Rizk et al; 2019	8-14	Maxillary Incisors	TAP/3 weeks	13/13 n=26	PRP	BC	MTA + Composite Resin
Rizk et al; 2020(1)	8-14	Maxillary Incisors	TAP/3 weeks	13(PRP); 12(PRF) n=25	PRP	PRF	MTA + Composite Resin
Rizk et al; 2020(2)	8-14	Maxillary Incisors	TAP/3 weeks	13/13	PRF	BC	MTA + Composite Resin
Bezgin et al; 2015	7-13	Single-Rooted Teeth	TAP/3 weeks	10/10 n=20	PRP	BC	MTA + Glass Ionomer+ Composite Resin
ElSheshtawy et al; 2020	8-16	Incisors	TAP/3 weeks	11/11 n=22	PRP	BC	MTA Composite Resin
Kavitha et al; 2022	15-35	Didn’t mention	TAP/2 weeks	5/5 n=10	CGF	PRF	Biodentine + Glass Ionomer

Ragab et al; 2019	7-12	Anterior Teeth	DAP/3 weeks	11/11 n=22	PRF	BC	MTA + Composite Resin
Ulusoy et al; 2019	8-11	Maxilary Incisors	TAP/4 weeks	18(PRP); 17(PRF); 17(PP); 21(BC) n=73	PRP; PRF; PP	BC	MTA + Composite Resin
Shivashankar et al; 2017	6-28	Anterior Teeth	TAP/3 weeks	20(PRF); 15(BC); 19(PRP) n=54	PRP; PRF	BC	MTA+ Didn’t Mention Final Restoration
Markandey et al; 2022	15-36	Single rooted (mature & immature)	Calcium Hydroxide/4 weeks	12(BC); 12(PRP); 11(PRF) n=35	PRP; PRF	BC	Biodentine + Glass Ionomer+ Composite Resin

The results found in this systematic review demonstrate varying outcomes in periapical healing following regenerative endodontic treatments. Abo-Heikal et al. (2023), Rizk et al. (2019), Rizk et al. (2020(1), Rizk et al. (2020(2), and Kavitha et al. (2013) reported 100% periapical healing in their findings. ElSheshtawy et al. (2022) reported 85.7% healing with PRF and 88% with BC, while Ragab et al. (2019) observed 63.6% healing with PRF and 45.4% with BC. Shivashankar et al. (2017) reported 100% healing with PRP, 75% with PRF, and 80% with BC. Ulusoy et al. (2019) documented an overall healing rate of 97.2%, with 2.8% of cases still presenting signs or symptoms. Bezin et al. (2015) reported a healing rate of 90%, with 9 out of 10 samples achieving complete resolution. Finally, Markandey et al. (2022) did not provide specific results regarding periapical healing.

The results observed regarding the restoration of tooth function following regenerative endodontic therapy show that none of the included studies provided direct evidence addressing this specific outcome.

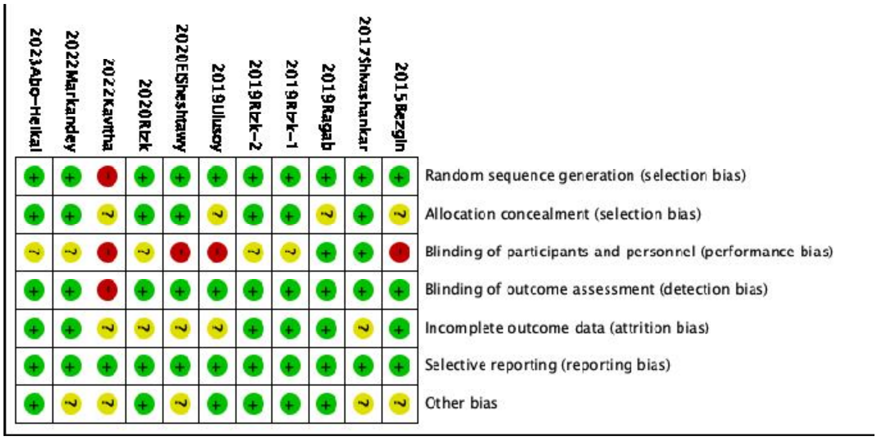
The evaluation criteria in continued root formation were: increased root length, increased thickness, and reduction of the apical foramen.

In the statistical analysis, studies that presented BC as the control group were selected, comparing it with different autogenous scaffolds and analyzing the three mentioned criteria. Studies in which BC was not considered the standard were excluded from the statistical evaluation.

The age of the patients in the articles selected for the meta-analysis ranged from 6 to 36 years. This variation occurred because root development was interrupted during childhood but was not necessarily treated at the same time, so some patients seek its treatment during adulthood.

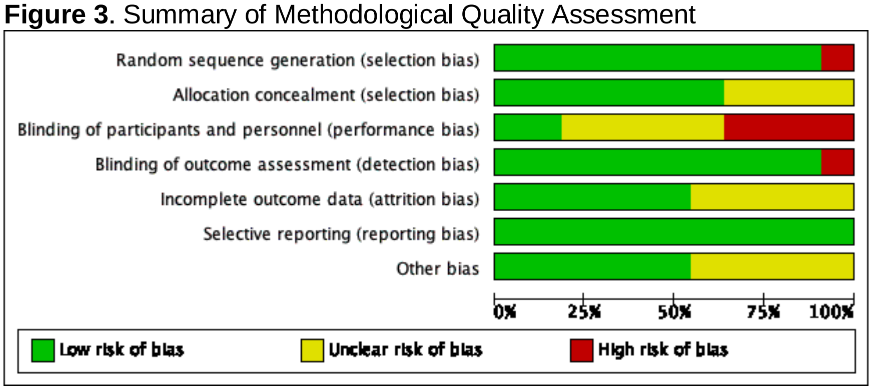
The risk of bias assessment using the RoB 2 protocol resulted in 4 studies classified as high risk and 7 as moderate risk (Figures 2 and 3).

