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SYSTEMATIC REVIEW

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Comparative efficacy of different doses of platelet-rich plasma injection in the treatment of knee osteoarthritis: a systematic review and network meta-analysis

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Abstract

Background Platelet-rich plasma (PRP) is increasingly used for knee osteoarthritis, but the optimal dosage still needs to be determined. This systematic review and network meta-analysis aimed to compare the efficacy of various PRP doses in treating knee osteoarthritis.

Methods We searched published data in Embase, PubMed, Scopus, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, with no language restrictions from the inception to 30 September 2024. We enrolled randomized controlled trials (RCTs) that compared the clinical efficiency of different doses of PRP injection in patients with knee osteoarthritis. The outcomes were reduction in the Visual Analogue Scale (VAS) pain score or improvement of the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. We finally extracted data for four groups, including single PRP injection (PRP1), two PRP injections (PRP2), and three PRP injections (PRP3). We carried out network meta-analyses with the frequentist approach, using a random-effects model to pool the data.

Results A total of 10 eligible RCTs were included, comprising 719 patients. In the 1st month of follow-up, PRP2 and PRP3 demonstrated significantly better VAS and WOMAC scores compared to PRP1, with PRP3 being the most effective in both measures. By months 3 and 6, PRP3 continued to show superior efficacy in both outcomes. PRP2 also exhibited significant improvement in the WOMAC score compared to PRP1 at months 1 and 3. No significant differences were found in the VAS pain score between PRP1 and PRP2 at months 3 and 6. Finally, no major adverse events leading to treatment discontinuation were reported for any PRP groups.

Conclusion This network meta-analysis highlights the superior efficacy of higher-dose PRP, particularly PRP3, in reducing pain and improving function in patients with knee osteoarthritis.

Keywords Platelet-rich plasma, Knee osteoarthritis, Systematic review

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Introduction

Knee osteoarthritis is a common degenerative joint disease and a major cause of pain, functional disability, and diminished quality of life. It involves joint cartilage breakdown, subchondral bone changes, and chronic inflammation [1, 2]. Treating knee osteoarthritis poses significant challenges, as traditional methods such as physical therapy, pain relievers, and non-steroidal anti-inflammatory drugs often offer only temporary symptom relief and do not address the long-term progression of the disease [3–5]. As a result, there has been increasing interest in regenerative medicine as a therapeutic strategy, with platelet-rich plasma (PRP) injections emerging as a promising option.

PRP is an autologous concentration of platelets in plasma, rich in growth factors like platelet-derived growth factor, transforming growth factor-beta, and vascular endothelial growth factor, which promote tissue repair, cellular growth, and angiogenesis [6]. PRP has gained attention as a biologic therapy for musculoskeletal conditions, including knee osteoarthritis, due to its potential to reduce inflammation, enhance tissue regeneration, and possibly repair cartilage [7, 8]. However, the optimal dosage and administration of PRP in knee osteoarthritis remain debated; there are inconsistencies in whether higher doses or repeated injections offer better pain relief and functional improvements [9–11]. These contradictions complicate the establishment of clear treatment guidelines for PRP in knee osteoarthritis. Moreover, previous meta-analyses examined and compared the efficacy of only one or two groups of PRP doses, or focused on a single follow-up time [12–14].

With the lack of consensus and the growing use of PRP as a treatment for knee osteoarthritis, there is a pressing need for a thorough evaluation of different PRP dosing regimens. This systematic review and network meta-analysis was designed to fill this gap by comparing the efficacy of various doses of PRP injection in the treatment of knee osteoarthritis. By synthesizing data from randomized controlled trial (RCT) studies, our findings will provide valuable insights into the optimal PRP dosing strategies, guiding clinicians in making evidence-based decisions, and advancing research on improving patient outcomes in knee osteoarthritis.

Methods

Information sources and search strategy

This study was presented in line with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses guideline [15]. We performed a comprehensive literature search in Embase, PubMed, Scopus, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, covering all publications up to 30 September 2024 without language restrictions. The search utilized the keywords "(*Platelet-Rich Plasma* OR *PRP*) AND (*Knee*)" in the Title or Abstract applying a clinical trials filter (supplementary file). Moreover, we manually reviewed the reference lists of pertinent studies identified through the database search to find any additional articles.

Inclusion and exclusion criteria

For the purpose of this systematic review, we concentrated on RCTs that compared the clinical effectiveness of different doses of PRP in patients with knee osteoarthritis. Our selection criteria were formulated using the PICO framework as outlined below:

- Population: Subjects with knee osteoarthritis.
- Interventions: Single- or multiple injections of PRP.
- Comparisons: PRP groups.
- Outcomes: Primary) Decrease in the Visual Analogue Scale (VAS) pain score or improvement of the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score in different follow-up from the baseline; higher VAS and WOMAC scores reflected a worsening of the outcomes. Secondary) Major adverse events leading to treatment discontinuation.

We excluded review articles, case reports, editorials, letters to the editor, duplicate publications, and surveys with unextractable data on the specified outcomes.

