Meta-analysis

# Platelet-Rich Plasma Combined With Hyaluronic Acid Improves Pain and Function Compared With Hyaluronic Acid Alone in Knee Osteoarthritis: A Systematic Review and Meta-analysis

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**Purpose:** To evaluate the efficacy of platelet-rich plasma (PRP) combined with hyaluronic acid (HA) injections versus HA injections alone for the management of knee osteoarthritis (OA). **Methods:** This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Eligible randomized-controlled trials and observational studies directly comparing combined PRP-HA injections with HA injections alone were identified through a search of PubMed, Scopus, and Cochrane Central databases from inception to May 2020. A random effects model meta-analysis was conducted and the $I^2$ statistic was used to assess for heterogeneity. **Results:** Four studies comprising 377 patients (PRP-HA: 193, HA: 184) with knee OA ranging from I-IV Kellgren–Lawrence grading scale were included. The final follow-up was 12 months in 3 studies and 6 months in 1 study. Patients who received PRP combined with HA had significantly greater improvements compared with those injected with HA alone in terms of visual analog scale scores at 3-month (standardized mean difference [SMD] 1.13; 95% confidence interval [CI] 0.56-1.70; $I^2 = 56.7\%$; $P < .001$), 6-month (SMD 1.08; 95% CI 0.54-1.62; $I^2 = 67.9\%$; $P < .001$), and 12-month (SMD 1.13; 95% CI 0.74-1.52; $I^2 = 0.0\%$; $P < .001$) and 12-month Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical functioning (SMD 0.91; 95% CI 0.65-1.17; $I^2 = 0.0\%$; $P < .001$) and 12-month WOMAC stiffness (SMD 1.09; 95% CI 0.80-1.38; $I^2 = 0.0\%$; $P < .001$) scores. No difference was identified in terms of 12-month WOMAC pain score (SMD 0.36; 95% CI −0.19 to 0.91; $I^2 = 74.1\%$; $P = .195$). **Conclusions:** Symptomatic patients with knee OA who were injected with a combination of PRP and HA demonstrated greater improvement in pain and function compared with patients who received HA injections only, as assessed by 3-, 6-, and 12-month visual analog scale scores and 12-month WOMAC physical function and stiffness scores. This study provides encouraging evidence for the use of the combined PRP-HA injections in the management of symptomatic patients with knee OA. **Level of Evidence:** III (meta-analysis of randomized and non-randomized comparative trials).

Knee osteoarthritis (OA) can be a major cause of gradual degeneration of articular cartilage, debilitating pain, and progressive loss of joint function.[1,2] Several approaches have been suggested for the treatment of OA, including nonpharmacologic, pharmacologic, and surgical treatment for patients with a more advanced stage of disease.[3] Intra-articular injection therapies constitute a viable option in the nonsurgical management of the disease and traditionally have included a corticosteroid and hyaluronic acid

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(HA) as a means to mitigate joint inflammation and improve joint lubrication.[4-6] More recently, orthobiologic agents have been incorporated in current approaches for the treatment of OA and agents such as platelet-rich plasma (PRP), bone marrow aspirate concentrate, adipose tissue, and allogenic amniotic fluid are commonly used as injectable therapies.[5,7,8]

HA is a component of the synovial fluid, capable of increasing viscosity and joint lubrication, and has been shown to reduce OA symptoms by limiting the inflammatory pathways and decreasing knee pain.[9,10] Despite the fact that there are no data demonstrating the ability of HA to halt the progression of the disease, the Osteoarthritis Research Society International (OARSI) recommends the use of HA injections in patients with symptomatic mild-to-moderate knee OA, due to the sufficient level of evidence supporting their beneficial effect against the symptoms.[11] In contrast, PRP is currently not included in the same guidelines because of the low quality of available evidence and lack of standardization of PRP formulations.[11] PRP is an autologous formulation derived from the patient's whole blood that can be obtained on the same day as the injection. The blood sample is centrifuged, yielding a product highly concentrated with platelets and growth factors. PRP is considered to be cost-effective and convenient for patients.[2,12-14] In addition, evidence shows that an intra-articular application of PRP may reduce pain and inflammation associated with knee OA as well as influence tissue regulation due to the high level of growth factors present in platelets.[15-18]

More recently, PRP and HA combinations increasingly have been used as an intra-articular injection treatment of knee OA under the assumption that the combined application could provide a synergistic effect, resulting in a clinically significant improvement in both pain and function.[19-21] The number of clinical studies evaluating combined PRP-HA injections is limited, and there is only one meta-analysis published comparing the effect of the conjugates versus PRP alone.[22] Therefore, the purpose of the current study is to evaluate the efficacy of PRP combined with HA injections versus HA injections alone for the management of knee OA. It was hypothesized that the combined PRP-HA injections would result in superior outcomes in terms of improvements of pain relief and physical functioning.

## Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[23]

### Search Strategy and Search Eligibility Criteria

A comprehensive search was systematically conducted in Medline/PubMed, Scopus, and Cochrane Central databases. The following search algorithm was used: (osteoarthritis OR OA OR arthritis OR gonarthrosis OR degeneration) AND ("platelet-rich plasma" OR PRP OR "platelet rich plasma" OR "platelet-rich fibrin" OR PRF) AND ("hyaluronic acid" OR HA OR HHA OR hyaluronate OR hyaluronan OR viscosupplementation) AND knee. The search was performed by 2 independent investigators and was reupdated just before the final analyses on May 4, 2020. The detailed PICO (population, intervention, comparison, outcomes) format strategy applied to this clinical scenario is presented in Appendix Table 1.

A study was included in this meta-analysis if it fulfilled the following 4 predefined criteria: (1) randomized controlled trials (RCTs) or observational analyses comparing PRP combined with HA knee injections versus HA only injections in patients with knee OA, (2) studies that reported quantitative clinical outcomes data, and (3) studies published in the English language.

The predefined exclusion criteria were (1) studies including patients with knee OA treated with injectables other than combined PRP and HA or HA, (2) case series/case reports, (3) cadaveric, laboratory or animal studies, and (4) secondary research articles (eg, systematic reviews, meta-analyses, letters to the editor or commentaries).

### Study Selection

Two investigators (T.K., T.T.) assessed the titles and abstracts of all identified records independently. The same investigators independently screened the full texts of all potentially eligible studies, according to the inclusion criteria. In addition, the references of the included studies were retrieved and manually reviewed to identify further eligible articles, according to the snowball method.[24] Investigators were blinded to each other throughout the study selection and data-extraction processes. Any disagreements or discrepancies were resolved by consensus.

### Data Extraction and Outcomes

Two investigators (T.K., T.T.) independently extracted the relevant data from the eligible studies. All disagreements were resolved after discussion and the final decision was reached by consensus. Data were retrieved from all eligible studies in a predefined Microsoft Excel spreadsheet (Microsoft LLC, Redmond, WA) and included first author, year of publication, country of origin, enrollment period, number of patients, sex, age, knee OA grade, follow-up duration, and injection regimen used. The primary outcome was change in pain intensity as assessed by 6-month visual analog

