PRP Injections for the Treatment of Knee Osteoarthritis: The Improvement Is Clinically Significant and Influenced by Platelet Concentration

A Meta-analysis of Randomized Controlled Trials

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Background: Platelet-rich plasma (PRP) has emerged as a promising therapeutic intervention for knee osteoarthritis (OA), attracting substantial clinical and research attention. However, the clinical relevance of the treatment benefit remains controversial.

Purpose: To evaluate the effectiveness of PRP compared with placebo in patients with knee OA in terms of minimal clinically important difference (MCID) and to investigate the possible influence of platelet concentration on the clinical outcome.

Study Design: Meta-analysis. Level of evidence 1.

Methods: The search was conducted on 5 databases (PubMed, Cochrane Library, Scopus, Embase, Web of Science) using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Inclusion criteria were randomized controlled trials comparing PRP and placebo injections to treat knee OA, written in the English language, with no time limitation. The effects were quantified at 1-, 3-, 6-, and 12-month follow-up points. Visual analog scale (VAS) for pain and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were used, with subanalyses based on platelet concentration performed using a 1,000,000 ± 20% platelets/μL cutoff. The MCID values (VAS, 1.37; WOMAC, 6.4) were used to interpret clinical improvement. The articles' quality was assessed using the Revised Tool for Risk of Bias in Randomized Trials and the Grading of Recommendations Assessment, Development and Evaluation guidelines.

Results: Among the 5499 articles retrieved, 18 randomized controlled trials (1995 patients) were included. PRP presented statistically superior improvements in VAS and WOMAC scores compared with placebo at all follow-up points, exceeding the MCID at 3- and 6-month follow-up points for VAS and at all follow-up points for WOMAC. The subanalysis based on platelet concentration showed that high-platelet PRP provided clinically significant pain relief with the improvement exceeding the MCID compared with placebo at 3-, 6-, and 12-month follow-up points. In contrast, low-platelet PRP failed to offer a clinically perceivable benefit in terms of VAS score. WOMAC results showed that both products provided a clinically significant improvement at 3 and 6 months of follow-up. This benefit was maintained up to the 12-month follow-up in the high-platelet group but not in the low-platelet group, where the improvement compared with placebo did not reach statistical significance.

Conclusion: This meta-analysis showed that PRP offered clinically relevant functional improvement at 1-, 3-, 6-, and 12-month follow-up points and pain relief at 3- and 6-month follow-up points compared with placebo for the treatment of knee OA. Platelet concentration was found to influence treatment efficacy, with high-platelet PRP providing superior pain relief and more durable functional improvement compared with low-platelet PRP.

Keywords: platelet-rich plasma; PRP; knee; osteoarthritis; OA; placebo

Knee osteoarthritis (OA) is one of the most common orthopaedic diseases and represents a major cause of pain and disability in older adults.[41,43,55] The prevalence of knee OA is currently increasing, placing a heavy burden on health care systems worldwide.[14,36,74] OA is

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a multifactorial disease characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional modifications in the entire joint, including synovial inflammation, which is a target of several therapeutic interventions.[32,51,52] However, despite the considerable therapeutic advances made in recent years, unfulfilled medical needs persist for knee OA treatment.[10,18,32,54] Among the nonoperative treatments proposed in clinical practice to improve the altered joint environment, platelet-rich plasma (PRP) has emerged as a promising therapeutic intervention for knee OA, attracting substantial clinical and research attention.[5]

PRP has shown the potential to modulate the intra-articular environment, reducing inflammatory distress and stimulating anabolism in different tissues and exploiting the high concentration of growth factors, cytokines, and bioactive molecules stored in platelet α-granules.[22] The anti-inflammatory, immunomodulatory, and anabolic properties may mitigate the degenerative processes of knee OA and improve symptoms and function of the treated joints.[6] Given the safety of PRP and the simplicity of the preparation technique to obtain its biologically active content, PRP is now considered among many treatment options in clinical practice.[37] However, the efficacy of PRP remains a subject of debate, with conflicting evidence reported in the current literature: Although positive results have been documented in several trials, other studies have questioned the real benefit of PRP and its claimed superiority compared with placebo.[3,12,38,39,66] Moreover, although some outcomes have shown statistical superiority, it is not clear whether the benefit of PRP reaches a minimal clinically important difference (MCID)[62] and, therefore, a real improvement perceived by patients compared with the benefit of placebo.

The aim of this meta-analysis was to evaluate the effectiveness of PRP compared with placebo in terms of MCID in order to give clear indications on the real benefits offered by PRP injections in the management of knee OA.

METHODS

Data Source, Search, and Study Selection

The study was registered on the International Prospective Register of Systematic Reviews (PROSPERO registration No. CRD42023466146). The following databases were systematically searched on September 26, 2023, with no time limitation and without any filters: PubMed, Cochrane Library, Scopus, Embase, and Web of Science. The following string was used in the search: ((PRP OR platelet rich plasma OR plasma rich in growth factors OR PRGF OR platelet derived growth factor OR platelet derived OR platelet gel OR platelet concentrate OR PRF OR platelet rich fibrin OR ACP OR autologous conditioned plasma OR APS OR autologous protein solution OR platelet lysate) AND (knee osteoarthritis)).

