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SYSTEMATIC REVIEW

Clinical Outcomes of Biomaterial Scaffolds in Regenerative Endodontic Therapy: A Systematic Review and Meta-analysis

Hossein SHAHOON,[1] Anahita DEHGHANI SOLTANI,[2] Hormoz DEHGHANI SOLTANI,[3] Zahra SALMANI,[4] Berahman SABZEVARI,[5] Seyed Masoud SAJEDI[6]

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Shahed University, Tehran, Iran
[2]Department of Orthodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Periodontist, Private Practice, Tehran, Iran
[4]Department of Periodontics, Faculty of Dentistry, Alborz University of Medical Sciences, Karaj, Iran
[5]Orthodontist, Private Practice, Mashhad, Iran
[6]Department of Oral and Maxillofacial Medicine, Faculty of Dentistry, Shahed University, Tehran, Iran

ABSTRACT

Blood clot, platelet-rich fibrin, and plasma-rich plasma are the three most commonly used scaffolds in regenerative endodontic therapy. The current study aimed to evaluate the clinical outcomes of plasma-rich plasma (PRP) and platelet-rich fibrin (PRF) scaffolds and blood clot (BC) in regenerative endodontic therapy. For this systematic review and meta-analysis, international databases such as MEDLINE (PubMed and Ovid), Web of Science, and Scopus were searched between January 2013 and November 2023 using keywords relevant to the study objectives. Randomized controlled trials published in English that investigated the effects of BC, PRF, and PRP interventions compared to each other on permanent teeth with a six-month follow-up period were included in the study. The risk of bias was assessed using the Cochrane tool for randomized trials. Data were analyzed using STATA/MP software, employing odds ratios with fixed and random effects models in the meta-analysis. Fourteen randomized clinical trials involving 430 participants were reviewed. The present study did not reveal any statistically significant differences between BC and PRP regarding apical radiolucency healing (OR: -1.30, 95% CI; -2.68, 0.08; p=0.07, I^2=0%, p=0.91) and apical closure (OR: -0.29, 95% CI; -1.07, 0.49; p=0.47, I^2=32.63%, p=0.20). However, root-length increase in BC was greater compared to PRP (OR: 3.18, 95% CI; 2.78, 3.57; p<0.01) and PRF (OR: 1.75, 95% CI; 1.38, 2.13; p<0.01). The risk of bias was low for all studies, based on the Cochrane tool. BC is the preferred primary scaffold in regenerative endodontic therapy, while PRP and PRF are recommended for cases of severe canal bleeding.

Keywords: Blood clot, platelet-rich fibrin, platelet-rich plasma, scaffold

HIGHLIGHTS

- The root length is longer in blood clot than in platelet-rich fibrin.
- The increase of root length in both the blood clots and platelet-rich fibrin is significantly greater than platelet-rich plasma.
- Apical radiolucency repair and apical closure of biomaterial scaffolds are similar in root restorative treatment.
- Blood clot is considered as one appropriate choice for primary scaffold in regenerative endodontic therapy.

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Address for correspondence:
Seyed Masoud Sajedi
Department of Oral and Maxillofacial Medicine, Faculty of Dentistry, Shahed University, Tehran, Iran
E-mail: s.sajedi@shahed.ac.ir

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INTRODUCTION

The progress of the last decades has led to major changes in biologically based therapeutic strategies. Generally, the goal is to repair and grow the roots of necrotic, immature permanent teeth (1). Regenerative endodontic procedures (REPs) create new vascular tissue in the canal space and can play an important role in tooth root reconstruction and complete healing of apical periodontitis, but REPs cannot restore structure and physical activity (2). According to clinical and radiological findings, REPs are considered an appropriate treatment option (3–5). Apical bleeding into the pulp space creates a blood clot (BC) in the REPs, which is considered a biological scaffold (6); with this method, insufficient blood volume in the canal space and failure to induce apical bleeding remain major remaining problems (7–9). Therefore, recent use of other scaffolds such as autologous platelet concentrates has resulted good clinical and radiological results (10–12).

The two platelet sources of interest in REPs are plasma-rich plasma (PRP) and platelet-rich fibrin (PRF), with studies showing that PRP and PRF contain similar platelets (13, 14). PRP is a biological approach to improving healing that releases growth factors directly into the wound. PRP in surgery has useful results such as reducing bleeding, improving soft tissue repair and bone regeneration, and has numerous applications in the treatment of musculoskeletal injuries (15). PRF can be a suitable alternative in the treatment of immature human necrotic teeth since with this method, it is possible to continue the process of root development, increase the thickness of the dentine walls and close the apical foramen (16). Autologous platelets may improve the favorable biological outcome of REPs. Due to the widespread use of these treatment protocols in clinical practice, there are limited studies evaluating effectiveness. The aim of this study was to compare the clinical and radiological effectiveness of BC, PRF and PRP as scaffolds for root tissue regeneration.

METHOD

Search Strategy and Information Sources

Between January 2013 and November 2023, the international databases MEDLINE (PubMed and Ovid), Embase and Cochrane were searched for scientific evidence for the effectiveness of BC, PRF and PRP as scaffolds for root tissue regeneration using relevant keywords (Online appendix 1). Scopus Wiley Online Library, Web of Science, Cochrane Central Register of Controlled Trials, EBSCO, ISI, Elsevier and the Google Scholar search engine were also used. The present study is based on the 27-point checklist PRISMA 2020 (Online appendix) (17).

Selection Criteria

Inclusion criteria for studies in this research were articles published in English. The answers to the questions in the current study were based on the PICOS strategy, namely Population (P): permanent teeth ; Intervention (I): BC; PRP PRF; Comparison (C): three different scaffolds; Outcome (O): Clinical and Radiological Finding. Study design (S): randomized controlled trial (RCT); The follow-up period was six months. Review studies and books; qualitative studies; laboratory studies; animal studies; anecdotal studies and studies without comprehensive and relevant data; Data not reported in the scaffold category were excluded from the study.

Process of Selection and Data Collection

Two researchers separately collected data from subjects using a standard data collection form designed in advance to reduce reporting, data collection errors, and omissions. The research team created the original form, which included the following information: the authors' names, year of publication, tooth type, type of obstruction, number of participants, age range, irrigation technique, etiology, and medications.

