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The use of platelet-rich plasma in studies with early knee osteoarthritis versus advanced stages of the disease: a systematic review and meta-analysis of 31 randomized clinical trials

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Abstract

Purpose. Reports have concluded that platelet-rich plasma (PRP) is an effective and safe biological approach to treating knee osteoarthritis (OA). However, the efficacy of PRP in advanced stages of the disease is not entirely clear. The purpose of this study was to evaluate whether the use of PRP would be as effective in studies with early-moderate knee OA patients compared to studies including patients with end-stage OA based on the Kellgren-Lawrence classification. Methods. A comprehensive search in MEDLINE, EMBASE, Scopus, and Web of Science was conducted to identify randomized controlled trials (RCTs) comparing the effect of PRP injections versus other intra-articular treatments on pain and functionality. A meta-analysis was conducted using a random-effects model and the generic inverse variance method. Results. We included 31 clinical trials that reported data of 2705 subjects. Meta-analysis revealed an overall significant improvement of both pain (MD, -1.05 [95% CI -1.41 to -0.68]; I2 = 86%; P = < 0.00001) and function (SMD, -0.99 [95% CI -1.34, to -0.65]; I2 = 94%; P = < 0.00001), favoring PRP. Subanalysis for pain and functional improvement showed significant pain relief in studies with 1-3 and 1-4 Kellgren-Lawrence OA stages, and a significant functional improvement in studies with 1-2, 1-3, and 1-4 knee OA stages, favoring PRP. Conclusion. Our results indicate that including patients with advanced knee OA does not seem to affect the outcomes of clinical trials in which the efficacy of PRP in knee OA is assessed.

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Abstract

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Methods . A comprehensive search in MEDLINE, EMBASE, Scopus, and Web of Science was conducted to identify randomized controlled trials (RCTs) comparing the effect of PRP injections versus other intra-articular treatments on pain and functionality. A meta-analysis was conducted using a random-effects model and the generic inverse variance method.

Results . We included 31 clinical trials that reported data of 2705 subjects. Meta-analysis revealed an overall significant improvement of both pain (MD, -1.05 [95% CI -1.41 to -0.68];I^2 = 86%; P = < 0.00001) and function (SMD, -0.99 [95% CI -1.34, to -0.65];I^2 = 94%; P = < 0.00001), favoring PRP. Subanalysis

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for pain and functional improvement showed significant pain relief in studies with 1-3 and 1-4 Kellgren-Lawrence OA stages, and a significant functional improvement in studies with 1-2, 1-3, and 1-4 knee OA stages, favoring PRP.

Conclusion . Our results indicate that including patients with advanced knee OA does not seem to affect the outcomes of clinical trials in which the efficacy of PRP in knee OA is assessed.

Keywords : platelet-rich plasma; knee osteoarthritis; early; end-stage; systematic review; meta-analysis

What is already known about this topic?

Platelet-rich plasma is an effective and safe therapeutic alternative in the treatment of symptomatic knee osteoarthritis. Different aspects of the treatment are now being clarified in order to find an optimal therapeutic scheme. Thus, it is now described that multiple injections are better than a single application and that younger patients or earlier stages of the disease can benefit the most. However, the efficacy of PRP in advanced stages of knee osteoarthritis is not entirely clear.

What does this article add?

Based on a comparison dividing the studies according to different osteoarthritis stages (early, moderate or severe), our results indicate that patients with advanced knee osteoarthritis could also benefit from platelet-rich plasma therapy in terms of symptoms improvement.

Introduction

Osteoarthritis (OA) is a major cause of pain and disability in middle-aged and older adults. [1] Although multiple treatments have been recommended to relieve symptoms and extend the quality of life, there is not enough evidence to state whether one treatment is superior to another. [2] Nonsteroidal anti-inflammatory drugs continue to be the first line of pharmacological treatment; however, their use can be limited due to concerns about their therapeutic strength and the adverse effects that can appear with chronic use. [3] Other therapeutic solutions such as intra-articular injections of hyaluronic acid (HA) and platelet-rich plasma (PRP) have been developed and studied in the last few years with favorable results in patients with knee OA. [4] The use of HA has been widely studied, and there is more evidence on its use compared to the evidence on the use of PRP, which is a more recent therapeutic option for knee OA. [5, 6]