Study selection and data extraction

The review process began by importing the electronic database search results into EndNote X8.1 (Thomson Reuters, Stamford, Connecticut, USA). After duplicates were removed, the titles and abstracts of the remaining papers were independently screened using a pre-designed eligibility form to judge their suitability. Full-text reports of the eligible studies were then examined, with any discrepancies resolved through consensus. Relevant information, such as the first author's name, publication year, number of subjects, grade of osteoarthritis, mean age, sex, intervention details, and study outcomes, was extracted into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA). Lastly, continuous data (mean and standard deviation) for VAS and WOMAC scores were recorded for four groups, including single PRP injection (PRP1), two PRP injections (PRP2), and three PRP injections (PRP3), where available. Two authors (STE and MMAA) contributed to the aforementioned review processes.

Risk of bias assessment

We appraised potential bias in the included RCTs using the updated Cochrane risk-of-bias tool for randomized

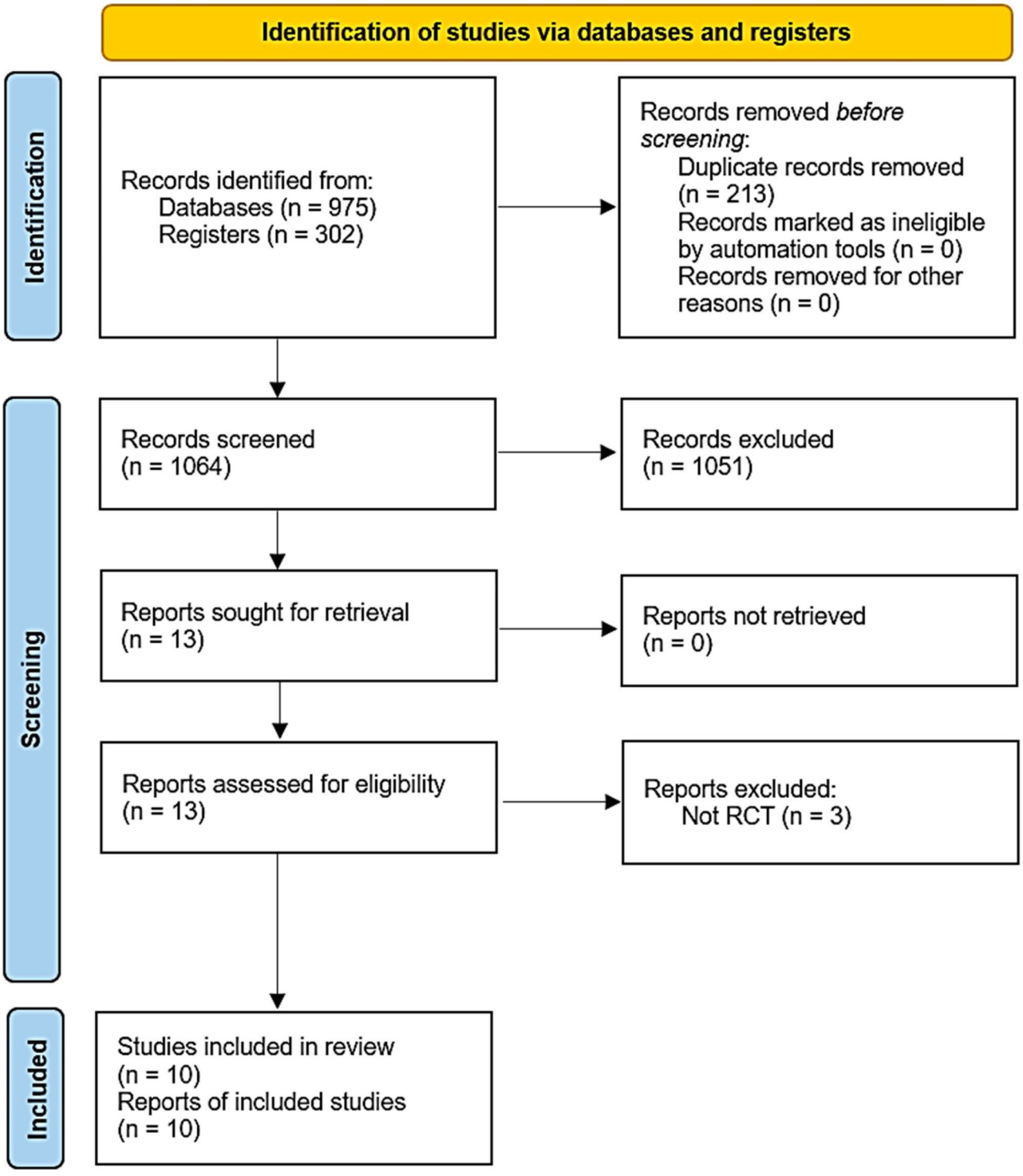

Fig. 1 PRISMA flow diagram

trials (RoB 2) regarding our primary outcome. The results were visualized through the robvis tool (https://mcguinlu.shinyapps.io/robvis/). RoB 2 evaluates bias across five key domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement methods, and selection of reported results. Each domain is rated as either 'high risk,' 'some concerns,' or 'low risk' for bias.

