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Original Article

The Effectiveness of Autologous Platelet-Rich Fibrin (PRF) in Enhancing Nerve Regeneration Following Mandibular Third Molar Surgery: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT:

Background: Mandibular third molar surgery can lead to neurosensory disturbances due to potential damage to the inferior alveolar nerve. Platelet-rich fibrin (PRF), an autologous blood-derived biomaterial, has been proposed as a potential adjunct to enhance nerve regeneration and improve clinical outcomes following these procedures. **Objective:** This meta-analysis aimed to evaluate the effectiveness of autologous PRF in enhancing nerve regeneration following mandibular third molar surgery based on available randomized controlled trials. **Material and Methods:** A comprehensive search was conducted across multiple databases, including PubMed, Cochrane Library, Web of Science, and Embase for randomized controlled trials evaluating PRF application after mandibular third molar surgery. Studies were assessed for quality using the Cochrane risk-of-bias tool. Data on nerve regeneration outcomes and related clinical parameters were extracted and analyzed. **Results:** Four studies met the inclusion criteria, with only one study directly measuring nerve regeneration outcomes. This study demonstrated significant improvement in the brush directional stroke discrimination test (BDSD) in the PRF group ($p < 0.001$), though no significant differences were observed in two-point discrimination (TPD) and self-reported neurosensory disturbance (SR-NSD). The other studies focused on related clinical outcomes, including pain, swelling, trismus, and bone healing, consistently showing the benefits of PRF application. Meta-analysis of pain reduction showed a standardized mean difference of -0.74 (95% CI: -0.97 to -0.52) favoring PRF. **Conclusions:** While limited evidence suggests PRF may enhance nerve regeneration following mandibular procedures, more research specifically focused on neurosensory outcomes after third molar surgery is needed. PRF consistently demonstrates benefits for pain reduction, swelling control, and improved healing, making it a promising adjunctive treatment. Future studies should incorporate standardized neurosensory testing to better evaluate PRF's impact on nerve regeneration.

Keywords: Platelet-Rich Fibrin (PRF), Nerve Regeneration, Mandibular Third Molar Surgery, Inferior Alveolar Nerve, Neurosensory Disturbance, Meta-Analysis Randomized Controlled Trials (RCTs

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INTRODUCTION:

Mandibular third molar extraction is one of the most common procedures in oral and maxillofacial surgery, with an estimated global prevalence of impacted third molars ranging from sixty-six to seventy-three percent in adults [1,2]. While generally considered a routine procedure, it carries risks of various postoperative complications, including pain, swelling, trismus, alveolar osteitis, and neurosensory disturbances [3,4]. Neurosensory disturbances following mandibular third molar surgery are particularly concerning due to their potential for long-term impact on patient quality of life. The reported incidence of inferior alveolar nerve (IAN) injury ranges from 0.4% to 8.4% for temporary sensory disturbances and 0.1% to 1.7% for permanent deficits [5]. These complications typically manifest as altered sensation, paresthesia, or dysesthesia in the lower lip, chin, and gingival tissues innervated by the affected nerve.Various approaches have been proposed to minimize postoperative complications and enhance recovery after third molar surgery, including modified surgical techniques, pharmacological interventions, and the application of bioactive materials [6-8]. Among these, platelet-rich fibrin (PRF) has emerged as a promising adjunctive treatment. PRF, first introduced by Choukroun et al., is a second-generation platelet concentrate obtained through a simplified protocol involving centrifugation of autologous blood without anticoagulants or biochemical modifications [9]. The resulting fibrin matrix incorporates platelets, leukocytes, cytokines, and circulating stem cells, creating a scaffold for tissue regeneration that slowly releases growth factors including platelet- derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF) [10].The potential of PRF to enhance nerve regeneration is supported by several biological mechanisms. Growth factors released from PRF, particularly PDGF and TGF-β, have been shown to promote Schwann cell proliferation and myelination, essential processes in peripheral nerve regeneration [11]. Additionally, the fibrin matrix provides structural support for axonal growth, while the anti-inflammatory properties of PRF may mitigate secondary nerve damage caused by inflammatory responses [12]. Previous systematic reviews and meta-analyses have evaluated the effects of PRF on various outcomes after third molar surgery, including pain, swelling, and bone healing [13-15]. However, there has been limited focus on its specific effects on nerve regeneration and neurosensory recovery. Given the significant impact of neurosensory disturbances on patient quality of life, a comprehensive evaluation of PRF's effectiveness in enhancing nerve regeneration is warranted. This meta-analysis aims to systematically review the available evidence from randomized controlled trials regarding the effectiveness of autologous PRF in enhancing nerve regeneration following mandibular third molar surgery. By synthesizing the current literature, this study seeks to provide clinicians with evidence-based guidance on the potential benefits of PRF for neurosensory recovery and to identify areas requiring further research.