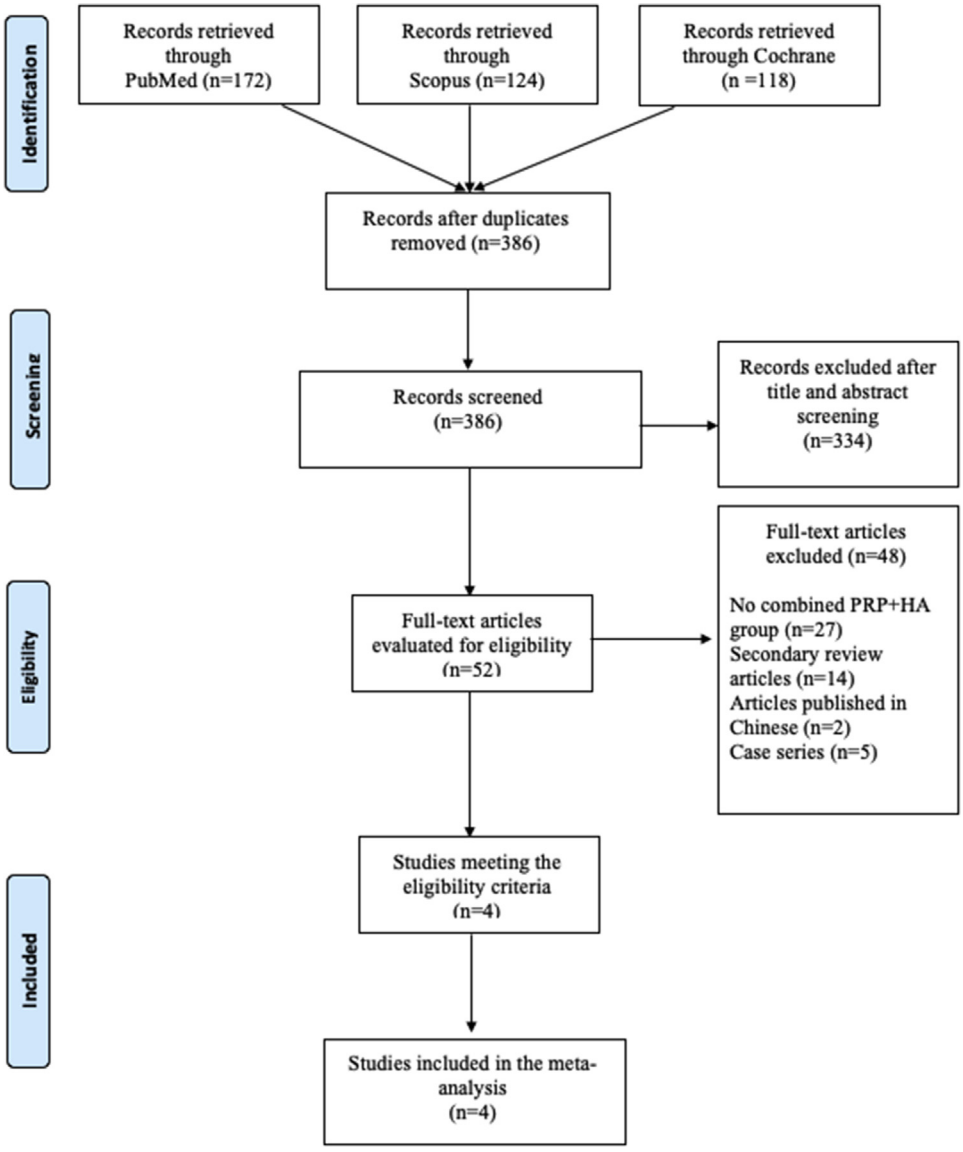


**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) search flow diagram. (HA, hyaluronic acid; PRP, platelet-rich plasma.)

scale (VAS). Secondary outcomes measures were 3-month and 12-month VAS scores, as well as 12-month Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, stiffness, and physical functioning scores. The same investigators (T.K., T.T.) assessed the eligible studies and their credentials based on the Center for Evidence-Based Medicine levels of evidence. Any disagreement was resolved by consensus.

## Risk of Bias Assessment

Risk of bias was assessed in the included studies by 2 investigators with the Cochrane tool for RCTs and the ROBINS-I (Risk Of Bias in Non-randomized Studies — of Interventions) tool for nonrandomized studies.[25,26] The Cochrane tool evaluates the following areas: adequate sequence generation, allocation concealment, blinding, baseline characteristics imbalance, patients lost to follow-up, measurement of data, and attrition bias. The following domains for the nonrandomized eligible study were evaluated: confounding, selection of participants, departure from intended intervention, missing data, measurement of outcomes, and selective reporting. Any discrepancies in quality assessment were resolved via consensus.

## Statistical Synthesis and Analysis

Continuous variables were estimated as mean ± standard deviation, whereas categorical variables were reported with absolute and relative frequencies.[27] Standardized mean differences (SMDs) with the corresponding 95% confidence intervals (CIs) were used to evaluate the continuous outcomes. A random effects model was used to account for heterogeneity among

studies. Heterogeneity was assessed with Higgins $I^2$ statistic.[28] $I^2$ >50% indicated significant heterogeneity.[28] Forest plots were used to graphically display the effect size in each study and pooled estimates. The equation proposed by Hozo et al.[29] was used to estimate mean and standard deviation from median and interquartile range. A $P$ value < .05 was considered significant. STATA 14.1 (StataCorp LLC, College Station, TX) was used as statistical software.

## Results

### Literature Search and Eligible Studies

The literature search yielded 386 potentially relevant records, after duplicates were removed. After screening titles and abstracts, we retrieved 52 articles for full-text evaluation. Inclusion and exclusion criteria were then applied to full-texts and 48 studies were excluded for the following reasons: (1) studies with no combined PRP and HA group, (2) case series, (3) secondary review papers. and (4) studies written in Chinese language. Four studies met the predetermined eligibility criteria and were included in this meta-analysis. The PRISMA flowchart was applied to illustrate the step-by-step selection process (Fig 1).