Study Risk of Bias Assessment

The risk of bias in the reviewed articles was assessed using the Cochrane Risk of Bias tool (18). Seven components are used including random sequence generation, allocation concealment, participant blinding, outcome blinding, incomplete outcome data, selective outcome reporting, and other risk of bias assessment tools. Two researchers independently rated each article using a seven-point scoring table to determine risk of bias. In the event of a disagreement, an external researcher reviewed the article. This tool has a rating of 1, which means "low risk," and 0, which means "high risk" or "unclear risk." Accordingly, studies with scores between 0 and 2 (Total instrument scores) represent a high risk of bias, studies with scores between 3 and 4 represent a moderate risk of bias, and studies with scores between 5 and 7 represent a low risk of bias.

Certainty of Evidence

To determine the level of certainty of evidence for each primary outcome, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was applied. When creating the GRADE criteria, the following six factors were considered: publication bias, risk of bias, precision, consistency and study design. Clear evidence was used to initiate RCTs. Five elements could reduce the level of certainty of the evidence: publication bias, indirectness, inconsistency, risk of bias and imprecision. Based on these standards, we divided the evidence of each outcome into four categories (high, moderate, low, or very low).

Data Analysis

STATA/MP was used for data analysis. v17 program. The I^2 and Cochran test were used to assess the heterogeneity of the studies; An I^2 value of less than 25% means low heterogeneity, a value between 25 and 75% means moderate heterogeneity, and a value above 75% is considered high heterogeneity. Fixed and random effects models were used in the meta-analysis. In the studies considered, the effect of the variables was determined using the odds ratio. A 95% confidence interval was used to calculate the odds ratio.

RESULTS

The initial search identified 281 articles. In the first phase, 79 articles were eliminated due to duplicate records based on article titles. Studies that did not meet the inclusion criteria were excluded by reviewing the abstracts of 186 articles in the second step (n=152). In the third step, 20 articles with incomplete data or non-compliance with the inclusion and exclusion criteria were eliminated after examining the full texts of 34 articles. Ultimately, 14 articles were included in the present study (Fig. 1 and Table 1).

Study Characteristics

The present study included 14 randomized controlled trials with 430 participants aged 6 to 28 years. In four studies (19–

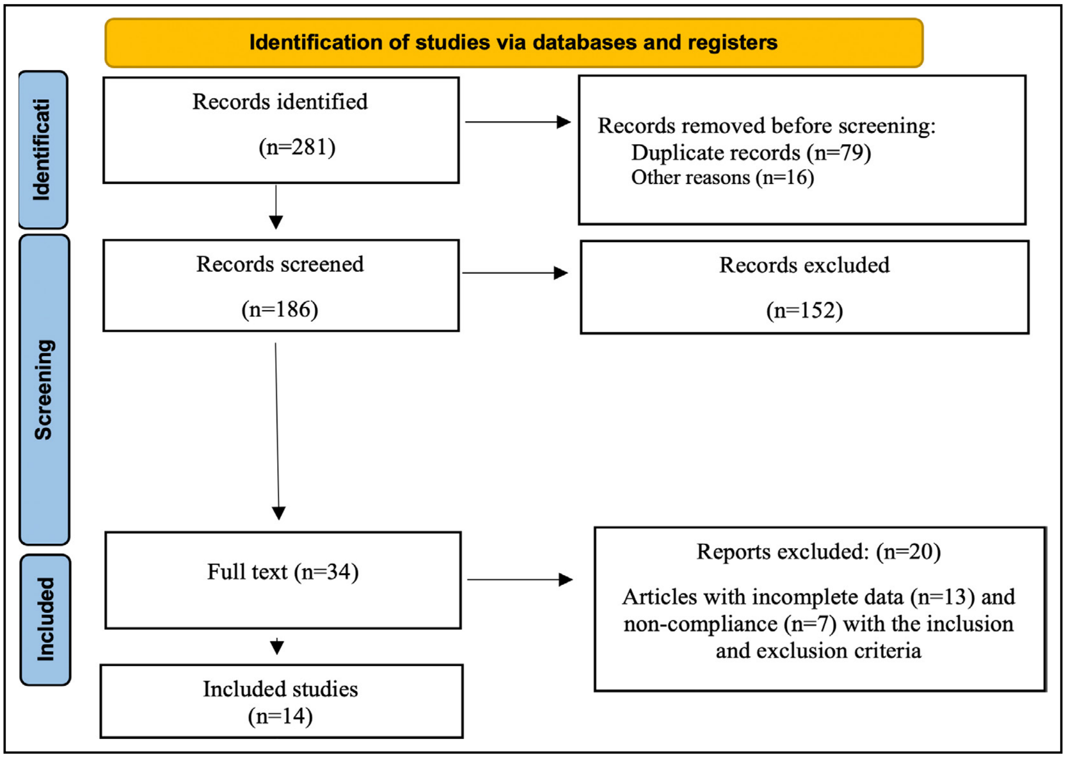

Figure 1. PRISMA 2020 flow diagram

22), gender was not reported. Among the ten studies that provided gender data, 119 females and 175 males were examined. One study (23) focused on maxillary anterior teeth, one study included single-rooted teeth (24), and the remaining studies examined incisors. Four studies tested all three scaffolds (BC, PRF, and PRP) (22, 25–27), while two scaffolds (BC, PRP) were evaluated in four studies (22, 28–30). PRF and PRP (20, 23, 24) and BC and PRF (19, 21, 31) were tested in three studies. A summary of study characteristics is provided in Table 1.

Assessments of Risk of Bias

All studies exhibited a low risk of bias concerning the randomization process, outcome measurement, selection of reporting outcomes, and overall. Missing outcome data were unclear in all studies. One study on the influence of innervation mapping had a high risk of bias (28). Three studies regarding adherence to interventions also had a high risk (20, 21, 31). However, the overall risk of bias for all included studies was low (Table 2). The meta-analysis based on apical radiolucency healing and apical closure demonstrated high certainty of evidence according to the GRADE assessment, while root-length increases showed moderate certainty of evidence (Table 3).

Blood Clot Versus Platelet-rich Plasma

The odds ratio for healing of apical radiolucency between BC and PRP was -1.30 (OR: -1.30, 95% CI; -2.68, 0.08; p=0.07), with minimal heterogeneity (I^2=0%, p=0.91). There was no statistically significant difference in the healing of periapical radiolucency between PRP and BC (Fig. 2).