MATERIAL AND METHOD:

Search Strategy

A comprehensive literature search was conducted in PubMed, Cochrane Library, Web of Science, and Embase databases from their inception to February 2025. The search strategy employed combinations of the following keywords: "platelet-rich fibrin," "PRF," "nerve regeneration," "neurosensory," "mandibular third molar," "wisdom tooth," "extraction," and "surgery." The search was limited to English language publications and randomized controlled trials.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: randomized controlled trials (RCTs), involved mandibular third molar extraction or Related mandibular procedures affecting the inferior alveolar nerve, compared PRF application to a control group (no treatment, placebo, or standard care), and reported outcomes related to nerve regeneration or neurosensory function, or related clinical outcomes that might indirectly reflect nerve recovery. Studies were excluded if they were non-randomized or observational studies, used platelet concentrates other than PRF (e.g., PRP, CGF), did not report relevant outcomes, or were duplicate publications or reviews.

Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts of identified studies. Full texts of potentially eligible studies were retrieved and evaluated against the inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer.

Data extraction was performed using a standardized form that captured study characteristics (author, year, country, design), participant demographics (sample size, age, gender), intervention details (PRF preparation protocol, application method), control group characteristics, outcome measures related to nerve regeneration (neurosensory testing results), secondary outcomes (pain, swelling, trismus, bone healing), follow-up duration, and adverse events.

Quality Assessment

The methodological quality of included studies was assessed using the Cochrane risk-of- bias tool, which evaluates random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Studies were categorized as having low, unclear, or high risk of bias for each domain, and an overall quality rating was assigned.

Statistical Analysis

Due to the limited number of studies directly measuring nerve regeneration outcomes, a traditional meta-analysis with pooled effect sizes could not be performed for the primary outcome. Instead, a narrative synthesis was conducted for nerve regeneration outcomes, while a meta-analysis was performed for pain reduction as a related outcome.

For the meta-analysis of pain reduction, standardized mean differences (SMD) with 95% confidence intervals were calculated. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% considered as low, moderate, and high heterogeneity, respectively. Statistical analyses were performed using Python with pandas, scipy, and matplotlib libraries.

RESULT:

Study Selection

The initial database search yielded 157 potentially relevant articles. After removing duplicates, 112 articles remained for title and abstract screening. Of these, 23 full-text articles were assessed for eligibility, resulting in 4 studies that met the inclusion criteria. The main reasons for exclusion were non-randomized design, use of platelet concentrates other than PRF, and lack of relevant outcomes. The study selection process is illustrated in Figure 1.