PRP is an autologous blood derivative with an increased concentration of growth factors that has shown symptomatic relief in knee OA. [7] Although PRP is a well-known therapy for knee OA, [8] several aspects of the treatment are not entirely clarified, including optimal formulation, dose, therapeutic scheme, or which patients can benefit the most. It has been suggested that PRP treatment is more effective only in early stages of the disease [9]. Some clinical trials have suggested that PRP can be more effective than placebo also in moderate knee OA. [10, 11] For example, Görmeli *et al* . performed a randomized, double-blind, placebo-controlled trial with a total of 163 patients with different stages of knee OA (mild to severe). [11] The study showed pain relief, and improved functionality in treatment groups (PRP and HA) compared to the control group (saline solution) in early-moderate and end-stage patients, but without significant results between the treatment groups. In this regard, results remain controversial, and the efficacy of PRP in advanced stages of knee OA is not entirely clear.

A previous systematic review and meta-analysis which evaluated HA vs. placebo intra-articular injections concluded that HA provided significant pain relief for patients with early-moderate knee OA, compared to patients with end-stage OA. [12] To the best of our knowledge, this situation has not been formally evaluated for PRP, which has been reported by various randomized trials to be, at least, just as effective as HA. Evaluating the effect of PRP in different stages of the disease could provide relevant information to clarify under which circumstances PRP treatment is most effective.

The purpose of this systematic review and meta-analysis was to evaluate whether the use of PRP would be as effective in patients with early-moderate knee OA compared to end-stage OA patients.

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Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13], and was guided by a registered protocol (PROSPERO registration: CRD42020202048).

Information sources and search strategy

The search strategy was designed by a librarian in collaboration with the study investigators. A combination of MeSH terms (knee osteoarthritis, knee joint, osteoarthritis, arthritis, degenerative, arthroses, arthrosis, osteoarthrosis, platelet-rich plasma, PRP, Autologous Conditioned Plasma, ACP, Kellgren-Lawrence, early knee osteoarthritis, end-stage knee osteoarthritis) and text words were selected to find original articles or abstracts in any language, including patients with a diagnosis of knee OA. MEDLINE, EMBASE, Scopus, and Web of Science were searched from their inception to December 2020. We looked for additional references that addressed our study question in other systematic reviews and unpublished clinical trials in ClinicalTrials.gov and greylit.org.

Eligibility criteria

Studies were screened for inclusion according to the following criteria:

- Design: Randomized controlled trials (RCT, parallel, or cross-over).
- Population: Patients diagnosed with knee OA for more than 3 months in which the disease stage was classified using the Kellgren-Lawrence radiological system.
- Intervention: Intra-articular injection of PRP or any derivative (autologous conditioned plasma, platelet-rich fibrin, and plasma rich in growth factors) in comparison with any other intra-articular treatment (hyaluronic acid, corticosteroid, peptide) in patients with early, moderate, or end-stage knee OA.
- Outcomes: Pain relief and functional improvement assessed by validated questionnaires or scales (*i.e.* , Visual Analogue Scale [VAS], Western Ontario and McMaster Universities Arthritis Index [WOMAC], International Knee Documentation Committee [IKDC], or Knee Injury and Osteoarthritis Outcome Score [KOOS]).

A minimum of one review outcome was considered sufficient for a study to be included in the review. Studies were excluded if they were not an RCT, did not have a full text available, did not include a control group, or were duplicated. We considered studies with a minimum follow-up of 3 months. There was no language restriction, and studies with relevant missing data regarding the outcomes of interest were also excluded.

Study selection process

Two reviewers screened the titles, abstracts, and full-text of manuscripts for eligibility in a 2-step approach. In the first step, the reviewers screened only the titles and abstracts of the studies. Studies approved by at least one reviewer were included. A full-text screening (step 2) was conducted to determine the inclusion of relevant studies. The same criteria were used for both screening phases. A chance-adjusted agreement was quantified using the kappa statistic [14], and disagreements were resolved by consensus. We used the Distiller Systematic Review Software (DistillerSR, Evidence Partners, Ottawa, Canada) for data management during the selection process.