### Characteristics of the Eligible Studies and Patients

Three of the included studies were RCTs,[20,30,31] and one was an observational cross-sectional study.[32] A total of 377 patients who underwent injection therapy for knee OA were included in this systematic review and meta-analysis. In total, 193 patients received combined PRP and HA injections, whereas 184 patients were injected with HA alone. The mean duration of follow-up was 10.5 ± 2.6 months, ranging from 6 to 12 months. Three studies followed up their patients for 12 months, whereas 1 study presented their outcomes up to a 6-month follow-up. The mean patient age was 56.9 ± 6.8 (range: 22-87) years, and 41.3% of the included patients were male. All patients were diagnosed with knee OA and Kellgren–Lawrence grading scale varied between I and IV. Significant baseline characteristics of all patients enrolled are summarized in Table 1. Injection approach was superolateral, anteromedial, or lateral mid-patellar and injections constituents were not consistent among the studies. The PRP used in all 4 studies was derived from the patient's own whole blood; however, the frequency of injections, formulations, and concentrations used were not standardized among the included studies. Injection formulations and the treatment strategy followed by each study are described in detail in Table 2. No study was assessed as having high risk of bias. The sole observational study was deemed low risk of bias across all examined domains. A detailed assessment or risk of bias for the included RCTs is available in Appendix Table 2.

**Table 1.** Important Characteristics of Patients Enrolled in the Included Studies

| Study, Year | Study Design | CEBM Level of Evidence | Total Patients, n | PRP+HA Patients, n | HA Patients, n | Mean Age, y (range) | Male, n | Kellgren– Lawrence Grade | Follow-up, mo | Outcomes Assessment Methods |
|---|---|---|---|---|---|---|---|---|---|---|
| Papalia et al., 2019[30] | RCT | I | 60 | 30 | 30 | NR (40-70) | NR | II, III | 12 | VAS, KOOS |
| Yu et al., 2018[31] | RCT | I | 184 | 96 | 88 | 48 (22-72) | 98 | I, II, III, IV | 12 | WOMAC |
| Saturveithan et al., 2016[32] | OBS CS | III | 64 | 34 | 30 | 64 (50-87) | 24 | III, IV | 6 | VAS, IKDC |
| Lana et al., 2016[20] | RCT | I | 69 | 33 | 36 | 60.9 (45-70) | 9 | I, II, III | 12 | VAS, WOMAC |

CEBM, Center for Evidence-Based Medicine; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; NR, not reported; OBS CS, observational cross sectional; PRP, platelet-rich plasma; RCT, randomized controlled trial; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

**Table 2.** Injection Strategy of Included Studies

| Author, Year | Approach | Schedule | PRP | HA |
|---|---|---|---|---|
| Papalia et al., 2019[30] | Superolateral | Three injections at interval of 1 wk for 3 consecutive wk | 8 mL of the patients' whole blood was collected and centrifuged at 3100 rpm for 9 min.<br>Manufacturer: RegenLab THT tubes<br>Leukocyte: rich | 2 mL of hybrid HA (Sinovial High-Low, 3.2% 64 mg/2 mL, IBSA) composed of 32 mg of HMW (1100-1400 kDa) and 32 mg of LMW (80-100 kDa) hyaluronan. Saline tamponed by HA sodium salt. Other components: NaCl, NaP, and water |
| Yu et al., 2018[31] | Anteromedial or lateral mid-patellar | Once weekly for 12 mo | 8 mL of PRP<br>Manufacturer: Sigma-Aldrich; Merck KGaA, Darmstadt, Germany<br>Leukocyte: NR | 0.20 mg of HA (Sigma-Aldrich; Merck KGaA) |
| Saturveithan et al., 2016[32] | NR | NR | PRP (2.5-3 mL of PRP with platelet concentration of 1.4 - 1.6 million/μL)<br>Manufacturer: NR<br>Leukocyte: Rich | 4 mL of HMW (1476 kDa) HA with concentration of 22 mg/mL |
| Lana et al., 2016[20] | Lateral mid-patellar | Three injections with interval of 2 wk between them | 5 mL of PRP with platelet concentration between 800,000 and 1,600,000 per $mm^3$ of plasma<br>Manufacturer: NR<br>Leukocyte: rich | 2 mL of HMW (2400-3600 kDa) noncross-linked HA, with concentration 10 mg/mL, extracted from bacteria cells (Eufflexa-Ferring) |

HA, hyaluronic acid; HMW, high molecular weight; LMW, low molecular weight; NR, not reported; PRP, platelet-rich plasma.

## Clinical Outcomes

### Visual Analog Scale

Two studies involving a total of 129 patients presented data on VAS scores 3 months after treatment.[20,30] The random effects model meta-analysis demonstrated that the combined PRP and HA group of patients had a greater decrease in VAS score at 3 months post injection, compared with HA alone (SMD 1.13; 95% CI 0.56-1.70; $I^2 = 56.7\%$; $P < .001$) (Fig 2A).

A total of 3 studies, including 193 patients, reported 6-month VAS scores.[20,30,32] A statistically significant difference in favor of the PRP combined with HA group was identified (SMD 1.08; 95% CI 0.54-1.62; $I^2 = 67.9\%$; $P < .001$) (Fig 2B). The analysis showed that patients receiving the combined regimen were associated with a greater reduction in VAS score, compared to the HA alone group.