Moderate heterogeneity (I^2=32.63%, p=0.20) was observed in the odds ratio for apical closure between BC and PRP (OR: -0.29, 95% CI; -1.07, 0.49; p=0.47) (Fig. 3).

With considerable heterogeneity (I^2=97.93%, p=0.00), the odds ratio for root-length increase between BC and PRP was 3.18 (OR: 3.18, 95% CI; 2.78, 3.57; p<0.01). A statistically significant difference in root length was found between BC and PRP. The root length was longer in BC than in PRF (Fig. 4).

Blood Clot Versus Platelet-rich Fibrin

With low heterogeneity (I^2=0%, p=0.70), the odds ratio for apical radiotherapy between BC and PRF was 0.01 (OR: 0.01, 95% CI; p=0.92, 0.94, p=0.99). The difference in apical radiograph improvement between BC and PRF was not statistically significant (Fig. 5).

The odds ratio for apical closure between BC and PRF was -0.25 (OR: -0.25, 95% CI; -1.08, 0.57; p=0.55) (low heterogeneity, I^2=0%, p=0.49). The difference in apical closure between BC and PRF was not statistically significant (Fig. 6).

With high heterogeneity (I^2=89.97%, p<0.001), the odds ratio for increased root length between BC and PRF was 1.75 (OR: 1.75, 95% CI; 1.38, 2.13; p<0.01). The difference in root-length increase between BC and PRF was statistically significant (Fig. 7).

For apical radiolucency healing, the odds ratio between PRP and PRF was 0.48 (OR: 0.48, 95% CI; -0.51, 1.48; p=0.34), showing minimal heterogeneity (I2=7.01%, p=0.37) (Fig. 8).

The odds ratio between PRP and PRF for apical closure was -0.08 (OR: -0.08, 95% CI; -0.91, 0.74; p=0.85), with minimal heterogeneity (I^2=0%, p=0.69). Figure 9 indicates no statistically significant difference in apical closure between PRF and PRP.

At a higher ratio (I^2=91.73%, p<0.001), the odds ratio for increased root length between PRP and PRF was 2.00 (OR: 2.00,

TABLE 1. Summary characteristics of studies

No.	Study	Number of participants	Gender of participants		Range of age	Teeth types	Treatment etiology	Scaffold types	Types of medicaments/ duration	Follow-up period (months)
			Female	Male						
1	Abo-Heikal et al. (23)	24	6	18	9–24	Maxillary anterior teeth	Trauma	PRF, PRP	Triple antibiotic/3 weeks	6, 12
2	Jayadevan et al. (24)	21	6	15	8–27	Single-rooted teeth	Trauma	PRF, PRP	Triple antibiotic/3 weeks	6, 12
3	Elsheshtawy et al. (28)	26	11	15	8–15	Incisors	Trauma	BC, PRP	Triple antibiotic	6, 9, 12
4	Rizk et al. (25)	13	6	7	8–14	Incisors	Trauma	BC, PRF, PRP	Triple antibiotic/3 weeks	6, 9, 12
5	Mittal and Parashar (19)	60	NR	NR	NR	Incisors	NR	BC, PRF	Double antibiotic/4 weeks	6, 12
6	Ragab et al. (31)	19	7	12	7–12	Incisors	Trauma	BC, PRF	Double antibiotic/3 weeks	6, 12
7	Ulusoy et al. (26)	77	33	44	8–11	Incisors	Trauma	BC, PRF, PRP	Triple antibiotic/4 weeks	6, 9, 12
8	Santhakumar et al. (20)	40	NR	NR	7–12	Incisors	NR	PRF, PRP	Triple antibiotic/3 weeks	6, 12, 18
9	Verma (29)	20	8	12	10–24	Incisors and premolars	NR	BC, PRP	Triple antibiotic/3 weeks	6, 9, 12
10	Shivashankar et al. (27)	60	28	32	6–28	Incisors	Trauma	BC, PRF, PRP	Triple antibiotic/3 weeks	6, 9, 12
11	Alagl et al. (30)	16	6	10	8–11	Incisors and premolars	Trauma and caries	BC, PRP	Triple antibiotic/3 weeks	6, 12
12	Sharma and Mittal (21)	16	NR	NR	10–25	Incisors	Trauma	BC, PRF	Triple antibiotic/4 weeks	6, 12
13	Narang et al. (22)	20	NR	NR	<20	NR	NR	BC, PRF, PRP	Triple antibiotic/4 weeks	6, 12, 18
14	Bezgin et al. (32)	18	8	10	7–13	Incisors and premolars	Trauma and caries	BC, PRP	Triple antibiotic/3 weeks	6, 9, 12, 18

PRF: Platelet-rich fibrin, PRP: Plasma-rich plasma, BC: Blood clot, NR: Not reported

TABLE 2. Bias assessment of cochrane risk of bias tool

Study	Risk of bias due to the randomization process	Effect of assignment of innervation	Effect of adhering to intervention	Missing outcome data	Measuring of outcome	Selection of the report result	Overall
Abo-Heikal et al. (23)	Low	Low	Low	Unclear	Low	Low	Low
Jayadevan et al. (24)	Low	Low	Low	Unclear	Low	Low	Low
Elsheshtawy et al. (28)	Low	High	Low	Unclear	Low	Low	Low
Rizk et al. (25)	Low	Low	Low	Unclear	Low	Low	Low
Mittal and Parashar (19)	Low	Low	Low	Unclear	Low	Low	Low
Ragab et al. (31)	Low	Low	High	Unclear	Low	Low	Low
Ulusoy et al. (26)	Low	Low	Low	Unclear	Low	Low	Low
Santhakumar et al. (20)	Low	Low	High	Unclear	Low	Low	Low
Verma (29)	Low	Low	Low	Unclear	Low	Low	Low
Shivashankar et al. (27)	Low	Low	Low	Unclear	Low	Low	Low
Alagl et al. (30)	Low	Low	Low	Unclear	Low	Low	Low
Sharma and Mittal (21)	Low	Low	High	Unclear	Low	Low	Low
Narang et al. (22)	Low	Low	Low	Unclear	Low	Low	Low
Bezgin et al. (32)	Low	Low	Low	Unclear	Low	Low	Low

High, Unclear, Low

TABLE 3. Certainty of the evidence (GRADE)