Figure 2. Quality Assessment Chart of the Selected Studies.



Source: Authors (2024)

Figure 3. Summary of Methodological Quality Assessment



Source: Authors (2024)

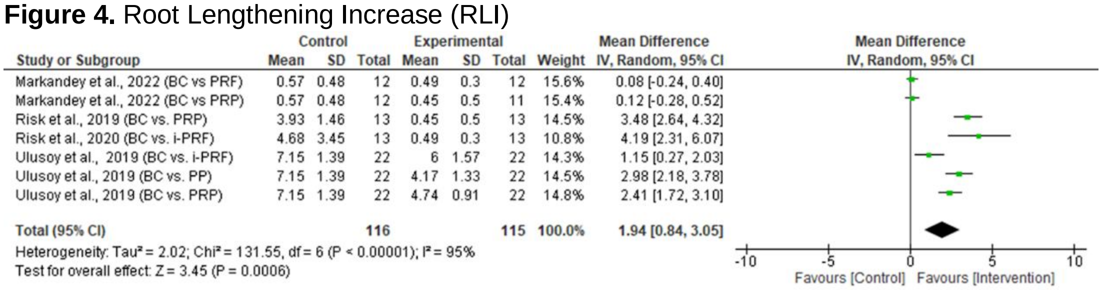
In the risk of bias assessment criteria, 1 article presented a high risk of bias in random sequence generation (selection bias), 4 were unclear regarding allocation concealment (selection bias), 5 were unclear, and 4 presented a high risk in participant and personnel blinding (performance bias), 1 had a high risk in outcome assessment blinding (detection bias), 5 were unclear in addressing incomplete outcome data (attrition bias), and 5 were unclear in the category of other risks. The other categories in the studies generally demonstrated a low risk of bias. (Figure 2).

Bezgin et al. (2015) study, assessed as having a high risk of bias, demonstrated shortcomings in reporting methods for allocation concealment and participant and personnel blinding. Similarly, ElSheshtawy et al. (2020), also classified as high risk of bias, exhibited low reliability in participant and personnel blinding, incomplete outcome data, and other risks. Khavita et al. (2022) also with a high risk of bias, showed significant flaws in random sequence generation, participant and personnel blinding, and outcome assessment blinding, with moderate shortcomings in allocation concealment, incomplete outcome data, and other biases.

The criterion of allocation concealment is crucial in determining the risk of bias, as researchers or participants may influence inclusion in the treatment or control group based on preferences or expectations, compromising randomness. Proper concealment ensures that all participants have an equal chance of being allocated to any group, protecting the integrity of the randomization process. Participant and personnel blinding is similarly essential, as knowledge of treatment allocation may lead to behavioral changes or modifications in treatment administration, potentially affecting outcomes. Likewise, researchers aware of the allocation group may interpret or measure results influenced by their expectations, even unintentionally.

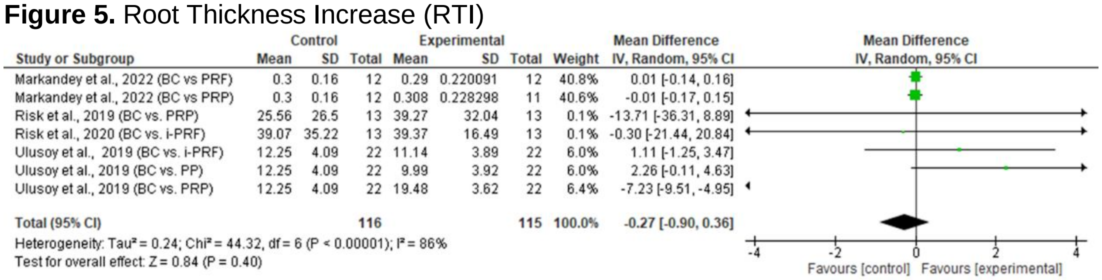
The meta-analysis evaluated the studies based on the criteria of Root Lengthening Increase (RLI), Root Thickness Increase (RTI), and Apical Foramen Reduction (AFR) (Figures 4, 5, and 6).

Figure 4. Root Lengthening Increase (RLI)



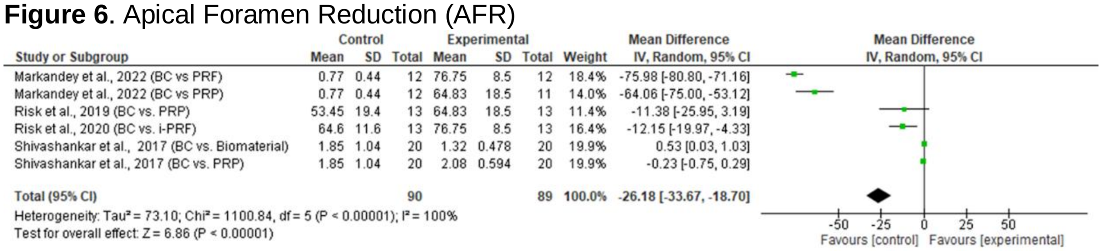
Source: Authors (2024)

Figure 5. Root Thickness Increase (RTI)



Source: Authors (2024)

Figure 6. Apical Foramen Reduction (AFR)



Source: Authors (2024)