Two studies, composed of 118 patients, assessed VAS score at 12 months after treatment.[20,30] PRP combined with HA was found to be associated with a greater decrease at VAS score, compared with HA alone, at this time point as well (SMD 1.13; 95% CI 0.74-1.52; $I^2 = 0.0\%$; $P < .001$) (Fig 2C).

### Western Ontario and McMaster Universities Osteoarthritis Index

WOMAC pain score was reported by 2 studies, who enrolled a total of 251 patients 12 months post-treatment.[20,31] No significant difference was found between PRP combined with HA and HA alone (SMD 0.36; 95% CI −0.19 to 0.91; $I^2 = 74.1\%$; $P = .195$) (Fig 3).

A total of 2 studies, including 253 patients, reported data on WOMAC physical function score 12 months after treatment.[20,31] Combined PRP with HA injections were associated with a greater reduction in this score compared with HA alone (SMD 0.91; 95% CI 0.65-1.17; $I^2 = 0.0\%$; $P < .001$) (Fig 4).

WOMAC stiffness score was assessed by 2 studies in 211 patients at 12 months after injections.[20,31] Results showed a greater decrease in the combined PRP and HA when compared with HA only (SMD 1.09; 95% CI 0.80-1.38; $I^2 = 0.0\%$; $P < .001$) (Fig 5).

## Discussion

This meta-analysis demonstrated that patients who received PRP combined with HA injections for the treatment of knee OA had a statistically significant greater pain relief compared with HA alone, as assessed by 3-, 6-, and 12-month VAS scores; 12-month WOMAC physical function and 12-month WOMAC stiffness score also presented better improvements in patients receiving PRP and HA than HA alone.

Recently, a great number of clinical trials have emerged comparing injectable treatments for the management of knee OA.[33,34] The majority of those studies are RCTs and had directly compared PRP with HA, evaluating their overall safety and efficacy through