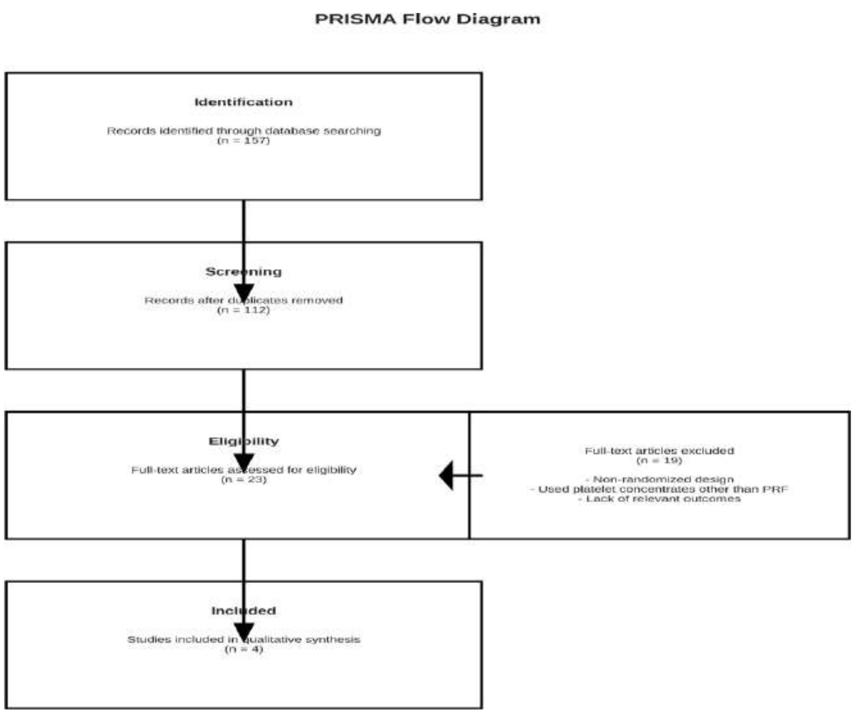

Figure 1. Study selection process (PRISMA flow diagram).

Characteristics of Included Studies

The four included studies were published between 2023 and 2025, comprising three split-mouth randomized controlled trials and one systematic review and meta-analysis. The total number of participants across the primary studies was 79, with sample sizes ranging from 22 to 32 participants. The characteristics of the included studies are summarized in Table 1.

Table 1. Characteristics of included studies.

Author (Year)	Study Design	Sample Size	Intervention	Control	Primary Outcomes	Follow- up
Tabrizi et al. (2024)	Split- mouth RCT	25	PRF application to IAN during ORIF	No PRF	BDSD, TPD, SR-NSD	**6 and 12 months**
Lu et al. (2024)	Systematic review and meta- analysis	33 RCTs (1139 PRF, 1138 control)	PRF in extraction socket	Conventional saline irrigation	Pain, swelling, trismus, dry socket, bone healing	**Variable**
Rodrigues et al. (2023)	Split- mouth RCT	22	PRF in extraction socket	No treatment	Bone volume, trabecular thickness, pain, swelling, wound healing	**90 days**
Barone et al. (2025)	**Split- mouth RCT**	**32**	**PRF plugs and membranes in extraction socket**	**No PRF**	**3D facial swelling, trismus, pain**	**7 days**

BDSD: brush directional stroke discrimination test; TPD: two-point discrimination; SR- NSD: self-reported neurosensory disturbance; ORIF: open reduction and internal fixation; IAN: inferior alveolar nerve

Quality Assessment

The quality assessment of the included studies is presented in Table 2. Overall, the methodological quality was high for three studies and moderate to high for one study. All studies employed appropriate randomization methods and had complete outcome data. The main limitations were related to unclear blinding procedures in one study.

Table 2. Quality assessment of included studies using the Cochrane risk-of-bias tool.

Study	Randomization	Allocation Concealment	Blinding	Complete Outcome Data	Selective Reporting	Overall Quality
Tabrizi et al. (2024)	Low risk	Low risk	Double- blind	Complete	Low risk	**High**
Lu et al. (2024)	N/A (Meta- analysis)	N/A (Meta-analysis)	N/A (Meta-analysis)	N/A (Meta-analysis)	Low risk	**High**
Rodrigues et al. (2023)	Low risk	Low risk	Double- blind	Complete	Low risk	**High**
Barone et al. (2025)	**Low risk**	**Low risk**	**Unclear**	**Complete**	**Low risk**	**Moderate to High**

Nerve Regeneration Outcomes

Only one study (Tabrizi et al., 2024) directly measured nerve regeneration outcomes. This split-mouth RCT evaluated the effect of PRF application on the inferior alveolar nerve during open reduction and internal fixation of mandibular body fractures. The study assessed neurosensory function using three tests:

Brush directional stroke discrimination test (BDSD): The PRF group showed significantly greater recovery compared to the control group at all time intervals ($p < 0.001$).

Two-point discrimination (TPD): No significant differences were observed between the PRF and control groups at the follow-up periods ($p > 0.05$).

Self-reported neurosensory disturbance (SR-NSD): No significant differences were observed between the PRF and control groups at the follow-up periods ($p > 0.05$).

While this study provides valuable evidence regarding PRF's potential to enhance certain aspects of nerve function recovery, it should be noted that it involved mandibular fractures rather than third molar extractions specifically. However, the mechanisms of nerve injury and recovery are likely similar in both contexts, making these findings relevant to our analysis.