The results of the combined effect for Root Lengthening Increase (RLI) (Z = 3.45, P= 0.0006) indicated a significant mean difference: 1.94 [0.84, 3.05], demonstrating comparatively favorable outcomes in the experimental group (autogenous scaffold groups). For the Root Thickness Increase (RTI) criterion, no statistical difference was observed between the control group (blood clot) and the autogenous experimental groups (Z = 0.84, P = .40): -0.27 [-0.90, 0.36]. In the analysis of Apical Foramen Reduction (AFR), a statistically significant difference was found favoring the control group compared to the experimental groups, indicating better results in reducing the apical foramen with blood clot induction (Z = 6.86, $P <$ 0.00001): -26.18 [-33.55, -18.70] (Figures 4, 5, and 6).
The studies revealed high heterogeneity, as reflected by elevated Tau^2, I^2, and Chi^2 indices across all evaluated parameters. This heterogeneity may be attributed to methodological differences identified during the screening of these studies. The leave-one-out method was performed to assess if a significant heterogeneity reduction was observed by removing data from each individual study, although no notable alteration was obtained.
The risk of publication bias was assessed by using Begg's and Egger's tests, analyzed both visually and statistically. A low risk of publication bias in the evaluated parameters is indicated by the results of statistical tests and the visual inspection of funnel plots. Symmetry in funnel plots suggests that studies are distributed evenly around the combined effect size, reflecting the absence of small-study effects or selective reporting. Specifically, the parameters evaluated): RLI (Z = 0.54, P= .58; t = 0.90, df = 9, P = .39) and AFR (Z = 1.5327, P= .12; t = 0.4073, df = 8, P= .69, b = 1.9627 [95% CI: 0.8934, 3.0321]).

Figure 7. Funnel Plotof Root Lengthening Increase (RLI)

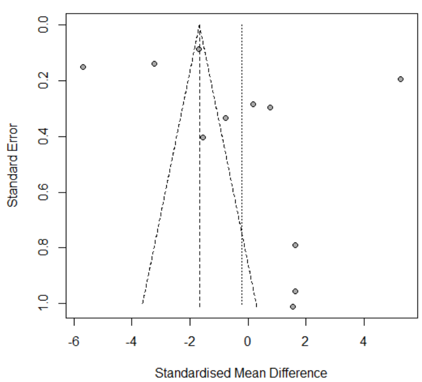
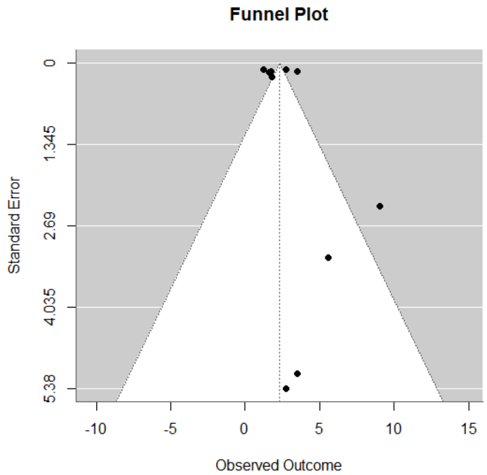


Figure 8. Funnel Plot ofApical Foramen Reduction (AFR)



DISCUSSION

The European Society of Endodontology (ESE) emphasizes that the protocol selection should be based on a selective clinical evaluation, considering the specific characteristics of each case and the available scientific evidence. The blood clot represents the standard approach in regenerative endodontic therapy. The ESE supports ongoing research into alternatives such as PRP and PRF to enhance clinical outcomes and expand the therapeutic options available to endodontic professionals. (European Society of Endodontology position statement: Considerations for regenerative endodontic procedures, Galler et al., 2016). Also, the European Society of Endodontology (ESE) supports the idea that the healing of periapical tissues and the promotion of root development in immature teeth with open apices are crucial for the long-term success of treatment. The primary goal of these treatments is to promote the healing of periapical lesions and enable the continued root development in immature teeth with pulp necrosis. This results in the strengthening of the dental structure, contributing to the restoration of the tooth's normal function after treatment(Galler et al., 2016).

Although most studies have reported no statistically significant differences ($p>0.05$), failures in apical healing have been attributed to several factors, including prolonged infections that can destroy essential cells for regeneration, severe initial clinical conditions that extend the time required for apical closure, and limitations of PRP, such as the short duration of its growth factors. Additionally, teeth with total necrosis pose greater challenges for regeneration due to the need to synthesize new pulp tissue, while the 18-month follow-up period may not have been sufficient to observe complete maturation (Bezgin et al., 2015).

ElSheshtawy et al. (2020) attributed the failure of apical healing to damage to the Hertwig's epithelial root sheath (HERS) caused by dental trauma or prolonged infections, as well as the presence of extensive periapical lesions, which compromise root regeneration. Furthermore, persistent inflammatory responses may inhibit stem cells and impair HERS function. Failures in apical healing in Ragab et al. (2019) were attributed to biological limitations, such as the absence of viable stem cells, difficulties in cell proliferation, and inadequate blood clot formation, which compromised regeneration. Shivashankar et al. (2017) associated failures with various factors, including technical limitations, such as inconsistent placement of MTA, which may have restricted tissue growth. In the case of PRF, its gel-like consistency might have hindered the uniform distribution of growth factors up to the apical foramen.

The failure rate reported by Ulusoy et al. (2019) in apical healing was attributed to factors such as a history of prior trauma, which could compromise tissue regeneration, and the presence of residual bacteria in the canals, limiting the healing potential.