Data collection process

Data were extracted independently and in duplicate using a standardized digital data extraction format. Eligible studies were reviewed, and the following data were extracted: (1) first author name; (2) publication year; (3) study design; (4) follow-up; (5) number of participants in the intervention and control groups; (6) study groups; (7) number and frequency of the injections; (8) OA stage based on the Kellgren-Lawrence classification; (9) injected volume; (10) type of PRP used; (11) age, gender, and body mass index of the study participants; and (12) reported pain and function scores at baseline.

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Risk of bias in individual studies

A systematic assessment of bias in the included studies was performed using the Cochrane Risk of Bias Tool version 2 (RoB 2.0), which covers the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the outcome measurement, and bias in the selection of the reported result [15]. There are five possible answers for each domain (yes, probably yes, no, probably not, and no information); according to the answers, an algorithm classifies the risk of bias as low, some concerns, or high.

Quantitative data synthesis

The meta-analysis was performed using the Review Manager statistical software (RevMan [Computer program], version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each study, a summary of the intervention effect was estimated by calculating mean differences (MD) or standardized mean differences (SMD) and 95% confidence intervals (CI) for pain (VAS) and functional outcomes (WOMAC, IKDC, and KOOS for function), respectively. Net changes in measurements (mean differences) were calculated as follows: measure at the end of follow-up—measure at baseline. The mean change from baseline was used for analysis. When numerical values were only available in figures (results presented as graphs or charts), the data were extracted with GetData (Graph Digitizer) software version 2.26 (http://getdata-graph-digitizer.com/). When only the standard error of the mean (SEM) was reported, the standard deviation (SD) was estimated using the following formula: SD = SEM x sqrt (n), where n is the number of subjects. If the outcome measures were reported in the median and interquartile range (or 95% CI), the mean and SD values were estimated with the methods described by Hozo *et al* . [16] and Wan*et al* . [17]. If we were unable to obtain the SD of a record after trying to contact the study authors, we used the range rule of thumb method to estimate the missing SD. This method estimates that the SD is a quarter of the range of a determined variable [17]. The SD of the mean difference was calculated using the following formula: SD = square root $[(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2$ - (2Rx $SD_{\text{pre-treatment}}$ x $SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) of 0.5.

Summary Measures

The meta-analysis was conducted using a random-effects model and the generic inverse variance method when the heterogeneity was above 50%; if the heterogeneity was below 50%, a fixed-effects model was used. The exploration of consistency, focused on the studies' heterogeneity, was examined by applying Cochrane's Q statistic test, and a p-value < 0.05 was considered statistically significant. Additionally, the I^2 statistic was used, considering 0–25% of heterogeneity between studies as unimportant, $>$ 25–50% as moderate, and $>$ 50% as important heterogeneity. Finally, we performed a sensitivity analysis to evaluate the influence of individual studies on overall effect size using the leave-1-out method. [18, 19] Where possible, publication bias was explored by performing funnel plots to evaluate asymmetry. [20]

Results

Search Output

The search strategy identified 1232 publications. A total of 1154 studies did not meet the inclusion criteria and were excluded. Subsequently, 78 full-text articles were reviewed for eligibility, and 47 were excluded for the following reasons: duplicated reports (19), non-RCT (8), not the intervention of interest (3), unavailable full-text article (8), not knee OA (4), and not the outcomes of interest (5). The resultant 31 clinical trials were selected and included in the present meta-analysis. The complete work-flow is shown in **Figure 1** .

