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KNEE ARTHROPLASTY

Efficacy and safety of platelet-rich plasma and hyaluronic acid combination therapy for knee osteoarthritis: a systematic review and meta-analysis

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Abstract

Background This study aimed to evaluate whether a combination of platelet-rich plasma (PRP) and hyaluronic acid (HA) is more effective and safer than injection alone for treating KOA.

Materials and methods MEDLINE (PubMed), the Cochrane Library, EMBASE, and Web of Science databases were systematically searched for articles published until January 2024, and gray literature and bibliographic references were searched. All published randomized controlled trials (RCTs) compared pain, functional outcomes, and adverse events (AEs) associated with PRP + HA therapy vs. PRP or HA treatments. Two independent researchers extracted the pertinent data and evaluated the methodological quality following the PRISMA guidelines. The primary outcomes were pain, functional outcomes, and AEs. A fixed-effects model was used for data analysis in cases with low heterogeneity ($P > 0.10$ and $I^2 < 50\%$). Otherwise, a random effects model was used.

Results Ten RCTs involving 943 patients were included in the analysis. The statistical findings did not differ between the treatment of PRP + HA and PRP alone, while a discernible enhancement in treatment efficacy was observed when compared to HA monotherapy: the visual analog scale scores at 1- (mean difference[MD], −1.00; 95% CI: −1.37 – −0.62; P < .001), 6- (MD, −1.87; 95% CI: −3.46 – −0.28; P = .02), 12-months (MD, −2.07; 95% CI: −3.77 – −0.38; P = .02), and the Western Ontario and McMaster Universities Arthritis Index total scores at 12-months (MD, −8.82; 95% CI: −14.48 – −3.16; P = .002). The incidence of adverse events was notably lower with PRP + HA than with HA alone (OR, 0.37; 95% CI: 0.19 – 0.69; P = .00) or PRP alone (OR, 0.51; 95% CI, 0.30 – 0.87; P = .01).

Conclusions PRP + HA therapy resulted in more pronounced pain and functional improvement in symptomatic KOA patients than HA treatments, and combination therapy may have higher clinical safety than PRP or HA monotherapy.

Keywords Platelet-rich plasma · Hyaluronic acid · Knee osteoarthritis · Meta-analysis

Introduction

Knee osteoarthritis (KOA), characterized by the loss of articular cartilage, development of osteophytes, alterations in subchondral bone, and synovial hyperplasia [1], even finally leading to disability [2], affects approximately 250 million individuals worldwide [3]. However, due to the unclear pathological mechanisms of KOA [1, 4], there are no well-established pharmaceuticals or interventions capable of altering the progression of KOA [5–7]. The current treatment focus is primarily on pain management and functional enhancement [7].

Prior to the final stage of total knee arthroplasty (TKA), non-pharmacological interventions, such as dietary adjustments and exercise, were frequently recommended [8],

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alongside analgesics, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs). Steroid injections are commonly used, but their efficacy diminishes after a month [9], and prolonged application may lead to adverse consequences for the existing cartilage [10]. Given the potential nephrotoxicity and gastrointestinal side effects associated with chronic NSAIDs and analgesic use [11, 12], there has been growing interest in advocating intra-articular injections of alternatives.

Hyaluronic acid (HA), a natural glycosaminoglycan found in the articular cavity [13], shows therapeutic potential owing to its viscoinductive properties and joint lubrication [14, 15], especially considering its reduced presence within the joints of individuals with osteoarthrosis [16]. Nevertheless, several studies [1, 3, 17, 18] strongly support the adoption of platelet-rich plasma (PRP) over the potentially limited efficacy of HA [3]. PRP is derived from centrifuged whole blood, resulting in a product with platelet concentrations higher than the baseline levels. They contain various growth factors and proteins that have been shown to enhance the regeneration of chondrocytes. PRP has emerged as a promising alternative biological treatment for pain alleviation and functional improvement in patients with KOA [2]. However, clinical evidence surrounding PRP remains contentious, with concerns raised about the potential impairment of PRP's overall effects by leukocyte [2, 19].

An additional and relatively recent development in these therapeutic approaches involves the concurrent administration of PRP and HA. The theoretical objective is to synergize the effects of these two agents to maximize and prolong their efficacy [20–23]. Considering that previous reviews either incorporated non-randomized controlled trials (RCTs) or analyzed a limited number of RCTs [6, 24–27], and that a significant number of additional RCTs have been published in recent years [5, 20, 28, 29]. we consider it imperative to conduct an updated systematic review and meta-analysis to offer a comprehensive evaluation of the efficacy and safety of PRP + HA therapy regimens for individuals with osteoarthritis.

Methods

This meta-analysis has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [30]. This systematic review was registered with PROSPERO on June 5, 2023.