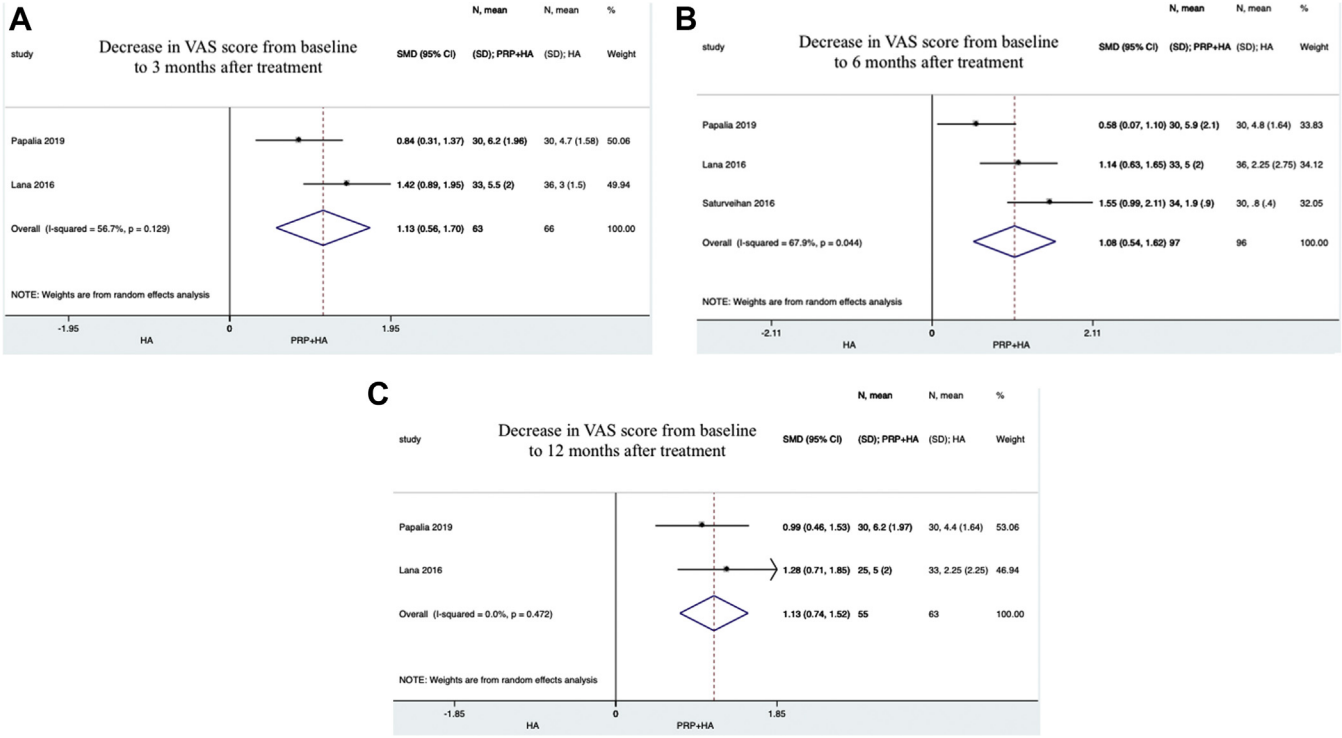


**Fig 2.** Forest plot comparing decrease in VAS score from baseline to (A) 3 months, (B) 6 months, and (C) 12 months after treatment in the PRP + HA and HA alone groups. (CI, confidence interval; HA, hyaluronic acid; N, number of patients; PRP, platelet-rich plasma; SD, standard deviation; SMD, standardized mean difference; VAS, visual analog scale.)

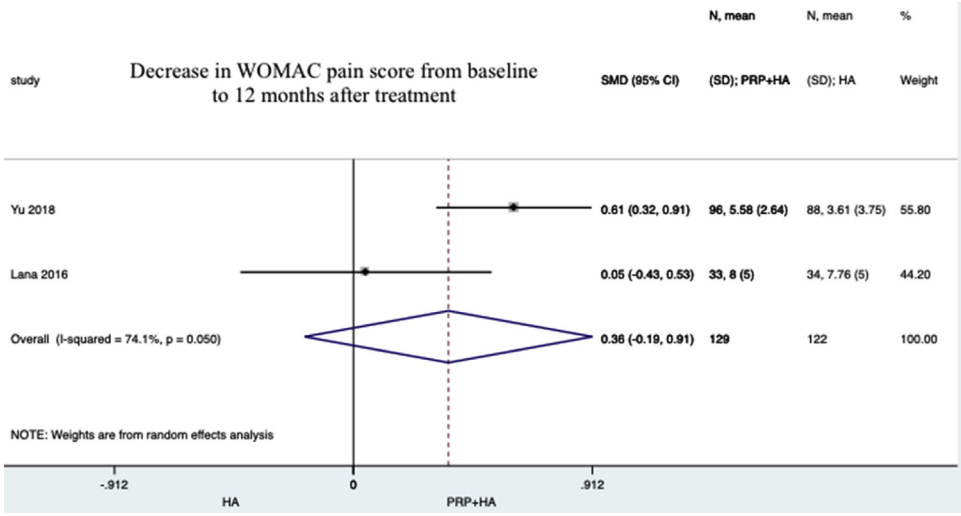


**Fig 3.** Forest plot comparing decrease in WOMAC pain score from baseline to 12 months after treatment in the PRP + HA and HA alone groups. (CI, confidence interval; HA, hyaluronic acid; N, number of patients; PRP, platelet-rich plasma; SD, standard deviation; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

WOMAC, VAS, or International Knee and Documentation Committee scores. Most of these studies concluded that intra-articular injections of PRP result in greater pain relief and improved function when compared with HA.[15,35-40] There is also an abundance of systematic reviews and meta-analyses, synthesizing primary studies and assessing improvements in pain and function, which overall demonstrated superiority of PRP over HA in knee OA up to 12 months postinjection.[14,15,35,41,42] Campbell et al.[5] conducted a systematic review of overlapping meta-analyses and supported that HA has a good safety profile and remains a viable option for patients with early knee OA, since it was demonstrated that it improves pain and function effectively for up to 26 weeks; however, no superiority was found when compared with non-steroidal anti-inflammatory drugs and PRP injections.[5]

Notably, only one meta-analysis from April 2020 has investigated the effect of PRP-HA conjugates, claiming to compare the combined injections with injections of PRP or HA alone.[22] However, this study is characterized by major weaknesses, regarding the HA alone group. First, although 7 studies were considered eligible for this analysis, only 2 of them included patients injected with HA alone.[31,43] Besides, the only outcome analyzed for the PRP-HA versus HA comparison was adverse events, where the following symptoms were pooled together: pain, proteinuria, redness, peripheral edema, constipation, and worsening of pain. No VAS or WOMAC scores were statistically analysed for the comparison between the 2 groups. In contrast, comparison of PRP-HA versus PRP alone showed greater improvements for the combined group in terms of 6-month VAS, 12-month WOMAC physical functioning,