Characteristics of the included studies

In total, this systematic review included data from 2705 subjects (1298 in the PRP arm and 1407 in the control arm). The included studies were published between 2012 [21] and 2020 [22–26]. Participants enrolled in the selected studies included individuals diagnosed exclusively with knee OA. The participants' follow-up varied among the studies from 3 months [25, 27] to 2 years [28]. The trials reported the use of different PRP

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formulations; six studies did not report sufficient information about the PRP used [27, 29–33], and they could not be classified. The most frequent PRP type used based on the Mishra [34] and PAW [35] classifications were the 4B and the P4XBb, correspondingly. The most frequent control group used in the studies was hyaluronic acid, followed by corticosteroid, prolotherapy, ozone, peptide, bone marrow aspirate, and saline solution. The included studies were divided into three categories according to their Kellgren-Lawrence OA classification: stage 1-2 with a total of 5 studies [9, 29, 30, 36, 37], stage 1-3 with a total of 20 studies [21, 22, 39–48, 23, 24, 27, 28, 31–33, 38], and stage 1-4 with a total of 6 studies [11, 25, 26, 49–51]. Complete information regarding the study characteristics and patients is shown in **Table 1.**

Risk of bias assessment

Fifteen studies were judged to be at low overall risk of bias [9, 11, 43–45, 48, 49, 24–26, 28, 37, 38, 40, 41], thirteen studies were classified as some concerns [21, 22, 47, 50, 51, 23, 27, 30, 32, 33, 36, 39, 46] and three as high risk of bias [29, 31, 42]. For the randomization process domain, three studies [29, 36, 42] were classified as some concerns, and the study by Camurcu et al. [31] was classified as high risk of bias. The rest of the studies had a low risk of bias. Nine studies were classified as some concerns in the domain related to deviations from intended interventions [29–31, 36, 39, 42, 46, 50, 51]. All the studies had a low risk of bias regarding the missing outcome data, except for the study by Guo et al. [42], which was classified as some concerns. Eleven studies had some concerns in the measurement of the outcome domain [21, 22, 50, 23, 27, 31–33, 39, 42, 47]. Finally, most of the studies had a low risk of bias for the selection of reported results; only two studies were classified as some concerns [29, 42]. The complete risk of bias assessment is shown in **Figure 2** .

Effectiveness of PRP according to Kellgren-Lawrence OA stages

A total of 22 and 30 studies reported pain and functional outcomes, respectively. The meta-analysis revealed an overall significant improvement of both pain (MD, -1.05 [95% CI -1.41 to -0.68];$I^2 = 86\%$; $p < 0.00001$;**Figure 3**) and function (SMD, -0.99 [95% CI -1.34, to -0.65]; $I^2 = 94\%$; $p < 0.00001$; **Figure 4**), favoring PRP.

Subanalysis for pain assessment was performed in studies including patients with 1-2 (MD, -0.63 [95% CI -1.62 to 0.36];$I^2 = 90\%$; $p = 0.21$), 1-3 (MD, -1.20 [95% CI -1.64 to -0.76]; $I^2 = 84\%$;$p < 0.00001$), and 1-4 (MD, -1.15 [95% CI -1.55 to -0.75]; $I^2 = 13\%$; $p < 0.00001$) Kellgren-Lawrence OA stage, showing a significant pain relief in studies with 1-3 and 1-4 knee OA (**Figure 3**). The sensitivity analysis revealed that the effect of PRP in 1-2 and 1-4 knee OA studies was affected after removing the studies by Khan *et al* . [29] and Pishghai *et al* . [26], respectively (**Table 2**). Subanalysis showed a significant functional improvement in studies with 1-2 (SMD, -1.25 [95% CI -2.35 to -0.14];$I^2 = 95\%$; $p = 0.03$), 1-3 (SMD, -0.83 [95% CI -1.19 to -0.47]; $I^2 = 91\%$;$p < 0.00001$), and 1-4 (SMD, -1.43 [95% CI -2.68 to -0.19]; $I^2 = 97\%$; $p = 0.02$) Kellgren-Lawrence knee OA, favoring PRP intervention (**Figure 4**). The sensitivity analysis indicated a lack of robustness for the effect of PRP in 1-2 knee OA studies (**Table 3**).

Publication Bias

Visual inspection of the generated funnel plot suggested an overall symmetry in the studies reporting pain (**Figure 5A**) and function (**Figure 5B**) for PRP injections in patients with knee OA. A possible asymmetry was detected for studies including patients with mild (Kellgren-Lawrence 1-2) and severe (Kellgren-Lawrence 4) knee OA.