Search strategy

Two independent researchers conducted a comprehensive search to identify eligible RCTs in the MEDLINE (PubMed), Cochrane Library, EMBASE, and Web of Science databases. Data was retrieved on April 23, 2023, and updated on January 14, 2024 (Supplemental Files, sTable 1). Additionally, we screened the reference lists of the retrieved publications to identify additional RCTs. In cases of disagreement among researchers, a third author was consulted to resolve the disagreement and evaluate all articles.

We included RCTs that compared the efficacy and safety of PRP + HA therapy with individual components in patients with KOA of any stage. All single ingredient and combination therapy regimens were included, regardless of the dose or number of PRP or HA injections. Patients who used PRP + HA therapy were the experimental group, while those who used either HA or PRP therapy served as the comparison group. Trials that included at least one of the following outcome indicators (visual analog scale [VAS] scores, Western Ontario and McMaster Universities Arthritis Index [WOMAC]) total scores, Knee Injury and Osteoarthritis Outcome Scores, International Knee Documentation Committee (IKDC) scores, Lequesne index scores, and adverse events (AEs) were considered eligible, provided that data for participants with osteoarthritis could be extracted.

Study selection and data extraction

After removing duplicates, two researchers independently screened the titles and abstracts, followed by a full-text assessment of the relevant articles. Disagreements regarding the inclusion of the studies were resolved by consensus. Data were independently extracted by the same researchers using a predesigned data extraction form. This form, designed by the senior author, encompassed various pieces of information, including publication year, first author, study design, number of included patients, patient characteristics, interventions, Kellgren-Lawrence (K-L) grades of KOA, follow-up periods, and relevant scoring data of clinical efficacy and safety. Both researchers reviewed the articles and extracted the necessary data using a predetermined form. In case of any disagreements or discrepancies between the extractions, a third investigator was consulted to resolve these issues. Before concluding the study, the database was searched again to ensure that all relevant literature was included, thereby confirming the completeness of the included studies.

Risk-of-*Bias* Assessment

Two independent researchers assessed the risk of bias in the RCTs using the Cochrane Risk of Bias tool [31]. The risk of bias within each domain was categorized as low, high, or unclear (Supplemental Files, sFigures 1 and 2). Quality assessments of the studies were conducted independently by the same researchers, and any discrepancies were resolved through consensus. Funnel plots could not assess publication

bias because none of the meta-analyses included more than 10 studies.

Statistical analysis

The mean difference (MD) served as the effect index for continuous variables, whereas the odds ratio (OR) was used as the effect index for dichotomous data. Additionally, 95% confidence intervals (CI) were calculated for all variables, and heterogeneity was evaluated using the Higgins I^2 statistic. Statistical significance was set at $P < 0.05$. If the heterogeneity was low ($P > 0.10$ and $I^2 < 50\%$), a fixed-effects model was used for data analysis. Otherwise, a random effects model was used. Sensitivity analyses were performed to evaluate the robustness of the synthesized results.

Statistical analyses of the data and risk assessments were conducted using STATA (version 18.0; StataCorp LLC, College Station, Texas, USA) software and Review Manager version 5.4.1 (The Cochrane Collaboration).

Study quality assessment

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria [32] were assessed by two researchers to evaluate the overall quality of evidence. The evidence quality dropped due to two reasons: high statistical variation ($I^2 > 50\%$) [33] and imprecise results (95% CI included the "0" line) (Supplemental Files, sTables 2 and 3).

Results

Literature screening process and results

A total of 1904 relevant articles were identified through the searches of four medical databases. 78 articles were deemed potentially eligible after title and abstract reviews, and 68 were excluded after full-text evaluation. Finally, for the meta-analysis, 10 studies [4, 5, 10, 16, 20, 28, 29, 34–36] met the predetermined eligibility criteria (Fig. 1).

Study participants

These studies collectively encompassed a total patient sample size of 943, comprising six two-arm studies and four three-arm studies (PRP + HA: 345; PRP: 281; HA: 245), and the follow-up period was extended from 6 to 24 months (Table 1). After treatment, short-term efficacy ranged from 1 to 6 months, medium-term efficacy ranged from 6 to 12 months, and long-term efficacy extended beyond 12 months.

Intervention characteristics

Within the pool of included RCTs, PRP was administered at doses ranging from 3 to 8 ml, and HA was administered at doses of 2 to 3 ml. The treatment duration varied from 3 to 8 weeks, with injection intervals spanning 1–2 weeks. Notably, PRP and HA were administered together in all trials except for two studies [10, 29], which had dosing intervals. (Table 2).