Duplicates were removed, and subsequently, all records were checked for eligibility by titles and abstracts. The full-text article was read if insufficient information could be retrieved from the abstract. The following inclusion criteria were used: randomized controlled trials (RCTs) of level 1 or 2 comparing PRP injections with placebo, published in English, and on humans. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used.[53] The article selection process was independently performed by 2 authors (A. Bensa, A.S.), with disagreement on study eligibility resolved by a third author (A. Boffa).

Data Extraction and Quality Assessment

Data extracted on trial method from all eligible trials included level of evidence, study design, PRP manufacturing method, and PRP characteristics. Data extracted from all eligible trials on characteristics of the study population included the number of patients, OA level, sex, age, body mass index, inclusion and exclusion criteria, activity level, previous surgical treatments on the index knee, associated lesions, clinical scores, adverse events, and radiological results. Two authors (A. Bensa, A.S.) independently extracted the trial information using a standardized extraction form. When possible, data were collected from the records; otherwise, corresponding authors were contacted. The risk of bias was assessed using the Revised Tool for Risk of Bias in Randomized Trials (RoB 2.0) approved by the Cochrane Collaboration Group, which defines 3 categories: low risk, some concerns, and high risk.[69] The overall quality of evidence for each outcome was graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines for high, moderate, low, and very low levels of evidence.[64]

Study Outcome and Statistical Analysis

The primary outcome of this meta-analysis was the overall Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score 12 months after the injection. Secondary outcomes were overall WOMAC score 1, 3, and 6 months after the injection and pain measured on the 0- to 10-point visual analog scale (VAS) at 1-, 3-, 6-, and 12-

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month follow-up points. WOMAC subscale scores (pain, stiffness, and function) were analyzed as well. The mean differences (MDs) between treatment groups were compared with the MCID reported in the literature for each score: 6.4 of 96 for the overall WOMAC score, 1.5 of 20 for the WOMAC pain subscale score, 0.6 of 8 for the WOMAC stiffness subscale score, 4.6 of 68 for the WOMAC function subscale score, and 1.37 of 10 for the VAS pain score.[1,65] The effect of PRP was assessed using a z test on the pooled MD for continuous variables. To account for study heterogeneity, we used a random-effects model. A subanalysis based on the platelet concentration was performed. To investigate further potential sources of heterogeneity, we analyzed the injection schedule (considering both injection number and timing) of the administered PRP and risk of bias of the included studies. A meta-regression based on PRP-injected volume was performed. Because a commonly accepted cutoff to define platelet concentration is 1,000,000 ± 20% platelets/μL,[24] the high–platelet concentration group included PRP above the cutoff of 1,000,000 ± 20% platelets/μL, whereas PRP <800,000 platelets was considered to have low concentration; the third group was represented by the articles not reporting platelet concentration.

A P value of .05 was considered significant for all the analyses. The statistical analysis was performed using meta (Version 4.9-7) and metafor (Version 2.1-0) packages in RStudio, R Core Team (Version 1.2.5019).

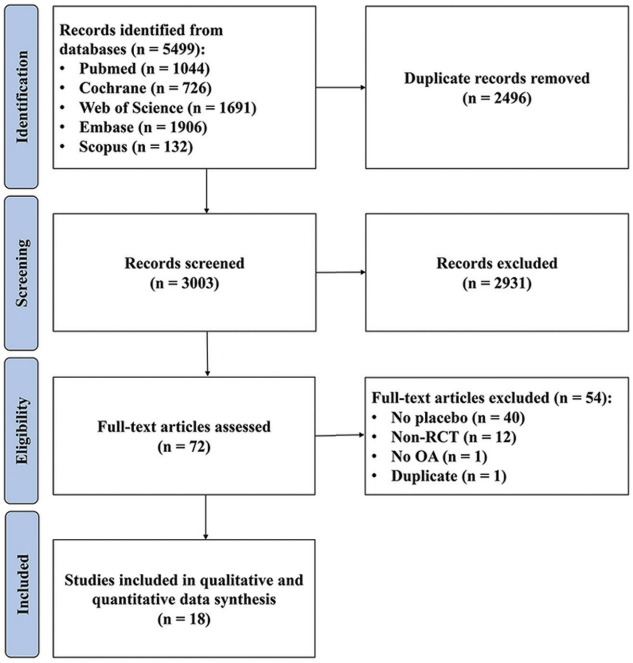

Figure 1. PRISMA flowchart of the study selection process. OA, osteoarthritis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.