Discussion

Our study's main findings showed an improvement in pain and function after PRP therapy, independently of knee OA stage. The overall pain improvement analysis showed to be significant in favor of PRP therapy. According to the subanalysis by OA stage, the results were favorable for PRP therapy, except for studies with grade 1-2 OA. For functional evaluation, both overall analysis and subanalysis resulted in a significant improvement favoring PRP therapy in studies including mild, moderate, and severe knee OA.

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Numerous active or placebo-controlled RCTs proved the efficacy of PRP in patients with symptomatic knee OA. However, several clinical and methodological differences need to be further investigated (*i.e.,*PRP dose, ideal PRP formulation, number of injections, and the time between them). Regarding these differences, there is no conclusive evidence as to whether PRP therapy is equally effective in symptom relief in the different knee OA stages. Some authors have stated that younger patients with early degenerative joint changes benefit the most with PRP injections [9, 11, 52, 53] but efficacy in late stages is yet to be proven since most clinical trials had not included patients with advanced or severe knee OA. In this regard, a recent retrospective and survival analysis concluded that more than 70% of 186 patients who received PRP therapy were delayed for total knee arthroplasty around 1.5 years [54]. The latter highlights the importance of conducting studies evaluating specific aspects that remain to be clarified regarding PRP therapy for treating knee OA.

Additionally, multiple systematic reviews and metanalysis have analyzed whether PRP can be more effective than other intra-articular treatments for knee OA such as HA, showing a positive response to PRP therapy [55–58]. Their results can be summarized in that PRP therapy is effective, safe, and with better clinical outcomes than HA in the long term. Only the PRP formulation has been further evaluated, suggesting that a PRP poor in leukocyte content is superior to a leukocyte-rich composition. [58] Despite such efforts, other aspects focused on finding the optimal characteristics of PRP therapy remain unelucidated. In this regard, in a previous systematic review, we found that a significant improvement in pain and functionality was observed using three PRP intra-articular injections [59].

An apparent discordant result was obtained for PRP efficacy over pain relief in patients with stage 1-2 OA. This discordant result can be explained by the fact that one study reported more pain relief for the comparative therapy (2 corticosteroid injections); nonetheless, pain relief had a similar significant improvement with both interventions (PRP and corticosteroid). [29] If we consider only the change from baseline, we can see that all studies report pain improvement (represented by a negative value in the forest plot). This situation was corroborated in the sensitivity analysis.

As stated before, a previous systematic review by Nicholls et al. [12] reported that studies that included patients with early-moderate knee OA had a significant pain improvement against studies that included patients with advanced knee OA. Those results were based on RTC that evaluated the efficacy of HA compared to saline solution. In addition, the use of HA was associated with a greater number of adverse effects such as mild pain, swelling, stiffness, and heaviness.

As knee OA progresses, so does structural damage and cartilage degeneration. It is expected that the possible restorative effects of PRP therapy in severe stages of the disease become limited [60]. Evidence from basic research indicates that once platelets are activated, they release several growth factors that can act, inducing the proliferation of mesenchymal stem cells and articular chondrocytes while increasing main components of the cartilage extracellular matrix such as proteoglycans and type II collagen. [61, 62] This growth factor release can also act as an anti-inflammatory stimulus by inhibiting activation of the nuclear factor kappa B (NF-ϰB) through interleukin-1 (IL-1). [63] Although it is not precisely known if these effects can induce a repair of damaged cartilage, they could delay the progress of the joint degenerative process.

Our meta-analysis included available evidence on the efficacy of PRP in different knee OA stages, but some limitations should be acknowledged. There was high clinical and methodological interstudy heterogeneity that might be explained by several factors: 1) PRP therapy was compared against various injected therapies, 2) the variety in PRP formulations, 3) differences in follow-up, and 4) distinct therapeutic schemes (number of injections and time between them). The administration technique, volume injected, and the methodological rigor of each study could have also influenced the heterogeneity. We handled the high heterogeneity by performing a meta-analysis with a random-effects model. An important limitation of our study was that we could not evaluate the specific response of each OA stage to PRP therapy, since information regarding this issue is limited in the vast majority of studies. Instead, we divided the studies according to patients with different OA stages (early, moderate or severe). Finally, participants with severe knee OA represent a minimum percentage of the population in clinical trials, so PRP therapy's real clinical effect in those patients has not been thoroughly studied. On the other hand, we analyzed data from 31 studies, including

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over 1,200 participants undergoing intra-articular injection with PRP. These studies represent a large sample size compared to the previous meta-analysis; besides, our results are based exclusively on RCT.