Table 1 Baseline characteristics of randomized controlled trials included in the systematic review

Study	Country	Interventions (Number of Subjects; Mean Age [y])	Grade of Osteoarthritis	Injection Interval	Outcome Reported (Follow-up)
Görmeli, 2017	Turkey	PRP1 ($n=44$; 53.8) PRP3 ($n=39$; 53.7)	Kellgren–Lawrence grades 0 to IV	1 week	VAS (6 months)
Kavadar, 2015	Turkey	PRP1 ($n=34$; 53.6) PRP2 ($n=34$; 54.9) PRP3 ($n=34$; 55.2)	Kellgren–Lawrence grade III	2 weeks	VAS and WOMAC (1, 3, and 6 months)
Lewis, 2022	Australia	PRP1 ($n=47$; 55.1) PRP3 ($n=27$; 59.4)	Kellgren–Lawrence grades 0 to II	1 week	VAS (1, 3, and 6 months)
Patel, 2013	India	PRP1 ($n=27$; 53.1) PRP2 ($n=25$; 51.6)	Ahlback grades I to III	3 weeks	VAS (6 months) and WOMAC (1, 3, and 6 months)
Simental-Mendía, 2019	Mexico	PRP1 ($n=18$; 54.6) PRP3 ($n=17$; 60.1)	Kellgren–Lawrence grades I and II	2 weeks	VAS and WOMAC (1, 3, and 6 months)
Subramanyam, 2021	India	PRP1 ($n=30$; 48.4) PRP2 ($n=30$; 46.7) PRP3 ($n=30$; 47.6)	Kellgren–Lawrence grades I and II	2 weeks	VAS (1, 3, and 6 months)
Tavassoli, 2019	Iran	PRP1 ($n=27$; 63.2) PRP2 ($n=27$; 66.0)	Ahlback grades I and II	3 weeks	VAS and WOMAC (3 and 6 months)
Uslu Güvendi, 2018	Turkey	PRP1 ($n=19$; 62.3) PRP3 ($n=14$; 60.4)	Kellgren–Lawrence grade III	1 week	VAS and WOMAC (3 and 6 months)
Yurtbay, 2022	Turkey	PRP1 ($n=62$; 53.3) PRP3 ($n=63$; 57.4)	Kellgren–Lawrence grades I to III	4 weeks	VAS (1, 3, and 6 months)
Zhuang, 2024	China	PRP1 ($n=36$; 58.8) PRP3 ($n=35$; 59.9)	Kellgren–Lawrence grades I to III	1 week	VAS and WOMAC (1, 3, and 6 months)

Abbreviations: PRP, Platelet-rich plasma; PRP1, Single PRP injection; PRP2, Two PRP injections; PRP3, Three PRP injections; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Statistical analysis

We carried out network meta-analyses using the frequentist model with the R package "netmeta" (https://cran.r-project.org/package=netmeta). Continuous data from individual studies on VAS and WOMAC were pooled using a random-effects model to calculate the mean difference (MD) with a 95% confidence interval (CI). Our analysis examined outcomes at one, three, and six months post-intervention. P-scores (ranging from 0 to 1) were used to rank interventions, with higher scores indicating a greater likelihood of a treatment being the most effective [16]. PRP1 was set as the reference treatment for comparison. Ultimately, network plots were generated to display the symmetry and structure of the evidence.

Results

Search results, study selection and characteristics

A total of 1,277 records were initially retrieved from the database searches. After duplicates and irrelevant studies were removed, 13 articles proceeded to detailed screening. During the full-text review, 3 studies were excluded, resulting in 10 eligible studies included in the final analysis, comprising 719 patients [17–26]. The PRISMA diagram in Fig. 1 illustrates the entire search and selection process. All 10 studies were published in English between 2013 and 2024. Four studies were conducted in Turkey, two in India, one in Australia, one in China, one in Iran, and one in Mexico. Six RCTs assessed groups PRP1 and PRP3, two evaluated groups PRP1, PRP2, and PRP3, and finally, two appraised groups PRP1 and PRP2. The grade of osteoarthritis was classified by the Kellgren–Lawrence or Ahlback criteria. Table 1 and Supplementary Table 1 summarize the characteristics of the publications enrolled in this systematic review. Figure 2 depicts the risk of bias assessment for all the included RCTs; most of the studies had a low risk of bias or some concerns of bias.

Network meta-analysis results

Month 1: Our analysis showed that groups PRP2 (MD=-3.19 [95% CI: -5.71 to -0.68]; P-score = 0.61) and PRP3 (MD=-4.20 [95% CI: -6.15 to -2.25]; P-score = 0.89) had significantly better VAS score than group PRP1 (Table 2 and Fig. 3). Also, we found that groups PRP2 (MD=-3.33 [95% CI: -5.92 to -0.74]; P-score = 0.62) and PRP3 (MD=-4.43 [95% CI: -7.05 to -1.81]; P-score = 0.80) achieved significantly greater WOMAC score improvement than group PRP1 (Table 2 and Fig. 3). There were no significant differences in the given outcomes between multiple injections of PRP.