Outcomes	Variable	No. of participants (no. of studies)	Risk of bias	Factors that downgrade the certainty of the evidence					Certainty of the evidence
				Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
Healing of apical radiolucency	PRF, PRP	85 (3)	RCT	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	⊕⊕⊕⊕/A
	BC, PRP	80 (4)		No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	
	BC, PRF, PRP	170 (4)		No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	
	BC, PRF	95 (3)		No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	
Root length increases	PRF, PRP	85 (3)		No serious inconsistency	No serious inconsistency	Serious	No serious inconsistency	No serious inconsistency	⊕⊕⊕⊖/B
	BC, PRP	80 (4)		No serious inconsistency	No serious inconsistency	Serious	No serious inconsistency	No serious inconsistency	
	BC, PRF, PRP	170 (4)		No serious inconsistency	No serious inconsistency	Serious	No serious inconsistency	No serious inconsistency	
	BC, PRF	95 (3)		No serious inconsistency	No serious inconsistency	Serious	No serious inconsistency	No serious inconsistency	
Apical closure	PRF, PRP	85 (3)		No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	⊕⊕⊕⊕/A
	BC, PRP	80 (4)		No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	
	BC, PRF, PRP	170 (4)		No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	
	BC, PRF	95 (3)		No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	

A: Refers to a high certainty of evidence; B: Refers to a moderate certainty of evidence. GRADE: Grading of Recommendations, Assessment, Development and Evaluation, PRF: Platelet-rich fibrin, PRP: Plasma-rich plasma, BC: Blood clot, RCT: Randomized controlled trial

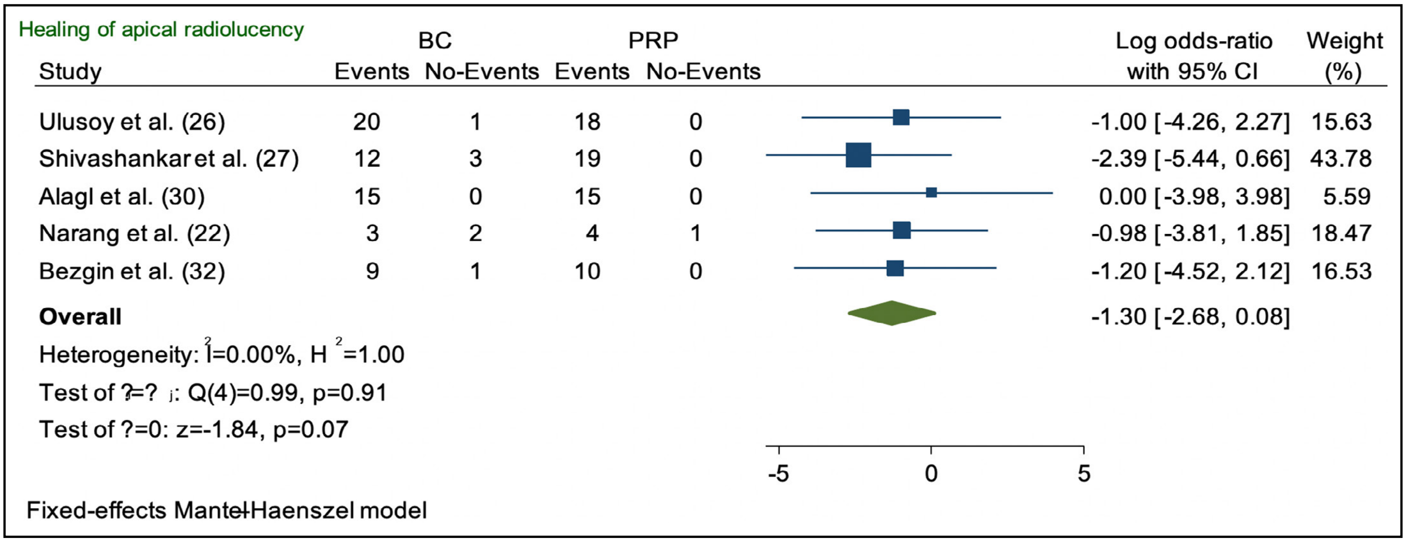

Figure 2. The ratio of survival rate of the apical radiograph between BC and PRP

BC: Blood clot, PRP: Plasma-rich plasma, CI: Confidence interval

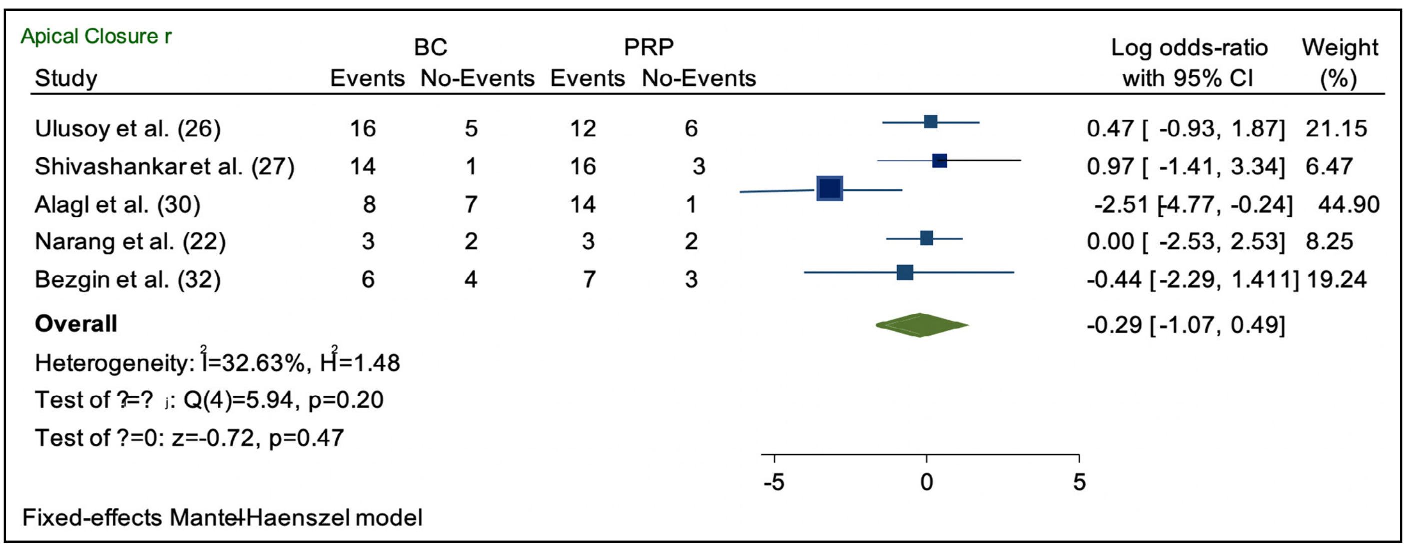

Figure 3. Odds ratio of apical closure between BC and PRP

BC: Blood clot, PRP: Plasma-rich plasma, CI: Confidence interval

95% CI; 1.38, 2.13; p<0.01). A statistically significant difference in root-length growth was observed between PRP and PRF (Fig. 10).