In conclusion, our findings indicate a significant improvement of pain and function in the studies that include early-moderate knee OA as well in those that included advanced stages of the disease. Including patients with advanced knee OA did not affect the outcomes of clinical trials in which the efficacy of PRP in knee OA was assessed.

Declarations

Funding . None to declare.

Conflicts of interest/Competing interests . No conflict of interest to declare.

Authors' contributions . FVC conceptualized and designed the study, carried out the statistical analyses and interpretation of data, drafted the initial manuscript, and approved the final version as submitted. JBS and AAGA contributed to carry out the statistical analyses and interpretation of data to conception, drafted the manuscript, and critically reviewed the manuscript. VMPM contributed to the conception, critically reviewed the manuscript, and approved the final version as submitted. CAAO contributed to the conception, critically reviewed the manuscript, and approved the final version as submitted. ASG contributed to the conception, critically reviewed the manuscript, and approved the final version as submitted. MSM contributed to conception and study design, drafted the manuscript, critically revised the manuscript, and gave final approval.

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Tables

Table 1 . Characteristics of the included studies.

Table 2 . Results of leave-one-out sensitivity analysis for pain.

Table 3 . Results of leave-one-out sensitivity analysis for function.

Figure legends

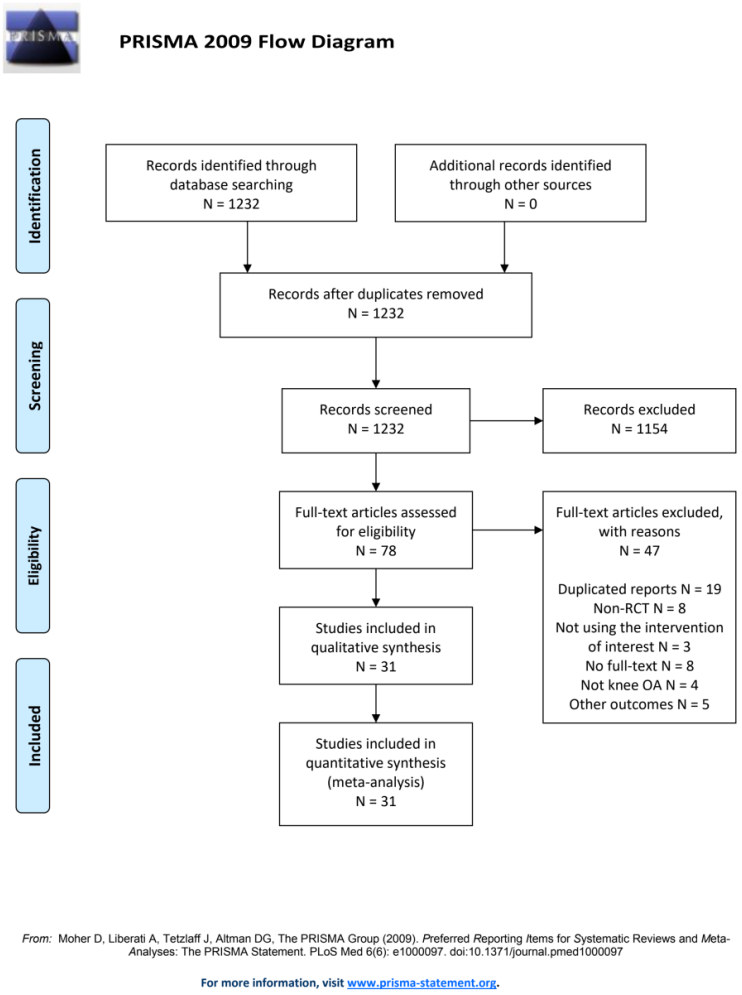
Figure 1 . Flowchart of the number of studies identified and included in this meta-analysis. RCT, randomized controlled trial; OA, osteoarthritis.

Figure 2 . Risk-of-bias assessment of the included studies according to the Cochrane guidelines.