Month 3: Based on our analysis, group PRP3 (MD=-2.44 [95% CI: -3.43 to -1.45]; P-score = 0.98) had significantly better VAS score than group PRP1 (Table 3 and Fig. 4). Regarding the WOMAC score, groups PRP2 (MD=-2.46 [95% CI: -4.91 to -0.01]; P-score = 0.51) and PRP3 (MD=-4.86 [95% CI: -7.13 to -2.58]; P-score = 0.97)

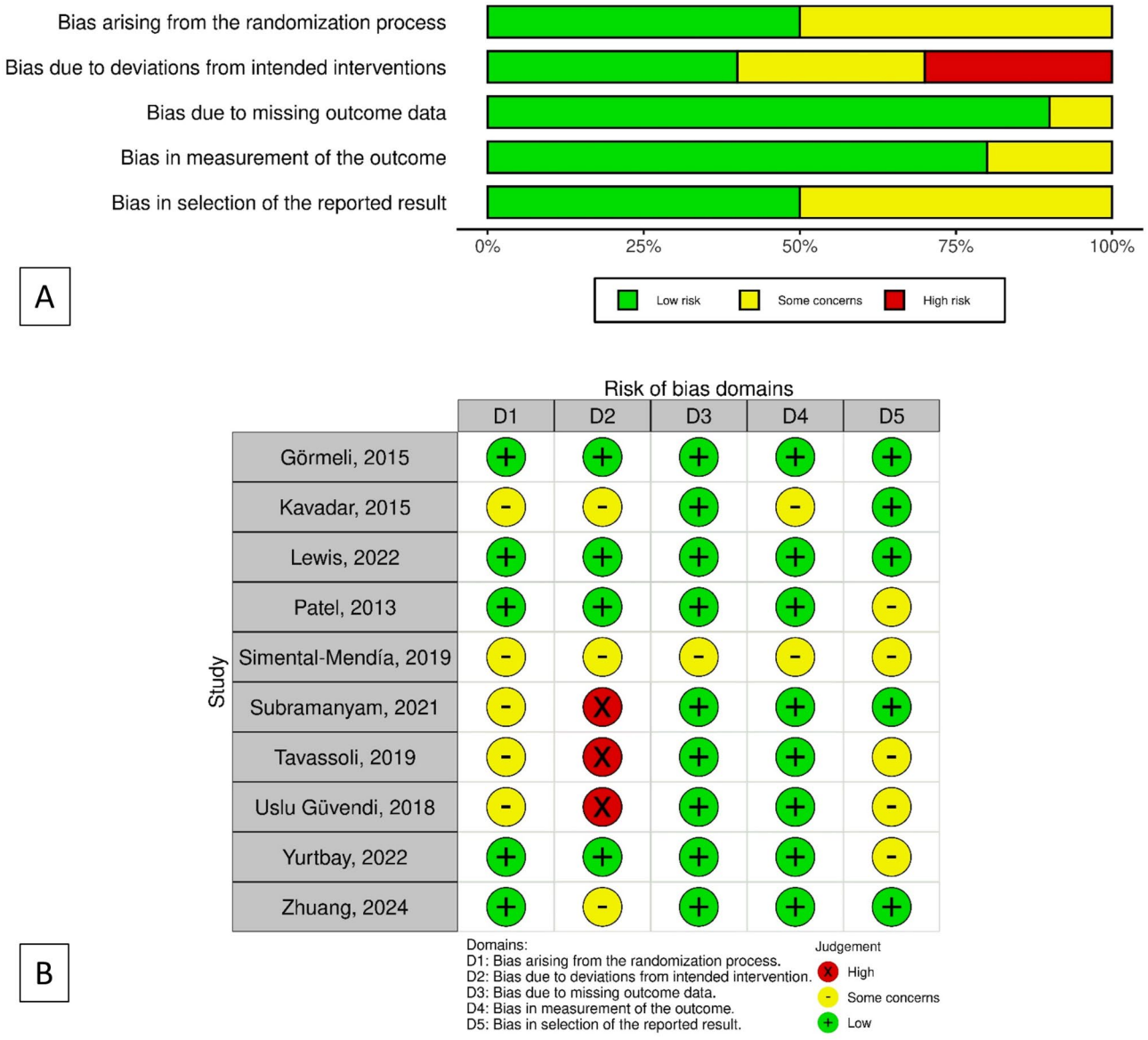

Fig. 2 Risk of Bias Assessment for the Individual Domains (**A**) and Studies (**B**)

Table 2 League table for network meta-analysis of reducing the visual analogue scale (VAS) and the total Western Ontario and McMaster universities osteoarthritis index (WOMAC) scores according to the treatments in the 1st month of follow-up

	WOMAC		
VAS	PRP3	-1.10 (-4.28 to 2.07)	-4.43 (-7.05 to -1.81)
	-1.01 (-3.68 to 1.67)	PRP2	-3.33 (-5.92 to -0.74)
	-4.20 (-6.15 to -2.25)	-3.19 (-5.71 to -0.68)	PRP1

Abbreviation: PRP, platelet-rich plasma

Note: The reported estimates are a mean difference and a 95% confidence interval in parentheses. For the VAS pain score, read from left to right and compare the columns with the rows. For the total WOMAC score, read from left to right and compare the rows with the columns. The boxes that are shaded green indicate a statistically significant difference

exhibited significantly greater reduction compared with group PRP1 (Table 3 and Fig. 4).