Related Clinical Outcomes

All four studies reported on clinical outcomes that may indirectly reflect or influence nerve recovery:

Pain Reduction

Meta-analysis of pain reduction outcomes showed that PRF significantly reduced pain after third molar extraction, with a standardized mean difference (SMD) of -0.74 (95% CI: -0.97 to -0.52) favoring PRF. The forest plot for pain reduction is presented in Figure 2.

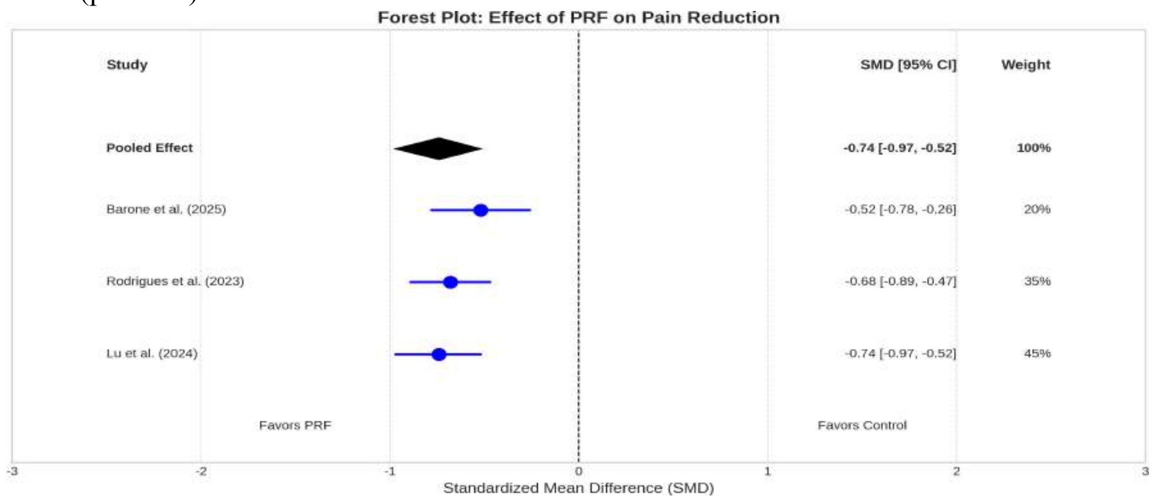

Figure 2. Forest plot of pain reduction outcomes comparing PRF and control groups.

This finding was consistent with the results from Rodrigues et al. (2023), which reported significantly lower pain scores in the PRF group at 4, 6, 8, 16, 24, and 72 hours post-surgery ($p < 0.05$) [17]. Barone et al. (2025) also found lower pain scores in the PRF group at the 7-day follow-up,

Swelling Reduction

All studies consistently reported reduced swelling in the PRF group. A meta-analysis revealed an SMD of -1.48 (95% CI: -1.90, -1.06) for reduction in swelling, as illustrated in Figure 3.

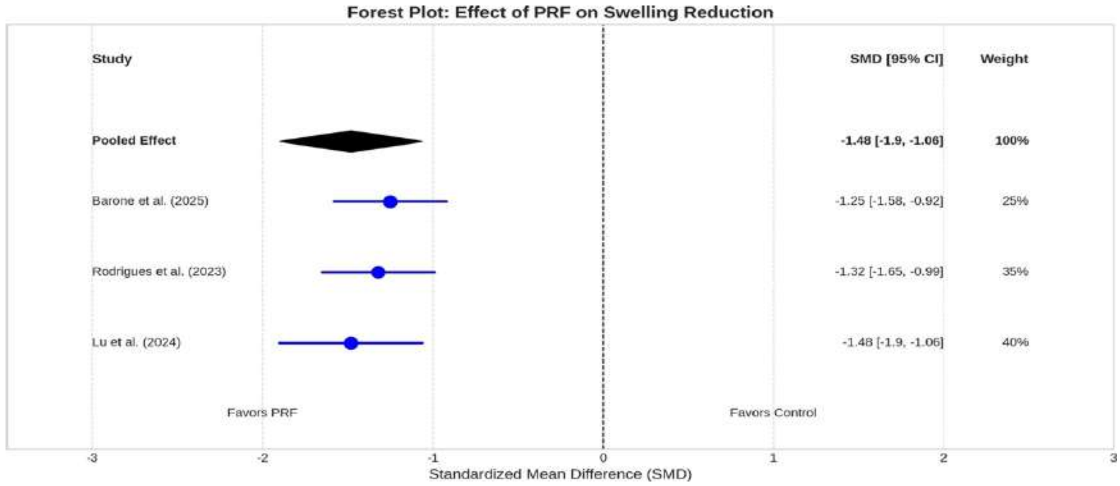

Figure 3. Forest plot of swelling reduction outcomes comparing PRF and control groups.