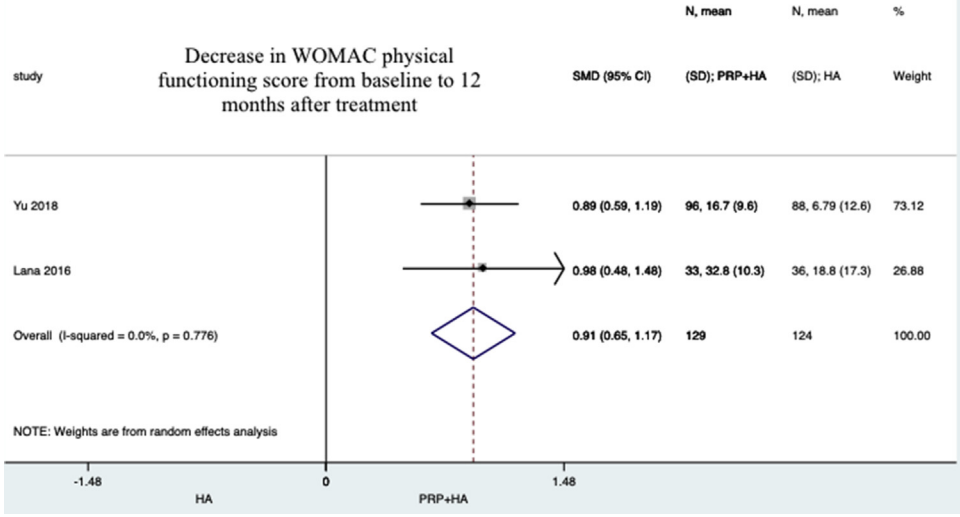


**Fig 4.** Forest plot comparing decrease in WOMAC physical functioning score from baseline to 12 months after treatment in the PRP + HA and HA alone groups. (CI, confidence interval;

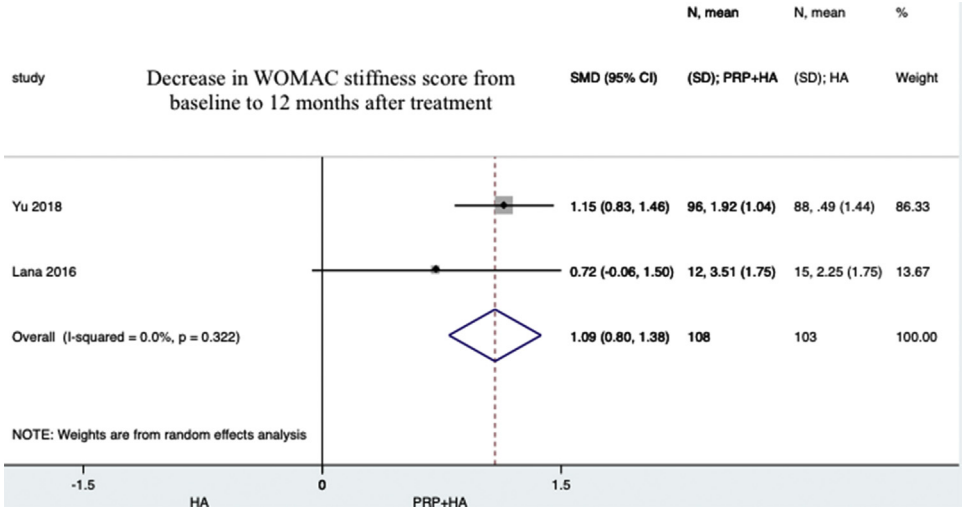


**Fig 5.** Forest plot comparing decrease in WOMAC stiffness score from baseline to 12 months after treatment in the PRP + HA and HA alone groups. (CI, confidence interval; HA, hyaluronic acid; N, number of patients; PRP, platelet-rich plasma; SD, standard deviation; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

12-month WOMAC total, and 12-month Lequesne scores. These findings are in line with the current study, which adds to the literature by demonstrating better improvement in pain and function for the combined group compared with the HA-alone injections, supporting the synergistic effect.

The basic concept of the combined approach is the potential synergistic effect of these biologic agents.[44] Specifically, viscosupplementation and elastic properties attributed to HA along with the potential chondroprotective effects of PRP, which also had been suggested to stimulate endogenous HA production, may facilitate the activity of inflammatory molecules, cytokines and catabolic enzymes. Hence this combination may contribute significantly to the treatment of OA, inhibiting degeneration and inducing cartilage regeneration.[20,44-48] The synergistic effect of PRP and HA had been investigated in vitro and in vivo in dogs and mice knee OA models, demonstrating that this combination enhances chondrocyte proliferation, increases glycosaminoglycan content, decreases apoptosis, and results in less cartilage damage, possibly due to augmented anti-inflammatory properties as well.[19,44,49] Laboratory studies had also demonstrated that PRP-HA conjugates significantly improve cell motility, by comparing migration properties of synovial fibroblasts in PRP and PRP-HA solutions. These findings supported the regenerative effects of PRP combined with HA, since cell migration play a crucial role in wound healing and tissue regeneration.[50]