DISCUSSION

This study aimed to examine the radiological and clinical findings using three scaffolds: BC, PRP, and PRF. When comparing the two groups, BC vs PRP, the current meta-analysis found no discernible differences in healing of apical radiolucency or apical closure. Both groups achieved comparable results with PRF. Similar insignificant findings were also observed for apical closure across all comparisons. However, a closer examination of the root-length increase data revealed that BC had a greater root-length increase than both PRF and PRP. Minimal differences in apical occlusion healing outcomes and radiolucency were noted between studies. Nonetheless, the results regarding root-length increase exhibited considerable heterogeneity, warranting caution in interpretation. Some studies found that collagen and PRF scaffolds outperform BC scaffolds (23, 30, 32). Most studies included in this analysis evaluated radiographic outcomes using two-dimensional radiography; however, only one study (21) accurately influenced these results due to the use of a beamforming computer.

The present study builds upon a previous meta-analysis (33) that focused on clinical research examining the influence of the investigated scaffolds on the success of root tissue regeneration. This previous report (33) indicated that the apical irradiation of the BC group improved more than that of the PRP group, which is in contrast with the findings of the current study. The discrepancy may be attributed to differences in selection criteria, as the follow-up period and timing of clinical findings can influence result collection.

A previous meta-analysis (33) reported contradictory conclusions to those of the present study, suggesting that BC and PRP were equally effective in improving apical radiolucency,