The results found in this systematic review regarding periapical healing showed significant variation in the factors involved and the success rates, which ranged from 45.4% to 100%, highlighting the challenges in conducting a statistical analysis (Abo-Heikal et al., 2023; Ragab et al., 2019; Rizk et al, 2019).

According to the American Association of Endodontists (2021), the success criteria for regenerative endodontic therapyare the resolution of the signs and symptoms as well as the periapical healing. The key outcomes of Regenerative Endodontic Therapy include increased root length, thickened dentinal walls, and apical foramen closure, as these signify the structural and functional restoration of the tooth.The increase in root length indicates the resumption of tooth development, providing greater support and stability. Thickening of dentinal walls strengthens fracture resistance, especially in immature teeth, with fragile walls. Apical foramen closure is essential for forming a natural biological seal, preventing microorganism reentry, and ensuring the stability of the internal environment. These indicators, widely recognized in theliterature, not only reflect clinical success but also highlight the regenerative potential of the procedure, promoting the functional longevity of the treated tooth. Thus, this study evaluated the five selected articles (Rizk et al., 2019; Rizk et al., 2020 (2); Markandey et al., 2022; Shivashankar et al., 2017; Ulusoy et al., 2019) for the meta-analysis based on these three criteria.

Eight out of the eleven studies found in this research used the blood clot as standard to evaluate the effectiveness of the technique against new scaffolds that have emerged with technological advances (Rizk et al., 2019; Rizk et al., 2020(2); Bezgin et al., 2015; Elsheshtawy et al., 2020; Ragab et al., 2019; Ulusoy et al., 2019; Shivashankar et al., 2017; Markandey et al., 2022).

Rizk et al. (2020(2)) and Ulusoy et al. (2019) studies argue for the need to test new scaffolds as the induction of bleeding can be challenging in certain cases. This justifies the search for a new autogenous material capable of inducing revascularization, which supports the inclusion of PRP/PRF/I-PRF/PP-based scaffolds in the present meta-analysis.

All authors who used the blood clot as a control group validated for the search of a new autogenous scaffold to stimulate continued root formation. Some argue for testing and evaluating whether a new autogenous scaffold offers significant advantages over the traditional method (Rizk et al., 2019; Elsheshtawy et al., 2020; Ragab et al., 2019; Shivashankar et al., 2017; Markandey et al., 2022). Others emphasize the need for innovative techniques to surpass the clinical outcomes of the blood clot (Rizk et al., 2020(2); Bezgin et al., 2015; Ulusoy et al., 2019).

Ragab et al. (2019), Ulusoy et al. (2019), and Markandey et al. (2022) studies, comparing the blood clot with other scaffolds, showed equivalent results, with no statistical difference between the blood clot and PRP/PRF. However, this was not observed in part of the present study, where the blood clot was superior only in the Apical Foramen Reduction (AFR) criterion.

In the studies by Rizk et al. (2019), Rizk et al. (2020(2), and Shivashankar et al. (2017), across all three evaluation criteria, the results favored PRF and PRP. On the other hand, in this review, PRP and PRF showed better results in the Root Lengthening Increase (RLI) criterion compared to the control group.

Three studies presented equivalence, suggesting that, overall, the blood clot and PRP/PRF show similar efficacy in the evaluated criteria (increase in root length and thickness, and apical closure). This indicates that the blood clot remains a viable and effective option, as observed in the present study, despite being a less complex and lower-cost technique. However, three studies showed PRP superiority. In these specific studies, heterogeneity in the treatment protocol was noted, possibly reflecting potential benefits in the experimental group, requiring more evidence to consolidate the advantages of PRP/PRF (Elsheshtawy et al., 2020; Ulusoy et al., 2019; Markandey et al., 2022).

Statistical analysis showed that most studies (Bezgin et al., 2015; Elsheshtawy et al., 2020; Ragab et al., 2019; Markandey et al., 2022) demonstrated comparable results between the blood clot and PRP/PRF. This suggests that the experimental group's benefits may not be statistically significant compared to the control. Even though some studies indicate a possible superiority of PRP/PRF, the cost and associated infrastructure equipment of these scaffolds must be considered. If the blood clot provides similar results, it may be more practical. Thus, the current evidence suggests no clear or consistent difference between the use of the blood clot and PRP/PRF, as observed in this study.

In the root canal revascularization RLI criterion, the results of the present study were favored the experimental group, as they combine biological and mechanical properties, such as high levels of growth factors (e.g., TGF-β, PDGF, and VEGF), which stimulate cell proliferation, angiogenesis, and differentiation of stem cells. However, blood clots depend on the natural and less controlled release of bioactive factors, resulting in more limited and less consistent regenerative stimulus (Alsousou et al., 2013; Jung et al., 2019; Araújo et al., 2022). Another possible factor is that PRP/PRF provides a more stable physical scaffold compared to blood clots, which can be fragile and prone to collapse (Huang et al., 2008). These scaffolds encourage the formation of new blood vessels more effectively, ensuring a constant supply of nutrients and oxygen. Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF) contribute with constant release of signaling molecules, improving the enrolment, retention, and proliferation of undifferentiated mesenchymal and endothelial cells from the periapical area. It encourages collagen production. It also outputs anti-inflammatory agents (ANTES/CCL5) (regulated upon activation, normal T-cell expressed, and secreted, a protein classified as a chemotactic cytokine or chemokine) that controls the local inflammatory response and improves soft- and hard-tissue wound healing. (Rizk et al., 2020(2))In blood clots the angiogenic stimulus is less intense and efficient, potentially limiting the regenerative potential (Huang et al., 2008).