Month 6: Concerning the VAS score, a significant reduction was identified in group PRP (MD=-2.14 [95% CI: -3.32 to -0.96]; P-score = 0.93) than group PRP1 (Table 4 and Fig. 5). Similarly, with respect to the WOMAC score, we found a significant decrease in group PRP3 (MD=-7.38 [95% CI: -11.05 to -3.71]; P-score = 0.94) versus group PRP1 (Table 4 and Fig. 5).

Adverse events

We collected information on the adverse events reported by the individual studies after PRP administration, including dizziness, headache, nausea, syncope, gastritis, sweating, tachycardia, knee pain and stiffness, and

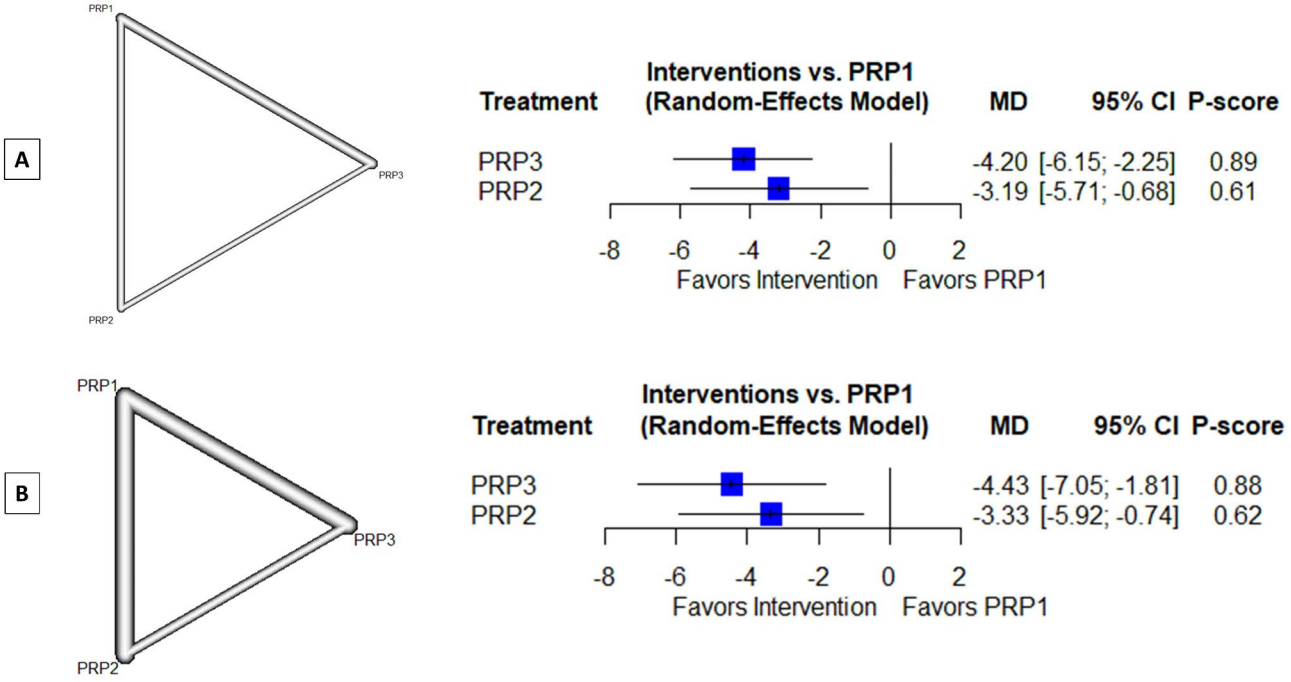

Fig. 3 Network plot and forest plot for reducing the Visual Analogue Scale (**A**) and the total Western Ontario and McMaster Universities Osteoarthritis Index (**B**) scores according to the treatments in the 1st month of follow-up. Regarding the network plot, the line width (connection size) corresponds to the number of studies comparing the treatments. PRP, platelet-rich plasma; MD, mean difference; CI, confidence interval

Table 3 League table for network meta-analysis of reducing the visual analogue scale (VAS) and the total Western Ontario and McMaster universities osteoarthritis index (WOMAC) scores according to the treatments in the 3rd month of follow-up

	WOMAC		
VAS	PRP3	-2.40 (-5.33 to 0.53)	-4.86 (-7.13 to -2.58)
	-1.23 (-2.60 to 0.15)	PRP2	-2.46 (-4.91 to -0.01)
	-2.44 (-3.43 to -1.45)	-1.21 (-2.51 to 0.08)	PRP1

Abbreviation: PRP, platelet-rich plasma

Note: The reported estimates are a mean difference and a 95% confidence interval in parentheses. For the VAS pain score, read from left to right and compare the columns with the rows. For the total WOMAC score, read from left to right and compare the rows with the columns. The boxes that are shaded green indicate a statistically significant difference

erythema. However, it should be noted that all the complications were short-duration and not of severity or concern, which did not require treatment discontinuation. Therefore, analyzing this outcome was not applicable.