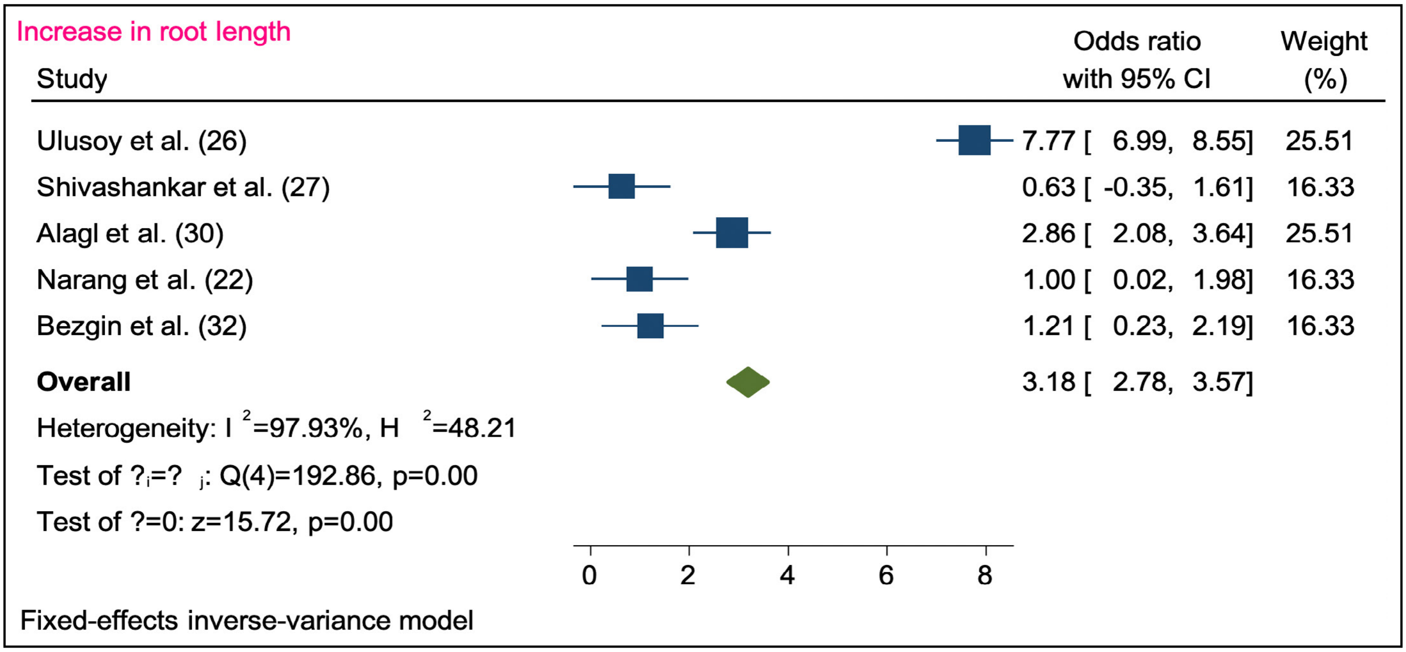

Figure 4. Odds ratio of root length increases between BC and PRP

CI: Confidence interval, BC: Blood clot, PRP: Plasma-rich plasma

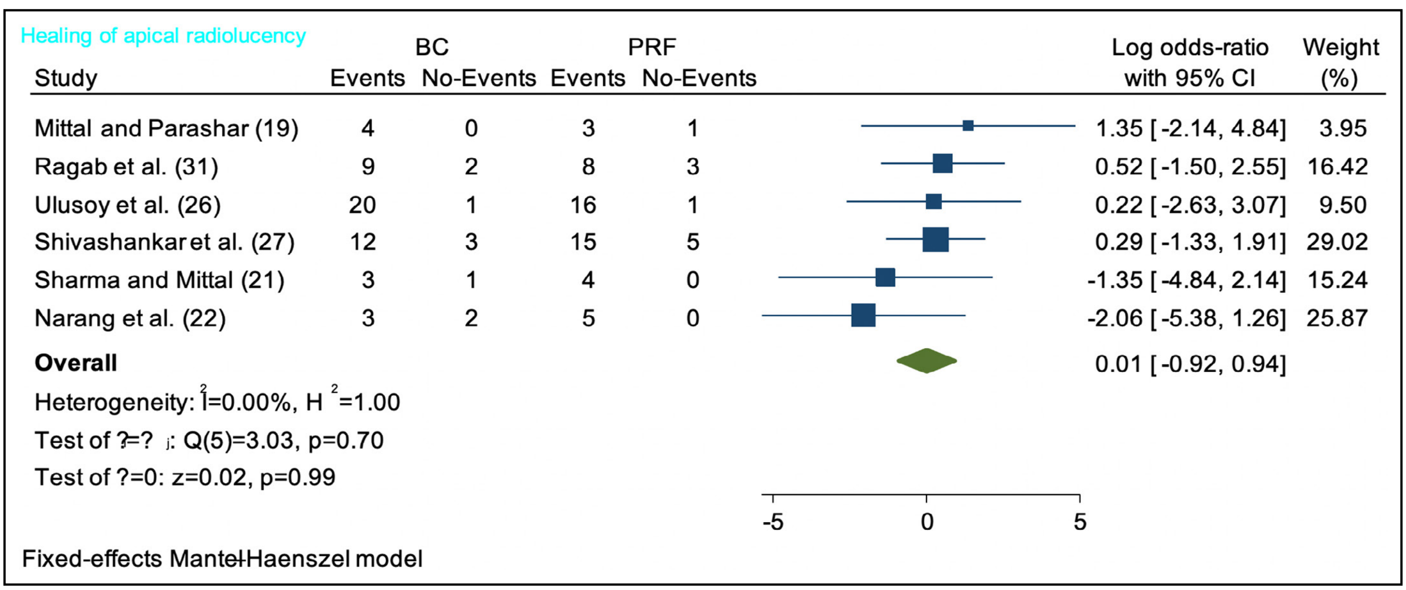

Figure 5. Odds ratio of apical radiolucent wound healing between BC and PRF

BC: Blood clot, PRF: Platelet-rich fibrin, CI: Confidence interval

apical closure, and the root length of non-vital immature permanent teeth during tissue regeneration. The differences in findings may stem from variations in clinical and radiographic results across different follow-up periods in the selected studies, as treatment outcomes may also be affected by extended follow-up durations. Furthermore, the results of this investigation align with the present study's findings on root elongation. A systematic review and network meta-analysis examined the influence of oral frameworks on the success of restorative root canal therapy (34). No statistically significant differences in clinical success were found among the BC, PRP, and PRF regimens, with apical root closure being consistent across all scaffolds, which is consistent with the results of the current study. The overall risk of bias in the selected studies was assessed as low. The root length was longer in BC than in PRF and PRP, with a statistically significant difference in root-length growth between PRP and PRF. Low heterogeneity was observed between studies, indicating the reliable results of the current study. However, high heterogeneity was noted when examining root length between PRP and PRF, PRF and BC, and BC and PRP. Heterogeneity among studies could be due to variability of the clinical protocols applied during regenerative endodontic procedures, measurement of parameters like apical radiolucency, apical closure and root-length growth, types of teeth, treatment etiology, types of medicaments, and duration of treatment.