In the RTI criterion, the results of the present study, between the control and experimental groups were equivalent as both protocols share a common biological basis. Both blood clots and PRP/PRF stimulate tissue regeneration through similar biological mechanisms, such as growth factors. Blood clots already contain platelets that release growth factors like TGF-β, PDGF, and VEGF, which are essential for dentin regeneration. PRP/PRF also promotes the release of these factors but may not provide a significant additional advantage. The formation of extracellular matrix in both protocols creates a scaffold that supports cell adhesion and proliferation, contributing to the formation of reparative tissue. Moreover, the controlled inflammatory response facilitated by both blood clots and PRP/PRF can mediate a regenerative response without exceeding harmful limits (Zhou et al., 2017; Glynis et al., 2021; LV et al., 2018).

In the AFR criterion, the results favored the control group (blood clot) over the experimental group (PRP/PRF). While PRP/PRF contains growth factors that can promote regeneration, in some cases, these factors may be released too quickly orin inadequate concentrations, impairing the formation of a favorable environment for tissue regeneration. Blood clots, as a natural process, involve a balanced release of growth factors and recruitment of progenitor cells compatible with the local microenvironment, leading to more predictable outcomes. Blood clots may exhibit greater compatibility with the existing periapical tissue, allowing for more uniform regeneration. Still, PRP/PRF can present challenges in integrating with local tissue (He et al., 2009).

While PRP/PRF may offer advantages in specific cases, it does not demonstrate generalized benefits over blood clots. The null hypothesis, which assumes no significant difference in outcomes between PRP/PRF and blood clots, could not be consistently rejected across the studies reviewed. This underscores the importance of conducting additional studies with larger sample sizes and standardized methodologies to robustly evaluate whether PRP/PRF offers statistically significant advantages for specific patient subgroups or clinical conditions.

The studies exhibited high heterogeneity, which could be attributed to methodological differences and variations in the groups of individuals selected for the sample. There were variations in interventions, with studies using different materials, irrigation methods, intracanal medications, or follow-up times, all of which impacted the results. A specific example is the varying concentrations of $NaOCl^-$, with Markandey et al. (2022) using a concentration of 1.5%, while Shivashankar et al. (2017) using 5.25%. Additionally, there was variability in evaluation criteria, as differences in how studies assessed increases in root length, wall thickness, and apical foramen closure could lead to divergent results. For example, studies employing different imaging techniques, such as radiography versus computed tomography (CBCT), produced results that were not directly comparable. Markandey et al. (2022) used CBCT, while Rizk et al. (2019) relied on periapical radiographs.

Bezgin et al. (2015), ElSheshtawy et al. (2020), and Ulusoy et al. (2019), along with other studies (except Khavita et al., 2022), showed a low risk of bias in the random sequence generation criterion. This is particularly important, as truly random sequences prevent researchers and participants from influencing patient allocation to a specific clot stimulus or scaffold group, thereby avoiding selection bias. Similarly, in these articles, blinding of outcome assessment was also deemed critical. When assessors are aware of the scaffold being tested and its protocol for participants, biased interpretation of outcomes may occur, even if unintentionally.

The limitations encountered during the meta-analysis included issues with incomplete data in the studies, as well as clinical, methodological, and statistical heterogeneity. These issues stemmed from the use of different statistical methods or study designs across articles, variations in sample size, short-term follow up periods and a high risk of bias. Based on these findings, it is evident that there is a critical need for more randomized controlled clinical trials on autogenous graft formation in regenerative endodontic therapy. These studies should preferably adopt standardized methodologies to enable a more precise evaluation of these parameters.

The results of the present study demonstrated that the blood clot yielded inferior outcomes in root lengthening. On the other hand, Alrashidi et al. (2021) reported better and comparable results between blood clot and PRF/PRP. Sabeti et al. (2022) noted that evidence of very low to low quality suggests both PRP and PRF achieve the greatest success when evaluating primary and secondary outcomes within 12 months postoperatively, compared to the traditional blood clot scaffold protocol.

The findings of this review underscore cost-effective options like blood clots for apical healing, while advanced scaffolds demonstrate superior results in root lengthening, enabling dentists to tailor treatments to specific patient needs and resources. This review provides dental practitioners with evidence-based guidance to optimize patient outcomes while balancing efficacy and feasibility in their practices.

The study makes significant contributions to regenerative endodontics by comparatively evaluating protocols for the formation of autogenous scaffolds in necrotic permanent teeth with incomplete root development. Based on a robust and methodologically rigorous systematic review following protocols such as PRISMA and PROSPERO registration, the work includes randomized clinical trials and employs the RoB 2 protocol to assess the risk of bias. Quantitative results highlight that PRP and PRF promote greater root lengthening, while the blood clot shows better outcomes in apical foramen closure, providing a balanced analysis of the advantages of each approach. The high heterogeneity of the studies was mitigated using random-effects models, strengthening the validity of the results.

Although the studies primarily addressed root development and apical closure—both essential for clinical success—these outcomes do not inherently ensure the restoration of the tooth's functional capacity. Consequently, the findings should be interpreted cautiously, particularly when making clinical decisions centered on functionality. The absence of studies directly examining functional outcomes, such as resistance to mastication and sensitivity, limits our understanding of the broader clinical impact of regenerative endodontic therapy. Despite the critical importance of restoring tooth function for clinical success, no research was identified that explicitly evaluated these aspects of recovery.