RESULTS

Characteristics of the Included Studies and Patients

A total of 18 placebo-controlled RCTs were included out of 5499 records retrieved (Figure 1). Since the first report in 2013, the publication trend increased over time, reaching a peak in 2021 (Figure 2). One study was triple-blinded,[3] 15 studies were double-blinded,[‖] and 2 studies were single-blinded.[66,73] In the included studies, 1047 patients underwent PRP injections, whereas 948 patients were included in the control groups. Among these, 1010 (96.5%) and 891 (94.0%) patients in the PRP and control groups, respectively, were followed until the last follow-up of the related studies. The male-to-female ratio was 0.71 in the PRP groups and 0.75 in the control groups. The patients' mean age ranged from 49.8 to 67.6 years in the PRP groups and from 46.6 to 68.0 years in the control groups. The mean body mass index ranged from 24.0 to 30.9 in the PRP groups and from 24.1 to 31.2 in the control groups.

Nine studies used low-platelet PRP,[¶] 6 studies used high-platelet PRP,[12,17,19,28,56,78] and 3 studies did not report platelet concentration.[36,61,66] The number of injections varied from 1 to 3, with 8 studies reporting a single-injection protocol,[26,38,56,59,72,73,76,78] 2 studies performing 2 injections,[17,58] and 10 studies performing 3 injections.[#] OA severity was evaluated using the Kellgren-Lawrence (KL) or Ahlbäck classifications. In the PRP group, 110 patients were classified as KL-1, 375 as KL-2, 294 as KL-3, 62 as KL-4, 92 as Ahlbäck-1, 43 as Ahlbäck-2, and 14 as Ahlbäck-3. In the placebo group, 112 patients were classified as KL-1, 379 as KL-2, 262 as KL-3, 56 as KL-4, 43 as Ahlbäck-1, 36 as Ahlbäck-2, and 14 as Ahlbäck-3. Further studies, patients, and treatment details are reported in Appendix 1 (available in the online version of this article).

Platelet-Rich Plasma Versus Placebo

The meta-analysis on the total WOMAC score showed a statistically and clinically significant superiority of PRP after 1 month (MD, –8.15; 95% CI, –13.75 to −2.54; P = .004), 3 months (MD, –15.90; 95% CI, –22.98 to −8.81; P < .001), 6 months (MD, –15.32; 95% CI, –21.94 to −8.69; P = .001), and 12 months (MD, –14.69; 95% CI, –25.89 to −3.50; P = .01) (Figure 3). The analysis of WOMAC subscale scores confirmed a statistically and clinically significant advantage of PRP. In particular, the improvement in terms of WOMAC pain was 2.29 (95% CI, –3.78 to −0.79; P = .003) after 1 month, 4.00 (95% CI, –5.97 to −2.02; P < .001) after 3 months, 3.97 (95% CI, –5.79 to −2.14; P < .001) after 6 months, and 3.88 (95% CI, –6.25 to −1.51; P = .001) after 12 months. Regarding WOMAC stiffness, the improvement was 0.84 (95% CI, –1.37 to −0.31; P = .002) after 1 month, 1.57 (95% CI, –2.18 to −0.95; P < .001) after 3 months, 1.41 (95% CI, –2.09 to −0.72; P < .001) after 6 months, and 1.34 (95% CI, –2.57 to −0.11; P = .03) after 12 months. Finally, for WOMAC function, the improvement was 5.56

[‖]References 12, 17, 19, 26, 28, 38-40, 56, 59, 61, 68, 72, 76, 78.
[¶]References 3, 26, 39, 40, 59, 68, 72, 73, 76.
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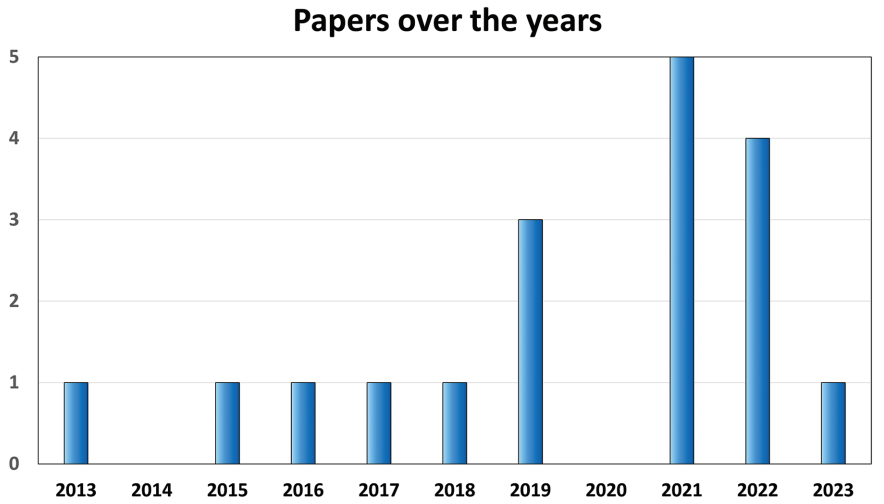

Figure 2. Number of randomized controlled trials published over time on the comparison of platelet-rich plasma and placebo for knee osteoarthritis.