Discussion

The results of this network meta-analysis provide important insights into the comparative efficacy of different doses of PRP in treating knee osteoarthritis. Our analysis spanned outcomes at 1, 3, and 6 months of follow-up, focusing on pain relief, measured by the VAS, and overall functional improvement, measured by the WOMAC score. The findings highlight the superior efficacy of higher-dose PRP regimens, particularly PRP3, in reducing pain and improving knee function compared to the lower-dose group, PRP1.

At Month 1, groups receiving higher doses of PRP (PRP2 and PRP3) demonstrated significantly better VAS and WOMAC scores compared to the lowest-dose group (PRP1). Notably, PRP3 showed the most significant improvements in pain and function. Interestingly, while all PRP groups outperformed PRP1 in both outcomes, no significant differences were observed between groups receiving multiple injections of PRP. This suggests that the overall dose, rather than the frequency of injections, may play a more critical role in therapeutic outcomes. By Month 3, the trend persisted, with PRP3 showing superior efficacy in pain reduction and functional improvement. PRP2 also significantly improved over PRP1, but PRP3 consistently outperformed PRP2 across all measures. This continued advantage of higher-dose PRP emphasizes the potential benefit of more concentrated platelet levels in achieving sustained symptom relief. At Month 6, the differences between groups became even more pronounced. PRP3 maintained its superior efficacy, significantly reducing VAS and WOMAC scores compared to PRP1 and PRP2. The magnitude of improvement in the PRP3 group suggests that higher doses of PRP provide better short-term relief and sustain these benefits over time. These findings indicate that PRP3 may offer knee osteoarthritis patients the most substantial and durable improvement in pain and function, underscoring

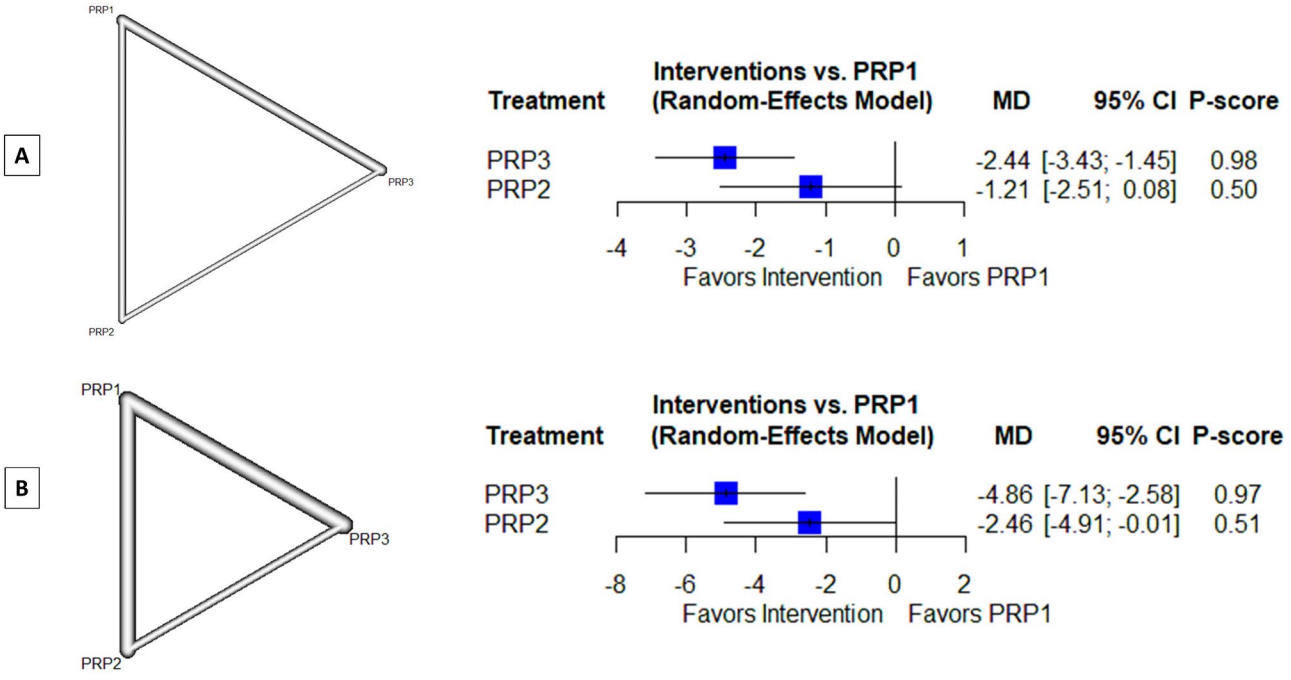

Fig. 4 Network plot and forest plot for reducing the Visual Analogue Scale (**A**) and the total Western Ontario and McMaster Universities Osteoarthritis Index (**B**) scores according to the treatments in the 3rd month of follow-up. Regarding the network plot, the line width (connection size) corresponds to the number of studies comparing the treatments. PRP, platelet-rich plasma; MD, mean difference; CI, confidence interval

Table 4 League table for network meta-analysis of reducing the visual analogue scale (VAS) and the total Western Ontario and McMaster universities osteoarthritis index (WOMAC) scores according to the treatments in the 6th month of follow-up