The analysis presented in the article was conducted with caution and rigorous criteria due to the limitations identified in the original studies, as confirmed by the application of the bias risk assessment form. Specifically, the methodological heterogeneity among the studies and the lack of reported data on the primary outcomes of periapical healing and functional recovery increased the risk of bias, as well as reporting flaws and the absence of information on blinding techniques or random allocation. Therefore, it is crucial for future research to address these gaps and adopt consistent methodologies to enhance the robustness of the available evidence.

The clinical implications of this research are profound, offering valuable insights into optimizing regenerative endodontic therapy (RET) protocols. The findings highlight the efficacy of autogenous scaffolds such as PRP and PRF in promoting root lengthening, enhancing the structural integrity and stability of immature teeth. At the same time, the demonstrated success of blood clots in achieving critical outcomes, such as apical closure, diameter reduction, and root thickness increase, underscores their importance as a cost-effective and accessible option in clinical practice. This study emphasizes the blood clot as an economical solution while positioning advanced scaffolds as promising alternatives for more complex cases, enabling personalized and optimized treatments tailored to the specific needs of patients.

These discoveries advance current knowledge by shedding light on the specific benefits and limitations of different scaffolding materials, allowing for a more evidence-based and case-specific approach to RET. Clinically, this can translate into improved patient outcomes, as practitioners can tailor treatments based on the biological and mechanical needs of each case. Furthermore, the study underscores the necessity of integrating functional assessments, such as masticatory function and tooth sensitivity, into future research, which could redefine success metrics in RET and further elevate the standard of care in regenerative endodontics.

4. CONCLUSION

Considering the studies included in this review, the comparison of the most used protocols in regenerative endodontic therapy yielded similar results across the three evaluation criteria. Regarding the RLI criterion, statistical analysis favored the experimental group, indicating that protocols like PRP, PRF, I-PRF, and PP showed better outcomes compared to the blood clot induction. For apical closure/apical diameter reduction, the analysis favored the blood clot stimulation group. In the RTI criterion, the results were equivalent, meaning both control and experimental groups showed successful and effective responses in increasing dentin thickness.The average results for apical healing ranged from 45.4% to 100%. The observed data on masticatory function were not reported in the selected articles.

ACKNOWLEDGEMENTS

The authors express their gratitude to theUniversity of Fortaleza (UNIFOR) for funding thispublication.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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APPENDIX 1

Mesh	KeyWords	Algorithm	
"Regenerative Endodontics"[Mesh]	"Endodontic, Regenerative" OR "Endodontics, Regenerative" OR "Regenerative Endodontic"	"Regenerative Endodontics"[Mesh] OR "Endodontic, Regenerative" OR "Endodontics, Regenerative" OR "Regenerative Endodontic"	1
"Endodontics"[Mesh]	"Endodontology"	"Endodontics"[Mesh] OR "Endodontology"	2
"Apexification"[Mesh]	"Apexifications" OR "Apexogenesis" OR "Apexogeneses"	"Apexification"[Mesh] OR "Apexifications" OR "Apexogenesis" OR "Apexogeneses"	3

"Calcium Hydroxide"[Mesh]	"Hydroxide, Calcium"	"Calcium Hydroxide"[Mesh] OR "Hydroxide, Calcium"	4
"Platelet-Rich Fibrin"[Mesh]	"Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin" OR "L-PRF" OR "Leukocyte- and Platelet-Rich Fibrin" OR "Leukocyte and Platelet Rich Fibrin"	"Platelet-Rich Fibrin"[Mesh] OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin" OR "L-PRF" OR "Leukocyte- and Platelet-Rich Fibrin" OR "Leukocyte and Platelet Rich Fibrin"	5
"Blood Coagulation"[Mesh]	"Blood Clotting" OR "Blood Clottings" OR "Clotting, Blood" OR "Coagulation, Blood"	"Blood Coagulation"[Mesh] OR "Blood Clotting" OR "Blood Clottings" OR "Clotting, Blood" OR "Coagulation, Blood"	6
"Tooth Injuries"[Mesh]	"Injuries, Teeth" OR "Injury, Teeth" OR "Teeth Injury" OR "Injuries, Tooth" OR "Injury, Tooth" OR "Tooth Injury" OR "Teeth Injuries"	"Tooth Injuries"[Mesh] "Injuries, Teeth" OR "Injury, Teeth" OR "Teeth Injury" OR "Injuries, Tooth" OR "Injury, Tooth" OR "Tooth Injury" OR "Teeth Injuries"	7

"Dental Pulp"[Mesh]	"Pulp, Dental" OR "Pulps, Dental" OR "Dental Pulps"	"Dental Pulp"[Mesh] OR "Pulp, Dental" OR "Pulps, Dental" OR "Dental Pulps"	8
"Dental Pulp Diseases"[Mesh]	Diseases"[Mesh] "Pulp Diseases, Dental" OR "Diseases, Dental Pulp" OR "Pulp Disease, Dental" OR "Dental Pulp Disease" OR "Disease, Dental Pulp"	"Dental Pulp Diseases"[Mesh] OR "Pulp Diseases, Dental" OR "Diseases, Dental Pulp" OR "Pulp Disease, Dental" OR "Dental Pulp Disease" OR "Disease, Dental Pulp"	9