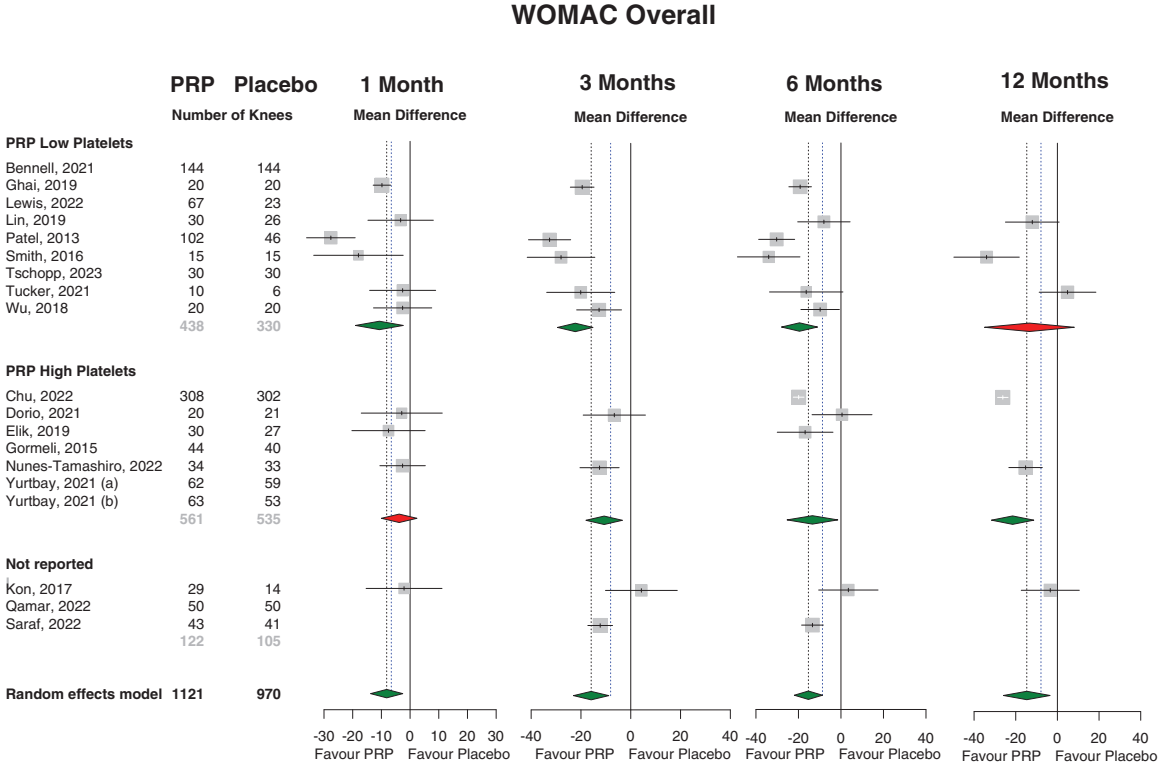

Figure 3. Forest plot of the individual studies and pooled weighted mean difference (MD) for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) improvement, including 95% CI. Platelet-rich plasma (PRP) produced statistically and clinically superior improvement compared with placebo at all follow-up points, with these improvements exceeding the 6.4 minimal clinically important difference (MCID). The subanalysis based on platelet concentration showed that both products provided a clinically significant improvement at 3- and 6-month follow-up points, but this benefit was maintained up to the 12-month follow-up only in the high-platelet group. The middle diamond for the 1-month follow-up point and the top diamond for the 12-month follow-up point indicate not statistically significant; all other diamonds indicate statistically and clinically significant (MD $>$ MCID).