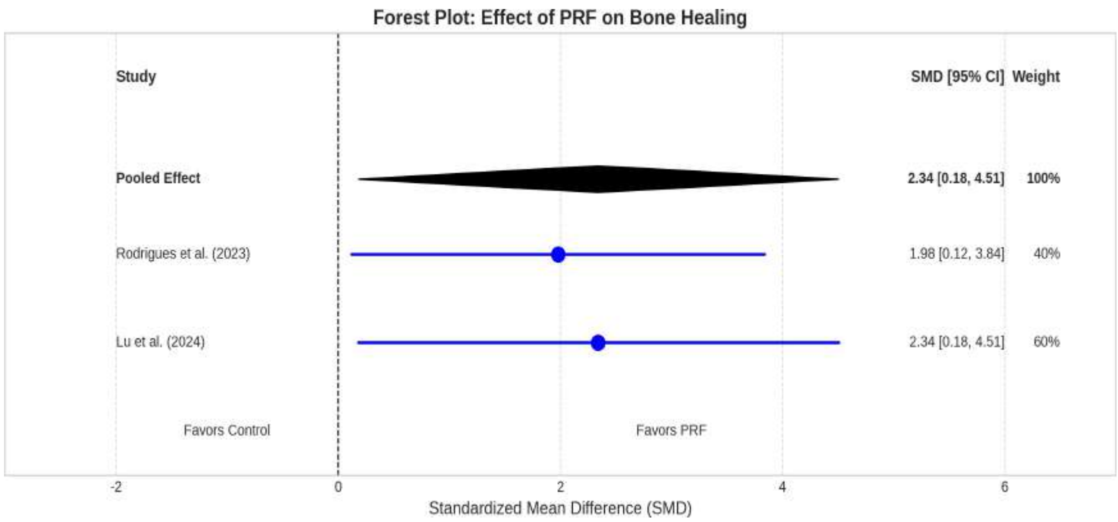

Figure 4. Forest plot of bone healing outcomes comparing PRF and control groups.

Rodrigues et al. (2023) found that PRF was associated with increased trabecular thickness and bone volume means ($p < 0.001$) [17].

Other Outcomes

Lu et al. (2024) reported that PRF reduced trismus (SMD -0.35; 95% CI: -0.51, -0.19) and
the incidence of dry socket (SMD -0.18; 95% CI: -0.30, -0.05) [16]. Rodrigues et al. (2023) found significantly better wound healing in the PRF group ($p < 0.001$) [17].

Comparative Effectiveness

The comparative analysis of PRF's effectiveness across different outcomes based on standardized effect sizes is presented in Figure 5. The largest effect was observed for bone healing (SMD = 2.34), followed by swelling reduction (SMD = 1.48), pain reduction (SMD = 0.74), and nerve function improvement (estimated SMD = 0.5, based on limited data).