Search Strategy

#1 OR #2 OR #3 = #10

#4 OR #5 OR # 6 = #11

#7 OR #8 OR #9 = #12

#10 AND #11 AND #12 = #13

Keywords to Other bases without MeSH	"Regenerative Endodontics" OR "Endodontic, Regenerative" OR "Endodontics, Regenerative" OR "Regenerative Endodontic" "Endodontics" OR "Endodontology" OR "Apexification" OR "Apexifications" OR "Apexogenesis" OR "Apexogeneses" "Calcium Hydroxide" OR "Hydroxide, Calcium" OR "Platelet-Rich Fibrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin" OR "L-PRF" OR "Leukocyte- and Platelet-Rich Fibrin" OR "Leukocyte and Platelet Rich Fibrin" OR "Blood Coagulation" OR "Blood Clotting" OR "Blood Clottings" OR "Clotting, Blood" OR "Coagulation, Blood" "Tooth Injuries" OR "Injuries, Teeth" OR "Injury, Teeth" OR "Teeth Injury" OR "Injuries, Tooth" OR "Injury, Tooth" OR "Tooth Injury" OR "Teeth Injuries" OR "Dental Pulp" OR "Pulp, Dental" OR "Pulps, Dental" OR "Dental Pulps" OR "Dental Pulp Diseases" OR "Pulp Diseases, Dental" OR "Diseases, Dental Pulp" OR "Pulp Disease, Dental" OR "Dental Pulp Disease" OR "Disease, Dental Pulp"	

PubMed

#1 OR #2 OR #3 = #10

#4 OR #5 OR # 6 = #11

#7 OR #8 OR #9 = #12

#10 AND #11 AND #12 = #13

Bases	Algorithm	N

PubMed	("Regenerative Endodontics"[MeSH Terms] OR "endodontic regenerative"[All Fields] OR "endodontics regenerative"[All Fields] OR "Regenerative Endodontic"[All Fields] OR ("Endodontics"[MeSH Terms] OR "Endodontology"[All Fields]) OR ("Apexification"[MeSH Terms] OR "Apexifications"[All Fields] OR "Apexogenesis"[All Fields] OR ("Apexification"[MeSH Terms] OR "Apexification"[All Fields]))) AND ("Calcium Hydroxide"[MeSH Terms] OR "hydroxide calcium"[All Fields] OR ("platelet rich fibrin"[MeSH Terms] OR "fibrin platelet rich"[All Fields] OR "platelet rich fibrin"[All Fields] OR "L-PRF"[All Fields] OR "Leukocyte and Platelet Rich Fibrin"[All Fields] OR "Leukocyte and Platelet Rich Fibrin"[All Fields]) OR 6[UID]) AND (("Tooth Injuries"[MeSH Terms] AND "injuries teeth"[All Fields]) OR "injury teeth"[All Fields] OR "Teeth Injury"[All Fields] OR "injuries tooth"[All Fields] OR "injury tooth"[All Fields] OR "Tooth Injury"[All Fields] OR "Teeth Injuries"[All Fields] OR ("Dental Pulp"[MeSH Terms] OR "pulp dental"[All Fields] OR "pulps dental"[All Fields] OR "Dental Pulps"[All Fields]) OR ("Dental Pulp Diseases"[MeSH Terms] OR ("Dental Pulp Diseases"[MeSH Terms] OR ("dental"[All Fields] AND "pulp"[All Fields] AND "diseases"[All Fields]) OR "Dental Pulp Diseases"[All Fields] OR ("pulp"[All Fields] AND "diseases"[All Fields] AND "dental"[All Fields])) OR "diseases dental pulp"[All Fields] OR ("Dental Pulp Diseases"[MeSH Terms] OR ("dental"[All Fields] AND "pulp"[All Fields] AND "diseases"[All Fields]) OR "Dental Pulp Diseases"[All Fields] OR ("pulp"[All Fields] AND "disease"[All Fields] AND "dental"[All Fields])) OR "Dental Pulp Disease"[All Fields] OR "disease dental pulp"[All Fields]))	1181

Scopus	(TITLE-ABS-KEY ("Regenerative Endodontics" OR "Endodontic, Regenerative" OR "Endodontics, Regenerative" OR "Regenerative Endodontic" "Endodontics" OR "Endodontology" OR "Apexification" OR "Apexifications" OR "Apexogenesis" OR "Apexogeneses") AND TITLE-ABS-KEY ("Calcium Hydroxide" OR "Hydroxide, Calcium" OR "Platelet-Rich Fibrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin" OR "L-PRF" OR "Leukocyte- and Platelet-Rich Fibrin" OR "Leukocyte and Platelet Rich Fibrin" OR "Blood Coagulation" OR "Blood Clotting" OR "Blood Clottings" OR "Clotting, Blood" OR "Coagulation, Blood") AND TITLE-ABS-KEY ("Tooth Injuries" OR "Injuries, Teeth" OR "Injury, Teeth" OR "Teeth Injury" OR "Injuries, Tooth" OR "Injury, Tooth" OR "Tooth Injury" OR "Teeth Injuries" OR "Dental Pulp" OR "Pulp, Dental" OR "Pulps, Dental" OR "Dental Pulps" OR "Dental Pulp Diseases" OR "Pulp Diseases, Dental" OR "Diseases, Dental Pulp" OR "Pulp Disease, Dental" OR "Dental Pulp Disease" OR "Disease, Dental Pulp"))	125