	WOMAC		
VAS	PRP3	-3.11 (-8.19 to 1.98)	-7.38 (-11.05 to -3.71)
	-0.97 (-2.69 to 0.76)	PRP2	-4.28 (-8.90 to 0.35)
	-2.14 (-3.32 to -0.96)	-1.17 (-2.82 to 0.47)	PRP1

Abbreviation: PRP, platelet-rich plasma

Note: The reported estimates are a mean difference and a 95% confidence interval in parentheses. For the VAS pain score, read from left to right and compare the columns with the rows. For the total WOMAC score, read from left to right and compare the rows with the columns. The boxes that are shaded green indicate a statistically significant difference

the importance of dose optimization in PRP therapy for this condition.

The meta-analysis by Vilchez-Cavazos et al. [12] including 5 RCTs reported that a single injection was as effective as multiple (double or triple) PRP injections in pain improvement, which was in agreement with our results; on the other hand, they declared that multiple injections seemed more effective in joint functionality than a single injection at 6 months, which was consistent with our study. A recent meta-analysis of 7 RCTs by Tao et al. [14] compared the efficacy of triple-dose versus single-dose of PRP treatment in VAS pain reduction. The authors concluded that administering three doses of PRP was more efficient than a single dose in providing pain relief lasting up to one year. Our study has a number of advantages over aforementioned studies. First, we enrolled more number of studies. Second, our study was a network meta-analysis, which provides stronger evidence than the pairwise meta-analysis done in above research. Lastly, we assessed the outcomes with more follow-up cut-offs (one, three, and six months).

The results of this network meta-analysis have several important clinical implications. First and foremost, they suggest that higher doses of PRP, specifically PRP3, are significantly more effective than lower doses in managing pain and functional limitations associated with knee osteoarthritis. This is particularly relevant for patients seeking non-surgical options that provide longer-lasting relief. Clinicians may consider tailoring PRP dosing regimens to optimize outcomes, prioritizing higher doses where feasible and appropriate based on patient characteristics and disease severity. The finding that multiple PRP injections did not significantly improve outcomes over single injections challenges the assumption that repeated treatments may be necessary to achieve optimal results. Instead, it appears that the total dose of PRP, rather than the frequency of administration, is a more critical factor. This has practical implications for both patients and providers, as fewer injections may reduce treatment burden and associated costs without compromising efficacy. Moreover, PRP3 demonstrated sustained effectiveness over six months, highlighting its potential as a long-term treatment option that could delay or reduce the need for surgical interventions such as knee