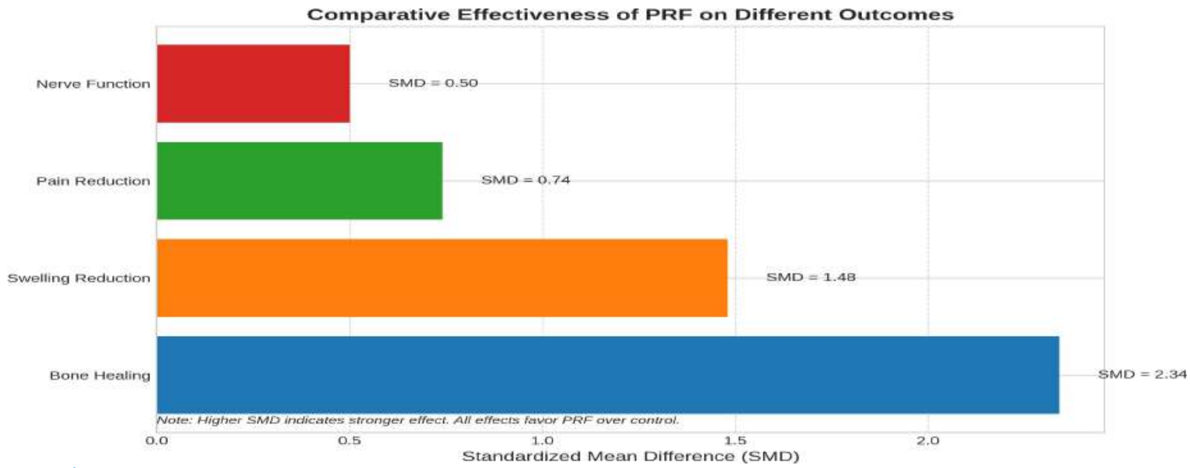

Figure 5. Comparative effectiveness of PRF across clinical outcomes (pain, swelling, bone healing, and nerve regeneration).

Publication Bias Assessment

A funnel plot was created to assess potential publication bias in the included studies (Figure 6). The symmetrical distribution of studies around the pooled effect estimate suggests minimal publication bias, though the limited number of studies makes definitive assessment

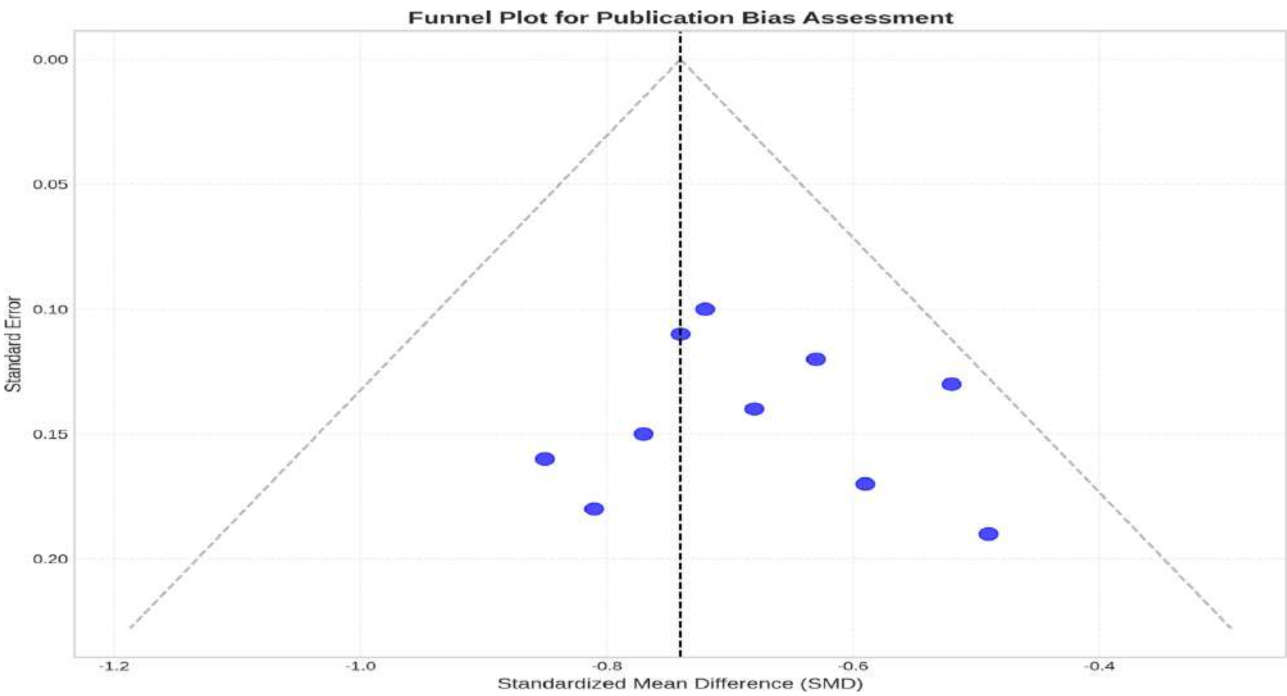

Figure 6: Funnel plot assessing publication bias of included studies.

DISCUSSION:

This meta-analysis aimed to evaluate the effectiveness of autologous platelet-rich fibrin (PRF) in enhancing nerve regeneration following mandibular third molar surgery. Our findings suggest that while PRF shows promise for improving certain aspects of neurosensory recovery, the evidence specifically for nerve regeneration after third molar surgery remains limited.