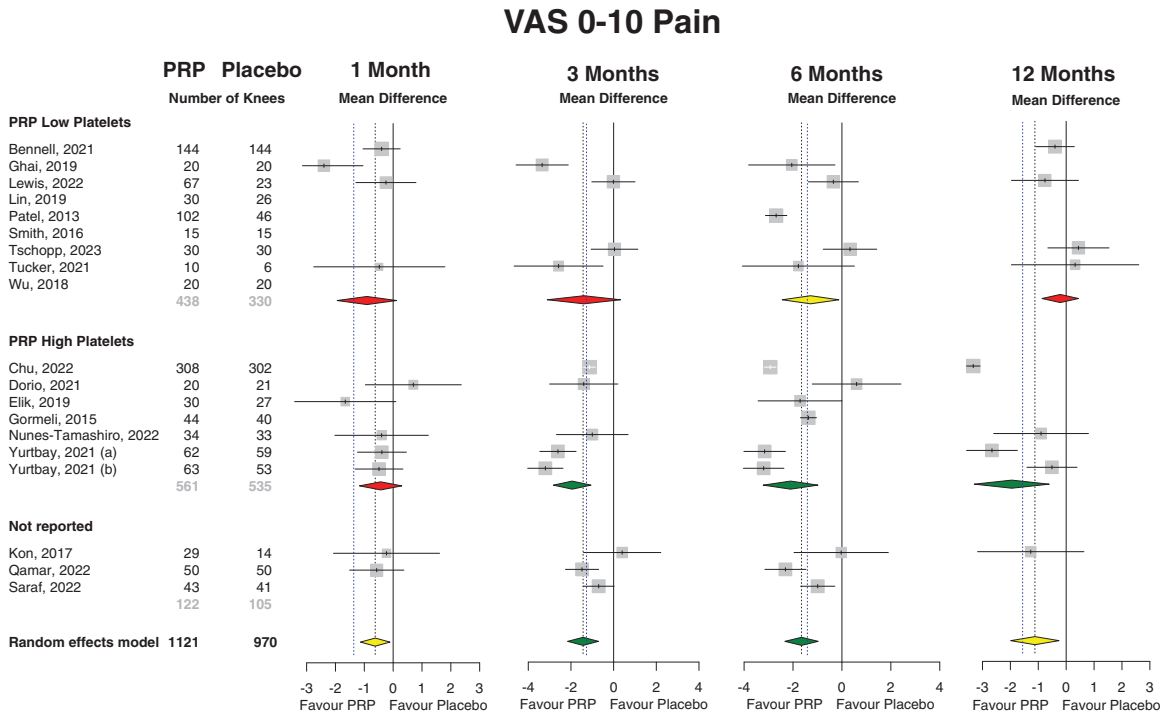

Figure 4. Forest plot of the individual studies and pooled weighted mean difference (MD) for visual analog scale (VAS) pain improvement, including 95% CI. Platelet-rich plasma (PRP) produced statistically superior improvement compared with placebo at all follow-up points, with these improvements exceeding the 1.37 minimal clinically important difference (MCID) at 3- and 6-month follow-up points. The subanalysis based on platelet concentration showed that the improvement of high-platelet PRP compared with placebo exceeded the MCID at 3, 6, and 12 months of follow-up, whereas low-platelet PRP failed to offer such clinically perceivable benefits. The top and middle diamonds for the 1-month follow-up point and the top diamond for the 3- and 12-month follow-up points indicate not statistically significant; the top diamond for the 6-month follow-up point and the bottom diamond for the 1- and 12-month follow-up points indicate statistically but not clinically significant (MD < MCID); the middle diamond for the 3-, 6-, and 12-month follow-up points and the bottom diamond for the 3- and 6-month follow-up points indicate statistically and clinically significant (MD > MCID).

(95% CI, –10.74 to −0.37; $P = .04$) after 1 month, 10.52 (95% CI, –16.88 to −4.17; $P = .001$) after 3 months, 10.90 (95% CI, –16.77 to −5.03; $P < .001$) after 6 months, and 8.40 (95% CI, –14.68 to −2.13; $P = .008$) after 12 months.

According to the meta-analysis on the VAS score for pain, the advantage of PRP over placebo was statistically significant at all of the follow-up points, whereas the MCID superiority was reached at the 3- and 6-month follow-up points. In particular, the difference favoring PRP over placebo was 0.62 (95% CI, –1.13 to −0.11; $P = .01$) after 1 month, 1.43 (95% CI, –2.16 to −0.71; $P < .001$) after 3 months, 1.65 (95% CI, –2.33 to −0.97; $P < .001$) after 6 months, and 1.12 (95% CI, –1.99 to −0.25; $P = .01$) after 12 months (Figure 4).

A further analysis was performed on the influence of platelet concentration on the clinical outcome. Further investigations on the possible role of injection schedule, volume, and risk of bias can be found in Appendix 2 (available online).

Subanalysis Based on Platelet Concentration

In terms of WOMAC total score, the subanalysis based on platelet concentration showed no difference at 1 month for high-platelet PRP. However, high-platelet PRP provided a statistically and clinically significant improvement compared with placebo at 3 months (MD, –10.68; 95% CI, –18.01 to −3.36; $P = .005$), 6 months (MD, –13.42; 95% CI, –25.36 to −1.48; $P = .01$), and 12 months (MD, –21.49; 95% CI, –31.66 to −11.32; $P < .001$) of follow-up. The improvement of the low-platelet concentration subgroup compared with placebo was statistically and clinically significant at 1 month (MD, –10.69; 95% CI, –19.00 to −2.38; $P = .01$), 3 months (MD, –22.28; 95% CI, –29.39 to −15.16; $P < .001$), and 6 months (MD, –19.50; 95% CI, –28.00 to −11.13; $P < .001$) of follow-up (Figure 3).