Web of Science	"Regenerative Endodontics" OR "Endodontic, Regenerative" OR "Endodontics, Regenerative" OR "Regenerative Endodontic" "Endodontics" OR "Endodontology" OR "Apexification" OR "apexification" OR "amelogenesis" OR "apoxogenesis" (All Fields) and "Calcium Hydroxide" OR "Hydroxide, Calcium" OR "Platelet-Rich Fibrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin" OR "L-PRF" OR "Leukocyte- and Platelet-Rich Fibrin" OR "Leukocyte and Platelet Rich Fibrin" OR "Blood Coagulation" OR "Blood Clotting" OR "Blood Clottings" OR "Clotting, Blood" OR "Coagulation, Blood" (All Fields) and "Tooth Injuries" OR "Injuries, Teeth" OR "Injury, Teeth" OR "Teeth Injury" OR "Injuries, Tooth" OR "Injury, Tooth" OR "Tooth Injury" OR "Teeth Injuries" OR "Dental Pulp" OR "Pulp, Dental" OR "Pulps, Dental" OR "Dental Pulps" OR "Dental Pulp Diseases" OR "Pulp Diseases, Dental" OR "Diseases, Dental Pulp" OR "Pulp Disease, Dental" OR "Dental Pulp Disease" OR "Disease, Dental Pulp" (All Fields)	119

Cochrane	"Regenerative Endodontics" OR "Endodontic, Regenerative" OR "Endodontics, Regenerative" OR "Regenerative Endodontic" "Endodontics" OR "Endodontology" OR "Apexification" OR "Apexifications" OR "Apexogenesis" OR "Apexogeneses" in Title Abstract Keyword AND "Calcium Hydroxide" OR "Hydroxide, Calcium" OR "Platelet-Rich Fibrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin" OR "L-PRF" OR "Leukocyte- and Platelet-Rich Fibrin" OR "Leukocyte and Platelet Rich Fibrin" OR "Blood Coagulation" OR "Blood Clotting" OR "Blood Clottings" OR "Clotting, Blood" OR "Coagulation, Blood" in Title Abstract Keyword AND "Tooth Injuries" OR "Injuries, Teeth" OR "Injury, Teeth" OR "Teeth Injury" OR "Injuries, Tooth" OR "Injury, Tooth" OR "Tooth Injury" OR "Teeth Injuries" OR "Dental Pulp" OR "Pulp, Dental" OR "Pulps, Dental" OR "Dental Pulps" OR "Dental Pulp Diseases" OR "Pulp Diseases, Dental" OR "Diseases, Dental Pulp" OR "Pulp Disease, Dental" OR "Dental Pulp Disease" OR "Disease, Dental Pulp" in Title Abstract Keyword - (Word variations have been searched)	47

LILACS	("Regenerative Endodontics" OR "Endodontic, Regenerative" OR "Endodontics, Regenerative" OR "Regenerative Endodontic" "Endodontics" OR "Endodontology" OR "Apexification" OR "Apexifications" OR "Apexogenesis" OR "Apexogeneses") AND ("Calcium Hydroxide" OR "Hydroxide, Calcium" OR "Platelet-Rich Fibrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin" OR "L-PRF" OR "Leukocyte- and Platelet-Rich Fibrin" OR "Leukocyte and Platelet Rich Fibrin" OR "Blood Coagulation" OR "Blood Clotting" OR "Blood Clottings" OR "Clotting, Blood" OR "Coagulation, Blood") AND ("Tooth Injuries" OR "Injuries, Teeth" OR "Injury, Teeth" OR "Teeth Injury" OR "Injuries, Tooth" OR "Injury, Tooth" OR "Tooth Injury" OR "Teeth Injuries" OR "Dental Pulp" OR "Pulp, Dental" OR "Pulps, Dental" OR "Dental Pulps" OR "Dental Pulp Diseases" OR "Pulp Diseases, Dental" OR "Diseases, Dental Pulp" OR "Pulp Disease, Dental" OR "Dental Pulp Disease" OR "Disease, Dental Pulp")	552

EMBASE	(('regenerative endodontics':ti,ab,kw OR 'endodontic, regenerative':ti,ab,kw OR 'endodontics, regenerative':ti,ab,kw OR 'regenerative endodontic':ti,ab,kw) AND 'endodontics':ti,ab,kw OR 'endodontology':ti,ab,kw OR 'apexification':ti,ab,kw OR 'apexifications':ti,ab,kw OR 'apexogenesis':ti,ab,kw OR 'apexogeneses':ti,ab,kw) AND ((('calcium hydroxide':ti,ab,kw OR 'hydroxide, calcium':ti,ab,kw OR 'platelet-rich fibrin':ti,ab,kw OR 'fibrin, platelet-rich':ti,ab,kw OR 'platelet rich fibrin':ti,ab,kw OR 'l-prf':ti,ab,kw OR leukocyte-:ti,ab,kw) AND 'platelet-rich fibrin':ti,ab,kw OR leukocyte:ti,ab,kw) AND 'platelet rich fibrin':ti,ab,kw OR 'blood coagulation':ti,ab,kw OR 'blood clotting':ti,ab,kw OR 'blood clottings':ti,ab,kw OR 'clotting, blood':ti,ab,kw OR 'coagulation, blood':ti,ab,kw) AND ('tooth injuries':ti,ab,kw OR 'injuries, teeth':ti,ab,kw OR 'injury, teeth':ti,ab,kw OR 'teeth injury':ti,ab,kw OR 'injuries, tooth':ti,ab,kw OR 'injury, tooth':ti,ab,kw OR 'tooth injury':ti,ab,kw OR 'teeth injuries':ti,ab,kw OR 'dental pulp':ti,ab,kw OR 'pulp, dental':ti,ab,kw OR 'pulps, dental':ti,ab,kw OR 'dental pulps':ti,ab,kw OR 'dental pulp diseases':ti,ab,kw OR 'pulp diseases, dental':ti,ab,kw OR 'diseases, dental pulp':ti,ab,kw OR 'pulp disease, dental':ti,ab,kw OR 'dental pulp disease':ti,ab,kw OR 'disease, dental pulp':ti,ab,kw)	8

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