Outcomes assessment

Comparison 1: PRP + HA vs. HA

VAS scores

Three studies documented VAS scores after treatment. At each follow-up time point, the results of subgroup analyses demonstrated a statistically significant difference in VAS scores at 1 month (MD, −1.00; 95% CI: −1.37 – −0.62; $P < 0.001$), 6-month (MD, −1.87; 95% CI: −3.46 – −0.28; $P = 0.02$), and 12-month (MD, −2.07; 95% CI: −3.77 – −0.38; $P = 0.02$) post-treatment (Fig. 2).

WOMAC total scores

Two studies recorded WOMAC total scores at 1-, 6-, and 12-months post-treatment. The pooled results indicated the absence of significant heterogeneity between two groups at 1 month (MD, −2.42; 95% CI: −13.44 – 8.60; $P = 0.67$) and 6-month (MD, −11.19; 95% CI: −22.72 – 0.34; $P = 0.06$), but exhibited a statistically significant difference at 12-month (MD, −8.82; 95% CI: −14.48 – −3.16; $P = 0.002$) (Fig. 3).

Comparison 2: PRP + HA vs. PRP

VAS scores

Three studies reported the VAS scores after treatment. The results at various follow-up time points revealed no significant differences at 1- and 6-months (Supplemental Files, sFigure 3).

WOMAC total scores

Four studies covered WOMAC total scores after treatment. The results of the subgroup analyses showed no significant

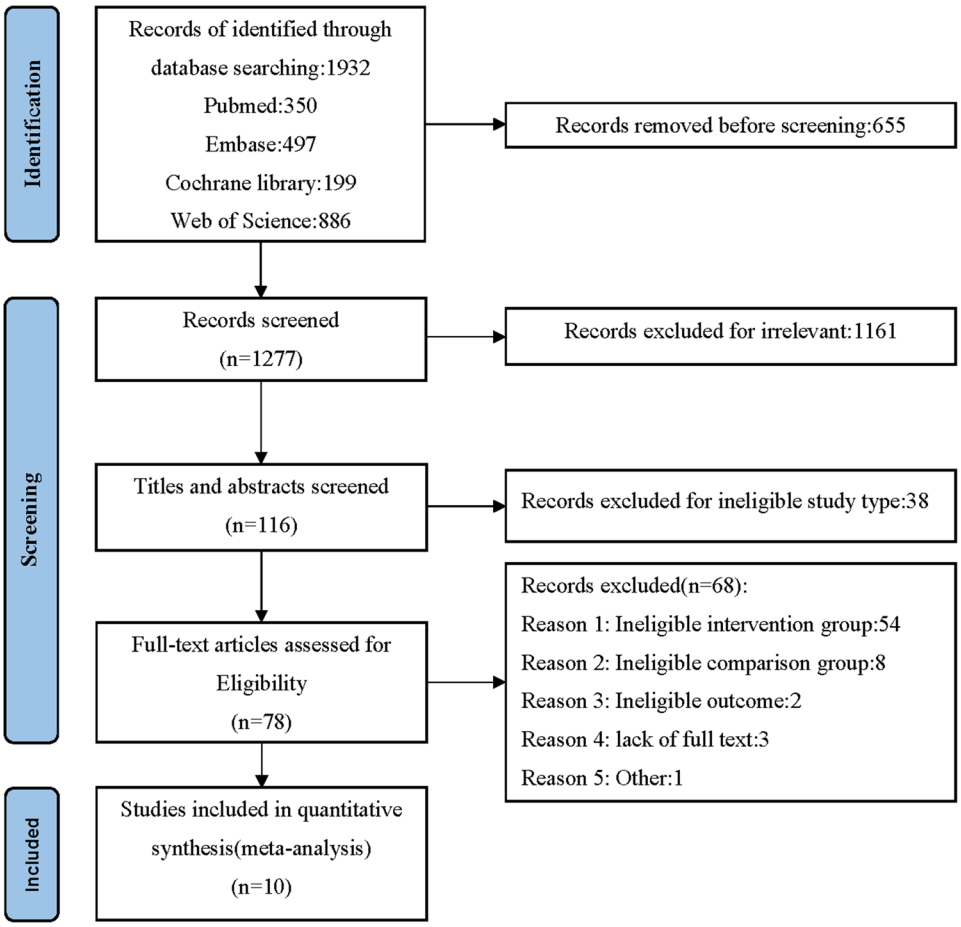

Fig. 1 PRISMA search flow diagram (last search: January 2024)

heterogeneity at 1-, 3-, 6-, 12-, and 24-months (Supplemental Files, sFigure 4).

IKDC scores

Two studies reported the IKDC scores post-treatment. The pooled results suggested no significant heterogeneity in IKDC scores at 4–6 weeks and 6 months (Supplemental Files, sFigure 5).