In terms of VAS pain score, the subanalysis based on platelet concentration showed that high-platelet PRP had no statistically significant results at 1 month but provided a statistically and clinically significant improvement compared with placebo at 3 months (MD, –1.94; 95% CI, –2.82 to −1.06; $P < .001$), 6 months (MD, –2.10; 95% CI, –3.22 to −0.98; $P < .001$), and 12 months (MD, –1.95; 95% CI, –3.29 to −0.60; $P = .01$) of follow-up. In contrast, the improvement of the low-platelet concentration subgroup compared with placebo was statistically significant (but not clinically significant) only at the 6-

TABLE 1
Grading of Recommendations Assessment, Development and Evaluation[a]

Outcomes	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other	Quality of Evidence
VAS, very short-term	No	Serious	No	No	No	No	Moderate
VAS, short-term	No	Serious	No	No	No	No	Moderate
VAS, midterm	No	Serious	No	No	No	No	Moderate
VAS, long-term	No	Serious	No	No	No	No	Moderate
WOMAC pain, very short-term	No	Serious	No	No	No	No	Moderate
WOMAC pain, short-term	No	Serious	No	No	No	No	Moderate
WOMAC pain, midterm	No	Serious	No	No	No	No	Moderate
WOMAC pain, long-term	No	Serious	No	Serious	No	No	Low
WOMAC stiffness, very short-term	No	Serious	No	No	No	No	Moderate
WOMAC stiffness, short-term	No	Serious	No	No	No	No	Moderate
WOMAC stiffness, midterm	No	Serious	No	No	No	No	Moderate
WOMAC stiffness, long-term	No	Serious	No	Serious	No	No	Low
WOMAC function, very short-term	No	Serious	No	No	No	No	Moderate
WOMAC function, short-term	No	Serious	No	No	No	No	Moderate
WOMAC function, midterm	No	Serious	No	No	No	No	Moderate
WOMAC function, long-term	No	Serious	No	No	No	No	Moderate
WOMAC overall, very short-term	No	Serious	No	No	No	No	Moderate
WOMAC overall, short-term	No	Serious	No	No	No	No	Moderate
WOMAC overall, midterm	No	Serious	No	No	No	No	Moderate
WOMAC overall, long-term	No	Serious	No	No	No	No	Moderate

[a]VAS, visual analog scale for pain; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

month follow-up (MD, –1.28; 95% CI, –2.44 to −0.12; P = .04) (Figure 4).

Risk of Bias and Quality of Evidence

The evaluation using the RoB 2.0 tool showed that 7 studies had a low risk of bias, 9 studies had "some concerns," and 2 studies had a high risk of bias. A summary of the risk of bias assessment of the included RCTs is provided in Figure 5.[48] The GRADE showed that the level of evidence of the results was moderate in almost all the outcomes, with only 2 outcomes having a low level of evidence. A summary of the quality of evidence assessment of the meta-analysis outcomes is provided in Table 1.

DISCUSSION

The main finding of this systematic review and meta-analysis is that PRP offers a clinically relevant functional improvement at 1, 3, 6, and 12 months of follow-up and pain relief at 3 and 6 months of follow-up compared with placebo for the treatment of knee OA. Platelet concentration was found to influence treatment efficacy, with high-platelet PRP providing superior pain relief and more durable functional improvement compared with low-platelet PRP.

Intra-articular injective therapies represent a well-established nonoperative approach to address knee OA, especially in the early to moderate stages. Available standard intra-articular injective treatments, including steroids and hyaluronic acid, provide only limited clinical benefits, with an effect that often is not completely satisfactory, decreases over time, and varies among patients. In this scenario, PRP has gained attention thanks to its biological properties and its disease-modifying potential to address joints that have OA.[6,7,70] The present study focused on the clinical relevance of the literature findings. In fact, although previous meta-analyses described statistically significant differences, the real effect on patient symptoms and function remained to be elucidated. This up-to-date analysis quantified these benefits on a large number of studies demonstrating statistically and clinically significant benefits of PRP over placebo. To this purpose, the most suitable MCID values available in the literature were selected for WOMAC overall scores and subscale scores and for VAS pain scores, based on the similarity with the present study regarding the type of pathology and treatment on which the MCID values were calculated.[1,65] The results were found to have a decisive clinical effect on patient-reported outcome measures, with WOMAC and VAS improvements exceeding the MCID at all follow-up points and at 3- and 6-month follow-up points, respectively. This represents a crucial aspect because statistically significant results do not always translate into clinically appreciable benefits for patients.[58] This meta-analysis demonstrated that PRP provided not only statistically significant improvements but also, and most importantly, clinically relevant benefits in terms of pain relief and functional improvement compared with placebo.