A great variety of PRP formulations with different characteristics and compositions have been described in the literature. First, even though platelet concentration and their amount are major factors that vary among PRP products, no correlation has been demonstrated between platelet content and clinical outcomes.[16,51-53] Leukocyte-rich versus leukocyte-poor PRP is another comparison characterized by limited clinical data that have not shown yet whether one is superior to the other.[54,55] In our systematic review and meta-analysis 3 of 4 included studies used leukocyte-rich PRP. Some more issues that need to be resolved are the volume of blood to harvest, the volume of PRP to inject and the preparation method.[56] When it comes to HA, higher molecular weight products $\geq$3000 kDa have been associated with better clinical outcomes and lower rates of knee effusion.[57] However, these results need to be validated by large-scale clinical studies. HA products also present great variability in terms of the generic substance (hyaluronan, sodium hyaluronate, hylan G-F20).[58] Their morphology can be linear or crosslinked and can either be obtained as bacterial fermentation products or avian derived.[57,58] Included studies of the present meta-analysis are characterized by a wide heterogeneity not only in formulations of PRP and HA, but also in protocols. This fact constitutes a major limitation for data synthesis, since available data are insufficient to evaluate which type of PRP or HA is associated with better outcomes. Need of an improved international consensus for standardization of PRP and HA injectable treatments is highlighted in the literature and therefore the upcoming studies must be standardized in terms of formulations, frequency of injections, and outcome measures.[33,59-61]

The short-term follow-up in combination with the small sample size of the studies included in our analysis limit the external validity of our results. Besides, since the only available information about the diagnosis of included patients was the range of Kellgren–Lawrence grading scale without reporting separate outcomes for each grade treated, it remains unclear throughout the literature which OA grades would benefit more from PRP and HA injections. Therefore, additional RCTs with long-term follow-up and use of the same standardized

protocol are needed to the development of an evidence-based treatment algorithm for the use of PRP and HA injections in the management of knee OA. It is also crucial to note that minimal clinically important difference (MCID) should be examined when statistical significance is reached, since it constitutes a patient-centered concept that provides physicians a great feedback on the effect of the interventions to the patient. When MCID is reached, implementation of the study results in clinical practice is enhanced. However, none of the included studies refer to MCID.

### Limitations

This study should be interpreted in the context of the following limitations. First, one of the included studies was not an RCT, which therefore increases the risk of selection bias and confounding. However, after bias assessment, this study was categorized as low risk of bias. Besides, we were unable to assess publication bias for outcomes of interest due to the fact that <10 studies were synthesized for each outcome.[62] Finally, not having access to patient-level data we were unable to analyze further clinical outcomes or adverse events, other than VAS and WOMAC scores. However, we attempted to systematically evaluate and meta-analyze the available data aiming to answer whether injections of PRP combined with HA cause greater improvement in pain and function compared with HA-alone injections, in patients suffering from knee OA.

## Conclusions

Symptomatic patients with knee OA who were injected with a combination of PRP and HA demonstrated greater improvement in pain and function compared with patients who received HA injections only, as assessed by 3-, 6-, and 12-month VAS scores and 12-month WOMAC physical function and stiffness scores. This study provides encouraging evidence for the use of the combined PRP-HA injections in the management of symptomatic patients with knee OA.

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**Appendix Table 1.** PICO Format Strategy

| PICO | Description |
|---|---|
| **P**opulation | Patients with knee osteoarthritis |
| **I**ntervention | Platelet-rich plasma combined with hyaluronic acid injections |
| **C**omparison | Hyaluronic acid injections alone |
| **O**utcomes | Change in pain intensity and function improvement |

**Appendix Table 2.** Risk of Bias Assessment for Randomized Controlled Trials

| Study | Adequate Sequence Generation | Allocation Concealment | Blinding | Baseline Characteristics Imbalance | Lost to Follow-Up | Measurement of Data | Incomplete Data (Attrition Bias) |
|---|---|---|---|---|---|---|---|
| Papalia et al., 2019[30] | + | ? | ? | ? | + | + | + |
| Yu et al., 2018[31] | + | + | + | + | + | + | + |
| Lana et al., 2016[20] | + | + | ? | ? | + | + | ? |

NOTE. "+" indicates low risk; "−" indicates high risk; and "?" indicates unclear risk.