Figure 3 . Forest plot displaying the mean difference and 95% CI for the effect of PRP on pain (visual analog scale) compared to a control group at different stages of knee osteoarthritis.

Figure 4 . Forest plot displaying the mean difference and 95% CI for the effect of PRP on functional scores (Western Ontario and McMaster Universities Arthritis Index, International Knee Documentation Committee, Knee Injury, and Osteoarthritis Outcome Score) as compared to a control group at different stages of knee osteoarthritis.

Figure 5 . Funnel plot detailing publication bias in the studies reporting the impact of PRP on pain (A) and function (B) at different stages of knee osteoarthritis.



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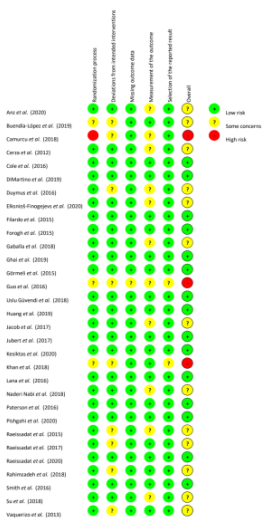

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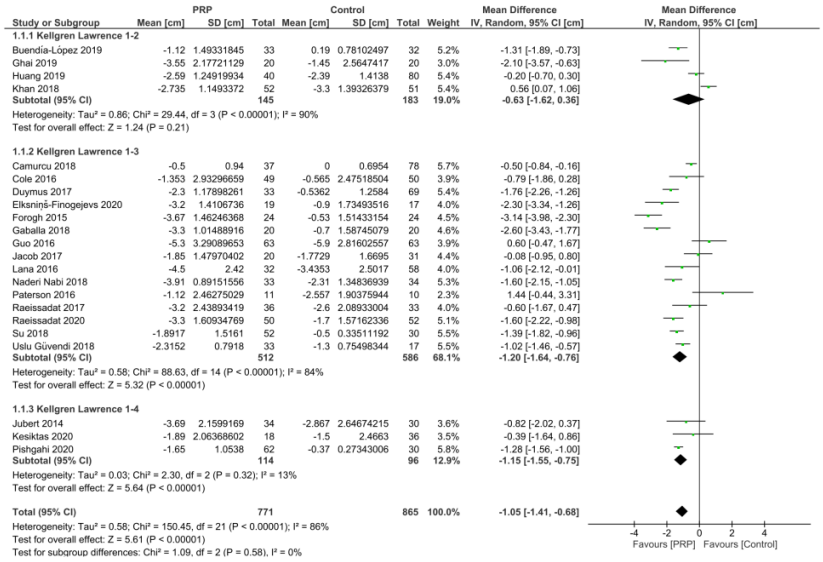

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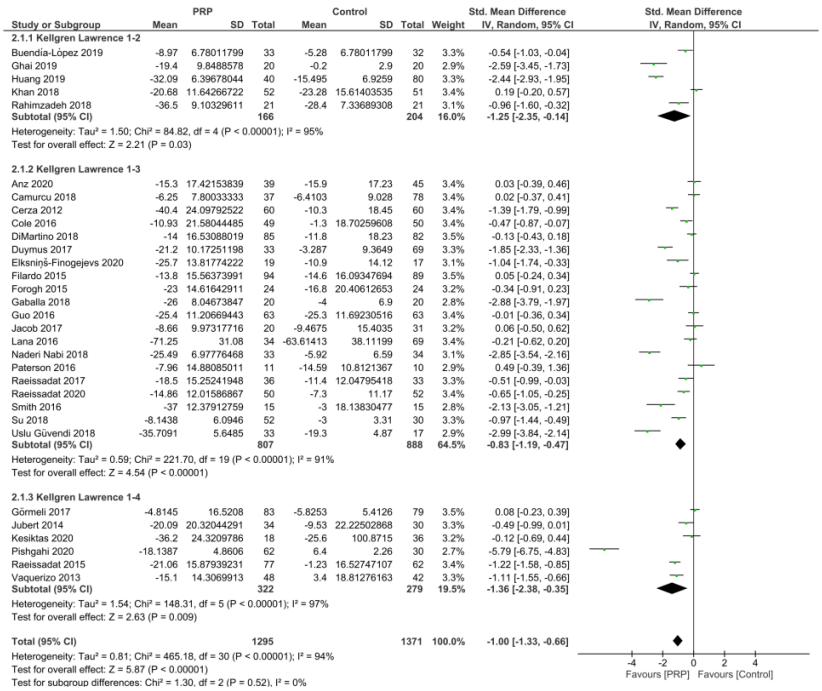