The comparison with placebo represents a crucial aspect in the evaluation of clinical improvement generated by injective therapies because the presence of a robust placebo effect, especially for biologic trials where patients perceive they are receiving a "regenerative medicine," has been reported.[23] A meta-analysis by Previtali et al[60] demonstrated that the placebo effect is an important component of the clinical effect of injective treatments for patients with knee OA, with saline injections providing relevant

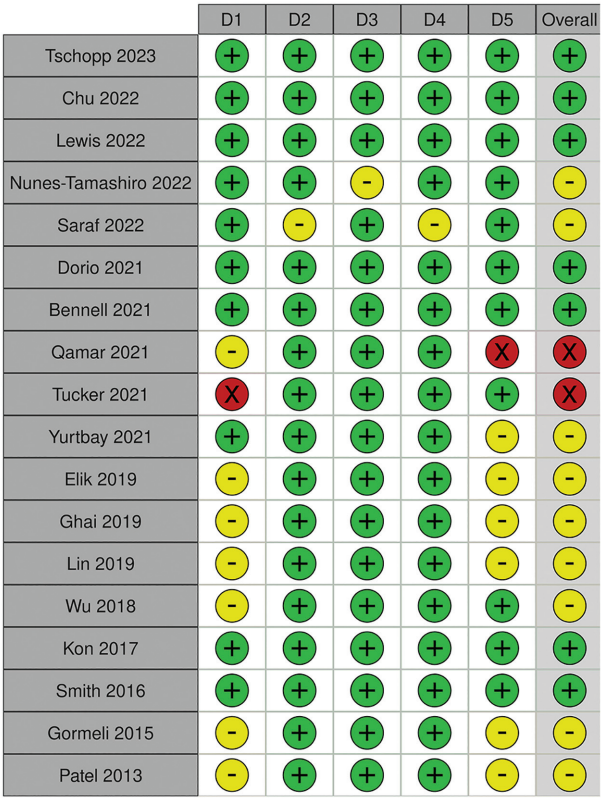

Figure 5. Cochrane risk of bias tool for randomized trials Version 2 (RoB 2.0). D, Domain; +, low risk; −, some concerns; X, high risk. RoB, Revised Tool for Risk of Bias in Randomized Trials.

and long-lasting results not only in terms of pain relief but also with respect to stiffness resolution and function improvement. Despite the proven role of placebo in PRP injections, the results of the present study based on high-level placebo-controlled studies showed that the benefits generated by this orthobiologic approach were both statistically and clinically superior to the mere placebo effect.

The overall positive findings, however, do not guide physicians in the choice of PRP among the several formulations, with considerable heterogeneity complicating the field of PRP injections. In fact, protocols differ in terms of blood volume harvested, use of anticoagulant, number and speed of centrifugations, final volume obtained, leukocyte content, overall number, integrity, and activation methods of platelets, the possibility of cryopreserving platelets or using fresh products, and the variability in application modalities such as single injections or injection cycles and different volumes and concentrations.[11,31,63] In this scenario, the presence of leukocytes has been one of the most debated aspects regarding PRP efficacy, and it has been used as one of the main discriminants to distinguish PRP products.[37] Some preclinical evidence suggests that leukocytes may play an important role in PRP efficacy, with some studies showing that leukocytes impair the overall effects of PRP and other findings supporting the use of leukocytes owing to the release of beneficial cytokines.[6,8,9,33,45] However, despite the claimed potential implications of the leukocyte content on PRP efficacy, a recent high-level RCT reported no differences in the clinical results of leukocyte-rich and leukocyte-poor PRP, suggesting that the effects of leukocytes shown in vitro may not be translated into clinically perceivable differences of PRP injections.[16] This prompts the investigation of further aspects that may influence the clinical benefit offered by platelet concentrates.

An important yet overlooked parameter differentiating the various blood-derived products is the platelet concentration, which might substantially influence the quantity of growth factors released after platelet activation, accountable for tissue repair and regeneration.[20] This represents a potentially key aspect contributing to the benefit of PRP injections, with a substantially increasing number of both preclinical and clinical studies suggesting the importance of growth factor dosage.[2,25,44] A large portion of these studies consider a high or very high concentration as the most beneficial for regenerative aims. A number of in vitro studies addressed the effect of PRP concentration on the proliferation of several cell types of mesenchymal origin, such as mesenchymal stem cells, chondrocytes, osteoblasts, or fibroblasts, reporting higher therapeutic potential for products with higher platelet dose.[29,30,42,46,50,67] Platelet concentration also influenced tenocyte proliferation and migration and matrix gene expression and synthesis in a dose-dependent manner.[4,34] Looking specifically at joint degeneration, investigators examined different doses of platelet concentrates in a rat knee OA model, showing a dose-dependent efficacy in relieving symptoms and preventing cartilage degeneration.[77] A faster healing time was also observed with higher platelet concentrations in horses with overuse musculoskeletal injuries.[71] Other studies support the use of moderate platelet dose to avoid a cell death phenomenon,[27] and a different effect on bone regeneration depending on platelet concentration was observed in a rabbit model, with a positive effect on bone regeneration only within an "intermediate" range.[75] Overall, these findings support the importance of investigating the effect of the platelet concentration when treating musculoskeletal targets.