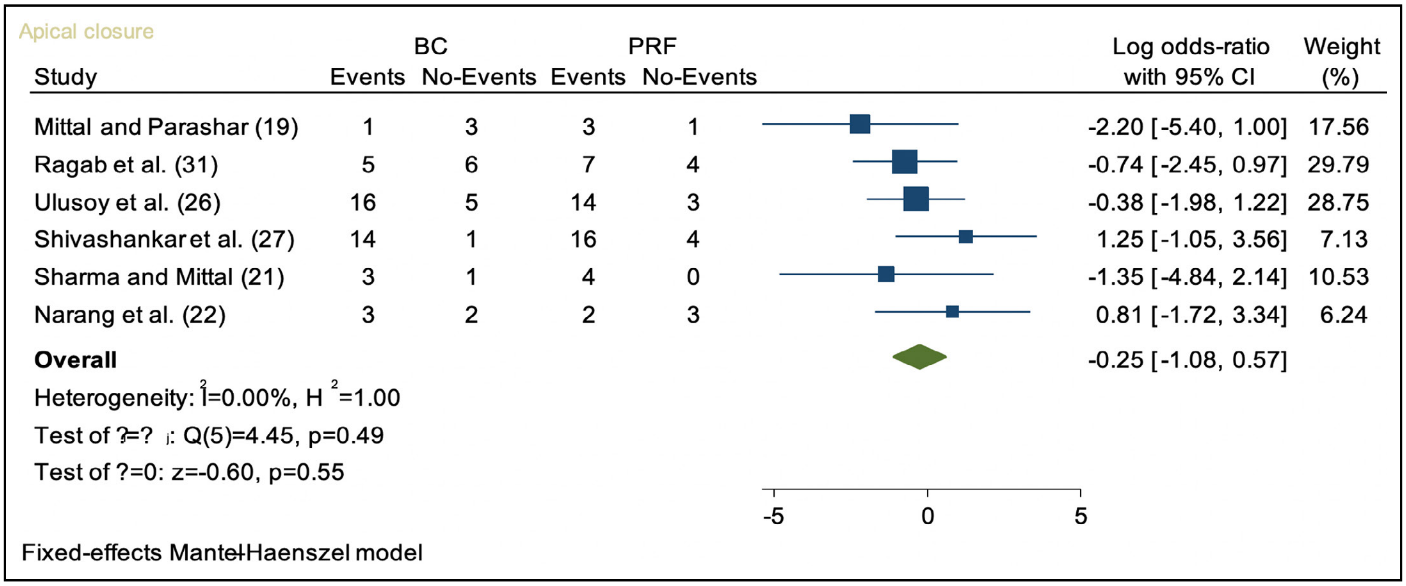

Figure 6. Apical closure of the BC and PRF

CI: Confidence interval, BC: Blood clot, PRF: Platelet-rich fibrin

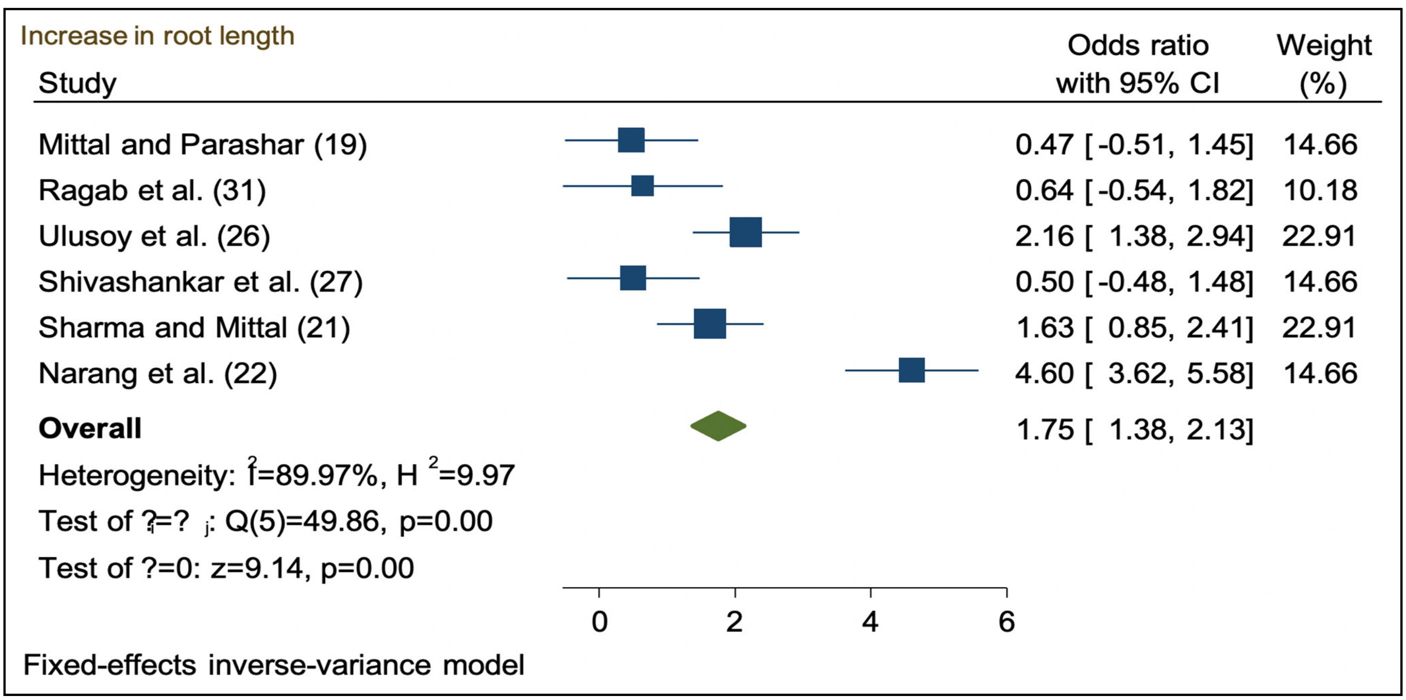

Figure 7. The ratio of the growth in root length between PRF and BC

CI: Confidence interval, PRF: Platelet-rich fibrin, BC: Blood clot

Many of these factors could be standardized in near future whereas few other factors would require extensive research. But the fact is that, the included studies in this analysis have been conducted during the last ten years and variability factors related to measurements of radiographic changes still remain in the included studies. Many factors cause heterogeneity during RCTs, and it is not possible to negate them through subgroup or moderator analysis. As a result, outcome data in this analysis shows high level of heterogeneity. Future studies should use similar and standard clinical protocols during root restorative procedures, also the length of the treatment period should also be reported in the studies, on the other hand, for RCT studies, the same protocols should be used from determining the sample size to data analysis. Also, further studies with similar methodologies and larger sample sizes are essential to confirm the present findings. The GRADE approach indicated that the evidence from randomized clinical trials examining the healing of apical radiolucency and apical closure of biomaterial scaffolds in regenerative endodontic therapy was high, while the selected studies examining root length provided moderate evidence.

Limitations of the present study include the small sample size and the lack of studies comparing different scaffold

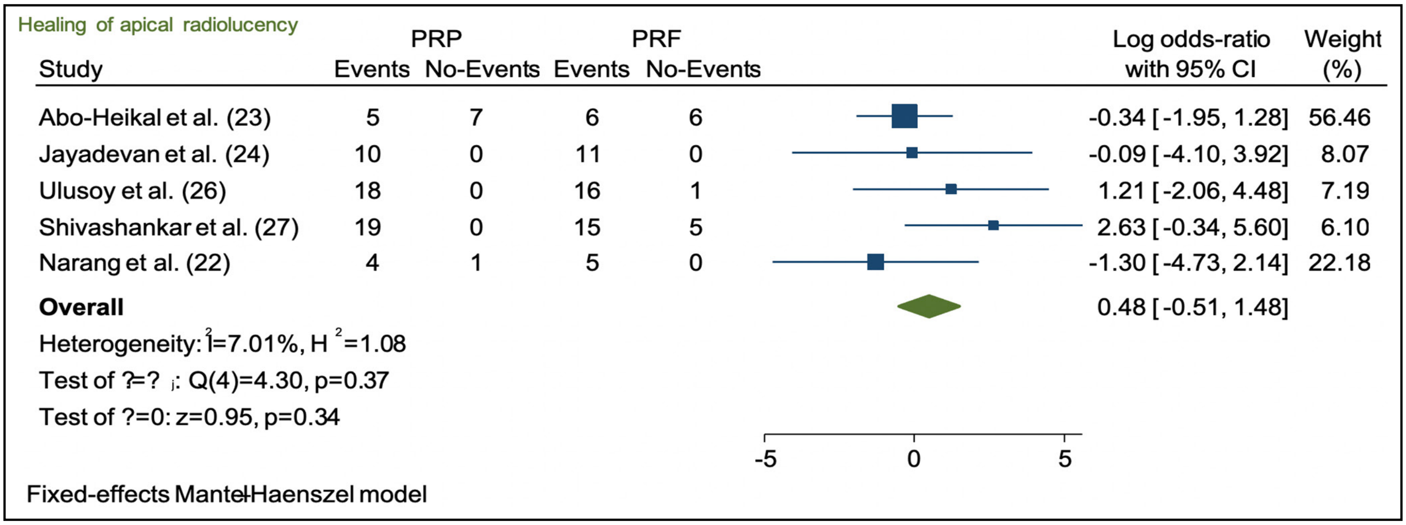

Figure 8. The unusual ratio of PRP to PRF in the treatment of apical radiolucency