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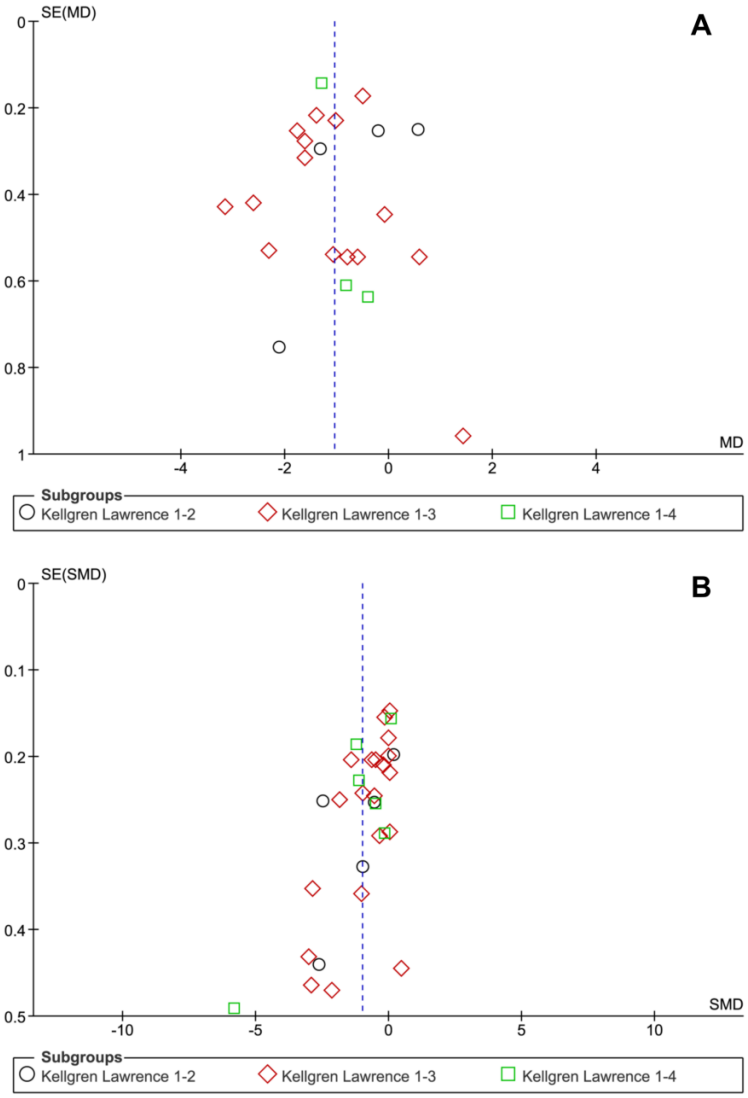

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Table 1. Study characteristics.pdf available at https://authorea.com/users/410365/articles/519753-the-use-of-platelet-rich-plasma-in-studies-with-early-knee-osteoarthritis-versus-advanced-stages-of-the-disease-a-systematic-review-and-meta-analysis-of-31-randomized-clinical-trials

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Table 2. Sensitivity analysis pain.pdf available at https://authorea.com/users/410365/articles/519753-the-use-of-platelet-rich-plasma-in-studies-with-early-knee-osteoarthritis-versus-advanced-stages-of-the-disease-a-systematic-review-and-meta-analysis-of-31-randomized-clinical-trials

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Table 3. Sensitivity analysis function.pdf available at https://authorea.com/users/410365/articles/519753-the-use-of-platelet-rich-plasma-in-studies-with-early-knee-osteoarthritis-versus-advanced-stages-of-the-disease-a-systematic-review-and-meta-analysis-of-31-randomized-clinical-trials

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