These findings have not yet been investigated in the clinical setting. The normal human range of platelet concentration is 150,000 to 450,000 platelets/μL of whole venous blood.[49] Concentrations of platelets in PRP differ widely, ranging from 2.5 to 8.0 times the concentration of platelets found in whole blood.[15] The range of platelets and concentration methods used lead to products with a high- or low-platelet concentration. Reportedly, the clinical benefit of platelet concentrates occurs more predictably when a 4-fold increase in platelet concentration is achieved.[13] Accordingly, in the present study, a subanalysis was performed comparing low- and high-platelet PRP using a previously reported cutoff of 1,000,000 ± 20% platelets/μL.[24,47] The results of the current meta-analysis showed that high-platelet PRP provided clinically significant pain relief, with the MD of the improvement compared with placebo exceeding the MCID at 3, 6, and 12 months of follow-up, whereas low-platelet PRP failed to offer such clinically perceivable benefits in terms of VAS.

In fact, the pain improvement generated by low-platelet PRP compared with placebo failed to exceed the MCID at all follow-up points. Functional results showed that both products provided a clinically significant improvement at 3 and 6 months of follow-up. However, a difference was documented: This benefit was maintained up to the 12-month follow-up in the high-platelet group but not in the low-platelet group, where the improvement compared with placebo did not even reach statistical significance, suggesting the ability of the former to provide more durable, clinically relevant, functional improvements.

These results offer valuable insights for both research interpretation and clinical practice. Patients receiving PRP with more platelets can experience more substantial improvements in pain reduction and functional outcomes, overcoming the MCID threshold more reliably compared with patients receiving PRP with fewer platelets. Therefore, the use of PRP with high-platelet concentrations should be considered over PRP with low-platelet concentrations, although direct comparisons in high-level studies, specifically focusing on investigating the influence of platelet concentration, are needed to confirm these suggestions. From a research perspective, studies should always report the platelet concentrations of the used PRP in order to facilitate comparisons and a more accurate interpretation of reported results. Nevertheless, these findings add important insight in the scientific discussion on the best type of products for knee OA, although these findings should still be considered with caution and only as a contributing factor in a multifactorial explanation to understand the differences in treatment results. In fact, low-platelet PRP provided better results at short-term assessment, which is probably due to the interplay of platelets and leukocytes. Low-platelet PRP also presented a smaller number of leukocytes, which has not been shown to alter the long-term results but still caused more pain and swelling after the injections and thus could be responsible for the lower short-term improvements.[21]

Several factors likely interact and contribute to the treatment effect, and a possible role may be played by other aspects like injection schedule and injected volume. However, current literature presents a limited number of studies supporting each subanalysis, which prevents us from drawing definitive conclusions on these aspects, which should be further investigated. Although the available data do not allow us to determine whether one factor has a dominant role over the others, this meta-analysis underlines the importance of not focusing PRP investigations solely on the presence of leukocytes, which has been one of the main research targets in the last decade and whose importance was only recently questioned in an RCT.[16] Future studies should explore how to combine these findings, testing whether low-leukocyte and high-platelet PRP products could lead to better results at both short- and long-term follow-up. Finally, it is important to note that the current study's conclusion could be affected by patient-specific factors, such as patient characteristics, severity of knee OA, and individual response to treatment, and future studies should investigate all these factors to optimize the use of PRP for the treatment of knee OA.

This meta-analysis presents some limitations that require consideration. First, the available RCTs presented substantial variability in terms of characteristics and dose of the injected PRP, reflecting the considerable heterogeneity in the field of PRP injections and the literature addressing this topic. This heterogeneity was also encountered in the analysis of placebo, where the number of injections ranged from 1 to 3, adding another element of variability to the analysis. Second, the selected RCTs lacked standardization in data collection and reporting of outcome measures and associated follow-up times, reducing the amount of data available for the meta-analysis. These aspects convey the urgent need for more high-level studies to identify standardized protocols that can optimize PRP administration, as well as the identification of patient subgroups that could obtain the greatest benefit from this treatment. Third, the MCID is primarily intended as a measure of clinically significant improvement in a patient undergoing a specific intervention, and the high variability in the MCIDs reported in the literature[57] suggests some caution when considering MCID in regard to the mean change in a heterogeneous population. Nonetheless, the MCID is increasingly used to interpret the relevance of the difference documented in a quantitative synthesis and is a useful tool to evaluate the clinical significance of obtained results.[35] Despite these limitations, the present meta-analysis provided important results, shedding new light on the complex and multifactorial field of PRP injections and suggesting the clinical relevance of platelet concentration for PRP injection efficacy in the treatment of knee OA. Far from allowing a definitive conclusion on this matter, these findings provide an important reference point for patients and physicians considering intra-articular injection of PRP, allowing them to form realistic expectations on the potential of this biological approach and offering a new perspective for future PRP investigations to optimize the clinical management of knee OA.

CONCLUSION

This meta-analysis underlined the potential of PRP as an effective intra-articular treatment for knee OA. This orthobiologic approach provides not only statistically significant improvements but also clinically meaningful benefits. Moreover, the differentiation of PRP formulations by platelet concentration suggests that formulations with higher platelet concentrations may be more advantageous. This finding has implications for both research and clinical practice, prompting efforts to select and develop more effective PRP treatments and allowing a more informed discussion between clinicians and patients regarding the optimal choice of PRP formulation for the treatment of knee OA.

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