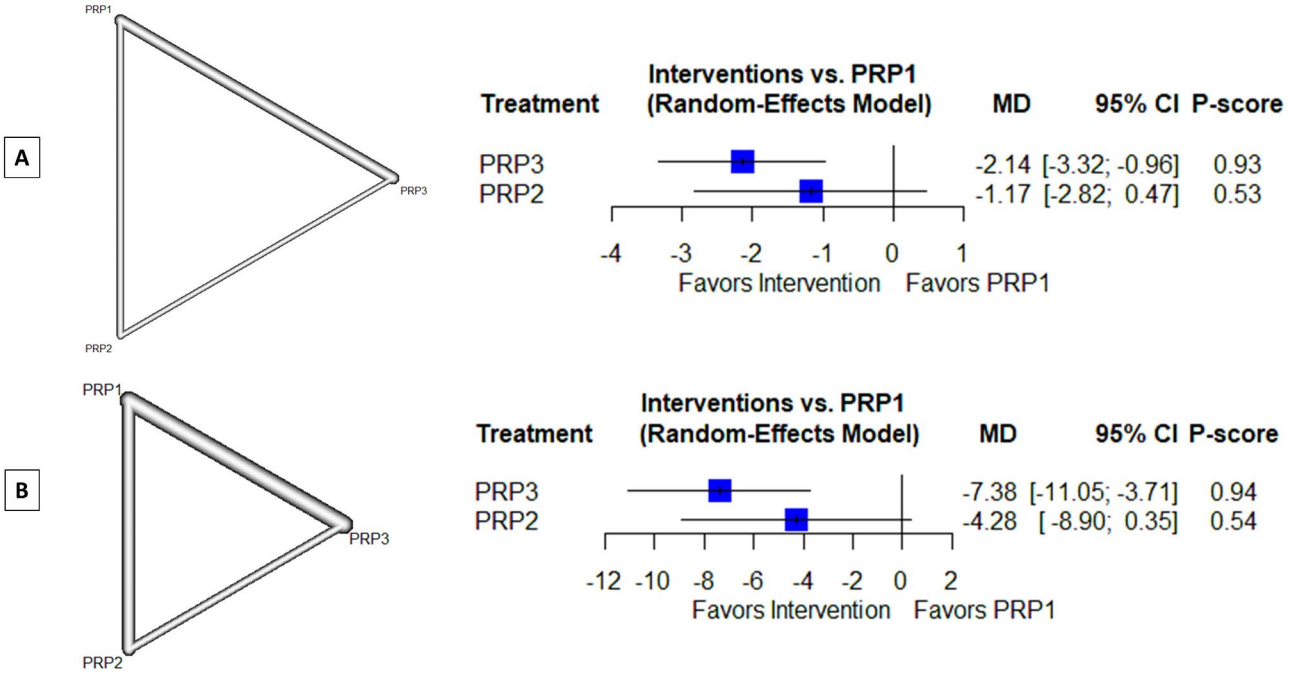

Fig. 5 Network plot and forest plot for reducing the Visual Analogue Scale (**A**) and the total Western Ontario and McMaster Universities Osteoarthritis Index (**B**) scores according to the treatments in the 6th month of follow-up. Regarding the network plot, the line width (connection size) corresponds to the number of studies comparing the treatments. PRP, platelet-rich plasma; MD, mean difference; CI, confidence interval

arthroplasty. The durability of symptom relief provided by higher doses of PRP underlines its relevance in the management of this chronic and progressive condition. Our results confirm that the higher-dose PRP groups achieved not only statistically significant but also clinically meaningful improvements in pain and function for knee osteoarthritis patients. The sustained benefits further support the efficacy of higher-dose PRP. Variability in minimal clinically important differences definitions and population differences should be noted when interpreting these findings. The superior performance of multiple PRP injections may be due to their cumulative biological effects, including sustained release of growth factors, enhanced cartilage repair, and prolonged modulation of inflammation, leading to improved joint regeneration and symptom relief over time [27]. Finally, the adverse events reported in the included RCTs were mild and transient, with no serious complications leading to treatment discontinuation. This indicates that PRP injections are potentially safe and well-tolerated, even at higher doses. Hence, clinicians can reassure patients about the low risk of severe side effects associated with PRP therapy, which may enhance patient acceptance and willingness to undergo treatment. Overall, given the chronic and progressive nature of knee osteoarthritis, identifying treatments that can provide durable symptom relief is crucial in improving patients' quality of life and minimizing healthcare costs.

While this study provides valuable insights into the optimal dosing strategy for PRP in knee osteoarthritis, several areas warrant further research. Understanding the biological mechanisms through which higher PRP doses confer greater benefits could help refine preparation protocols and optimize treatment. Investigating the interaction of specific growth factors with cartilage repair and inflammation pathways may offer crucial insights. Additionally, long-term studies are needed to assess whether the benefits of high-dose PRP persist beyond six months. Comparing PRP with other regenerative treatments, such as stem cell therapy, over extended periods could inform future clinical decision-making. Patient-specific factors, such as age, body mass index, and disease severity, may influence the response to PRP therapy. Future research should focus on stratifying patients to identify which subgroups are most likely to benefit, allowing for more personalized treatment approaches. Finally, considering the relatively high cost of PRP therapy, evaluating its cost-effectiveness is essential. Studies comparing high-dose PRP regimens, which may require fewer injections, to lower doses that require more frequent administration could help determine the most economical and effective approach for long-term knee osteoarthritis management.

This study has strengths that bolster the reliability and clinical relevance of its findings. First, the use of network meta-analysis enables the comparison of multiple PRP dosing regimens, even without direct head-to-head trials, providing a comprehensive assessment of dose

efficacy. Second, the inclusion of various time points (1, 3, and 6 months) offers a longitudinal perspective, which is important for managing chronic knee osteoarthritis. The finding that higher doses, particularly PRP3, show sustained benefits supports its potential as a long-term therapy. Lastly, the use of standardized outcome measures (VAS and WOMAC) ensures the results are clinically meaningful and applicable to real-world practice.

The present network meta-analysis faced limitations as well. First, the protocol of our study was not registered on a public database. Second, the variability in PRP preparation and administration protocols across studies may have influenced the results, complicating comparisons between doses. Third, the heterogeneities in the sample size and the osteoarthritis grade might affect the reliability of our findings. Fourth, the follow-up durations in the included studies (1–6 months) cannot be considered long-term for osteoarthritis, a chronic degenerative disease; besides, we could not analyze outcomes at longer follow-ups (one or two years) due to insufficient data. Finally, we could not asses the publication bias due to lacking enough number of studies [28]. Altogether, it is recommended that new RCTs be designed and performed to overcome these limitations in the future.

Conclusion

This network meta-analysis highlights the superior efficacy of higher-dose PRP, particularly PRP3, in reducing pain and improving function in patients with knee osteoarthritis. The sustained benefits of PRP3 over six months suggest that it may offer a long-term treatment option for patients seeking non-surgical interventions. While the exact mechanisms behind the greater efficacy of higher PRP doses remain to be fully understood, these findings have important implications for clinical practice. Future research should focus on elucidating the biological pathways involved, exploring long-term outcomes, and identifying patient-specific factors influencing treatment response. Ultimately, this study provides valuable evidence to guide the optimal use of PRP in managing knee osteoarthritis and offers a foundation for future investigations into regenerative therapies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-025-05650-1.

Supplementary Material 1

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Author contributions
MK and MMAA conceived and drafted the study. MMAA and STE contributed in data collection. MK, STE, and MMAA contributed in drafting the manuscript. All authors have read and approved the final draft of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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