PRP: Plasma-rich plasma, PRF: Platelet-rich fibrin, CI: Confidence interval

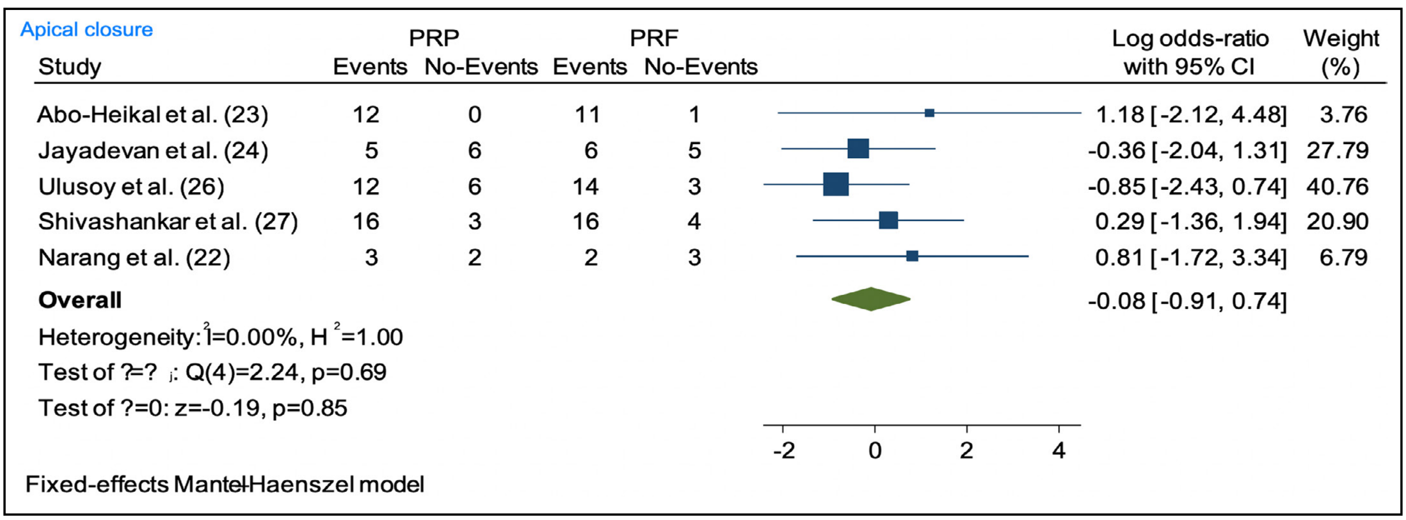

Figure 9. Apical closure ratio between PRF and PRP

PRP: Plasma-rich plasma, PRF: Platelet-rich fibrin, CI: Confidence interval

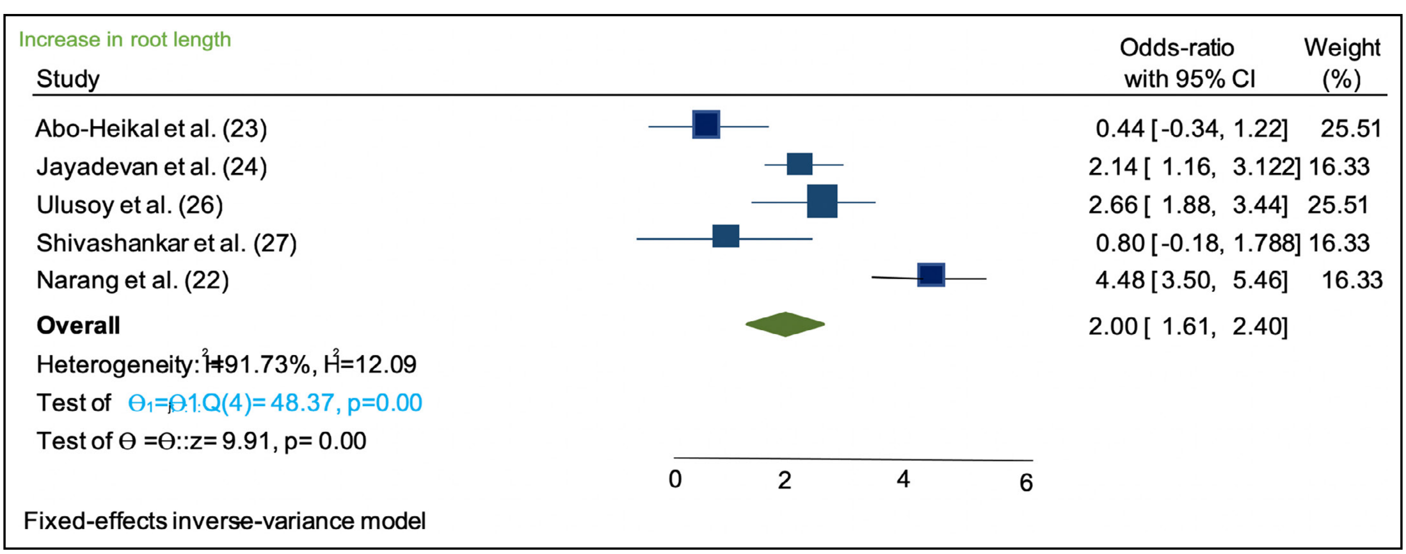

Figure 10. Root length between PRP and PRF

CI: Confidence interval, PRP: Plasma-rich plasma, PRF: Platelet-rich fibrin materials. Although the follow-up period in this study was one year and consistent across all studies, the follow-up periods in other studies varied. Future research should involve radiological evaluations and conventional clinical protocols, as well as larger sample sizes and follow-up periods of 18 to 24 months are required.

CONCLUSION

The current meta-analysis demonstrates that the increase in root length in BC is greater than that in PRP and PRF, respectively. The effects of BC, PRP, and PRF on the development of apical radiolucency and apical closure are not statistically significant. Therefore, BC is the preferred technique as a primary scaffold in regenerative endodontic therapy. In cases with problematic intracanal blood flow, PRP and PRF should be utilized.

Disclosures

Online Appendix: https://jag.journalagent.com/eurendodj/abs_files/EEJ-30922/EEJ-30922_(0)_supp._table.1.pdf

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