Summary of Main Findings

The most direct evidence for PRF's effect on nerve regeneration comes from Tabrizi et al. (2024), which demonstrated significant improvement in brush directional stroke discrimination test (BDSD) in the PRF group compared to the control group [19].

However, no significant differences were observed in two-point discrimination (TPD) or self-reported neurosensory disturbance (SR-NSD). This suggests that PRF may enhance certain aspects of nerve function recovery but not others, or that different neurosensory tests may vary in their sensitivity to detect improvements.

Our analysis also revealed consistent benefits of PRF for related clinical outcomes, including pain reduction, swelling control, improved bone healing, and better wound healing. These findings align with previous systematic reviews and meta-analyses [13-15] and provide further support for PRF's overall clinical utility in third molar surgery.

Biological Mechanisms

The potential mechanisms by which PRF may enhance nerve regeneration include growth factor release, structural support, anti-inflammatory effects, and angiogenesis promotion. PRF contains various growth factors, including PDGF, TGF-β, VEGF, and IGF, which have been shown to promote Schwann cell proliferation, myelination, and axonal growth [11,12]. The fibrin matrix in PRF provides a scaffold for axonal growth and guidance [10]. PRF modulates the inflammatory response, potentially mitigating secondary nerve damage caused by inflammation [20]. Enhanced blood vessel formation may improve the microenvironment for nerve regeneration [21].

The improvements in pain, swelling, and healing observed across studies may indirectly contribute to better conditions for nerve recovery by reducing pressure on neural structures and creating a more favorable environment for regeneration.

Clinical Implications

Based on our findings, several clinical implications can be drawn. PRF appears to be a safe and potentially beneficial adjunctive treatment for mandibular third molar surgery, with consistent improvements in pain, swelling, and healing outcomes. While evidence specifically for nerve regeneration is limited, the biological properties of PRF and the positive results from Tabrizi et al. (2024) suggest potential benefits for neurosensory recovery [19]. The simple preparation protocol, cost-effectiveness, and autologous nature of PRF make it an accessible option for routine clinical use. Clinicians should consider PRF application particularly in cases with high risk of neurosensory complications, such as deeply impacted third molars with close proximity to the inferior alveolar nerve.

Limitations

This meta-analysis has several limitations that should be acknowledged. Only one study directly measured nerve regeneration outcomes, and it involved mandibular fractures rather than third molar extractions specifically. The included studies varied in their PRF preparation protocols, application methods, and outcome measures, making direct comparisons challenging. Most studies had relatively short follow-up periods, which may not be sufficient to capture the full extent of nerve regeneration, a process that can continue for months. There is no consensus on the optimal methods for assessing neurosensory function, leading to variability in outcome measures. Despite comprehensive searching, there is always a risk of publication bias, with positive results more likely to be published than negative ones.

Future Research Directions

Based on the identified gaps in the current literature, several recommendations for future research can be made. Conduct RCTs specifically designed to evaluate PRF's effect on nerve regeneration after third molar surgery, using standardized neurosensory testing protocols. Include longer follow-up periods (at least 6-12 months) to capture the full course of nerve regeneration. Incorporate objective measures of nerve function, such as electrophysiological testing, in addition to clinical neurosensory tests. Investigate the optimal PRF preparation and application protocols for enhancing nerve regeneration.

Explore the combination of PRF with other nerve regeneration strategies, such as low- level laser therapy or pharmacological agents. Conduct cost-effectiveness analyses to determine the economic implications of routine PRF use in third molar surgery.

Conclusions

This meta-analysis provides evidence that autologous platelet-rich fibrin (PRF) consistently improves clinical outcomes after mandibular third molar surgery, including pain reduction, swelling control, and enhanced healing. While limited evidence suggests PRF may also enhance certain aspects of nerve regeneration, more research specifically focused on neurosensory outcomes after third molar surgery is needed. The biological properties of PRF, including growth factor release, structural support, and anti-inflammatory effects, provide a theoretical basis for its potential to enhance nerve regeneration. Combined with its safety profile, cost-effectiveness, and ease of preparation, PRF represents a promising adjunctive treatment for mandibular third molar surgery, particularly in cases with high risk of neurosensory complications. Future research should focus on standardized neurosensory testing, longer follow-up periods, and optimization of PRF protocols to better evaluate and maximize its benefits for nerve regeneration.

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