Lequesne index scores

Two studies reported Lequesne index scores at 1- and 6-months post-treatment. The results showed no significant heterogeneity at 1- and 6-months (Supplemental Files, sFigure 6).

Adverse reactions

Eight studies reported AEs after the treatment. The most frequently reported complications were mild inflammatory reactions characterized by redness at the treatment site. The pooled results demonstrated that the rate of AEs in the PRP + HA group was significantly lower than that in the HA group (OR, 0.37; 95% CI, 0.19 − 0.69; P = 0.00) or PRP group (OR, 0.51; 95% CI, 0.30 − 0.87; P = 0.01) (Fig. 4).

Sensitivity analyses

We conducted sensitivity analyses of all subgroup studies using random-effects models, and the findings of this meta-analysis remained stable.

Discussion

Principal findings

In summary, the meta-analysis indicated a clear and statistically significant advantage for the PRP + HA therapy group over the HA-alone therapy group in terms of short- to medium-term pain relief and functional improvement. Compared with patients receiving PRP alone, the current statistical results showed no better or prolonged beneficial effects in the PRP + HA therapy group. The lack of significant differences may be attributed to the limited

Table 1 Characteristics of patients in the included studies

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients			Gender (F:M)			Age, (years)			K-L Grade (I: II: III: IV)			Clinical outcomes	Follow-up Periods
				PRP+HA	PRP	HA	PRP+HA	PRP	HA	PRP+HA	PRP	HA	PRP+HA	PRP	HA		
Lana,2016[10]	RCT	Age between 40 to 70 years, history of chronic pain for at least four months and/or joint edema, radiographic evidence of mild to moderate OA according to K-L classification (grade I-III)	105	33	36	36	27:6	29:7	33:3	62±6.1	60.9±7	60±6.6	9:16:11:0	9:14:13:0	5:14:14:0	⑥	12 months
Jacob,2017[16]	RCT	Pain or swelling of knee >4 months, K-L 0-III on X-ray	51	31	20	–	–	–	–	–	–	–	–	–	–	①④⑥	6 months
Yu,2018[4]	RCT	The age range of 40–70 years, with symptom duration of more than 3 months, confirmatory X-ray diagnosis (K-L grade 1–4) within the past 3 months	360	96	104	88	46:50	54:50	40:48	46.5±7.5	46.2±8.6	51.5±9.3	–	–	–	②⑥	12 months

Table 1 (continued)

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients	Gender (F:M)	Age, (years)	K-L Grade (I: II: III: IV)	Clinical out-comes	Follow-up Periods
Barac,2019[28]	RCT	Age above 30 years and below 80 years, history (at least 4 months) of chronic pain or swelling of the knee, imaging findings of degen-erative changes of the joint (K-L Score up to 3 at X-ray evaluation, or US findings of degen-erative changes (in patients with no OA signs vis-ible with X-ray), and VAS score larger than 50.	53	19 (30knees) – 34 (60knees)	16:14 – 34:26	61.3±10.9 – 63.8±9.3	10:12:8:0 — 23:18:19:0	◎	12 months

Table 1 (continued)

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients			Gender (F:M)			Age, (years)			K-L Grade (I: II: III: IV)			Clinical outcomes	Follow-up Periods
Papalia,2019[34]	RCT	Symptoms duration of more than 3 months, radiographic signs of knee degeneration evaluated by Radiographs (RX) of the lower limbs under loading of the affected knee in the Rosenberg X-ray projection (a posteroanterior weight-bearing in 45° of flex- ion projection) and a lateral (full-extension) projection (K-L scale II and III).	60	30 (45knees)	–	30 (32knees)	–	–	–	–	–	–	–	–	–	①③	12 months

Table 1 (continued)

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients			Gender (F:M)			Age, (years)			K-L Grade (I: II: III: IV)			Clinical outcomes	Follow-up Periods
Sun,2021[35]	RCT	Aged 20–75 years, symptomatic KOA ≥ 6 months despite conservative treatment such as oral analgesics, NSAIDs and/or physical therapy, K-L grades 2 knee OA on radiographs taken within the previous 6 months, average pain at walking ≥ 30 mm on a 100-mm VAS, radiological evidence of bilateral KOA was accepted if global pain VAS in the contralateral knee < 30 mm	78	39	39	–	18:21	22:17	–	60.6±8.4	58.4±8.1	–	–	–	–	①②③⑥	6 months

Table 1 (continued)

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients			Gender (F:M)			Age, (years)			K-L Grade (I: II: III: IV)			Clinical out-comes	Follow-up Periods
Xu,2021[36]	RCT	Ability to provide informed consent, aged between 42 and 79 years, Diagnosis of K-L stage II ~ III, No prior injection therapy (HA, PRP, steroid, etc.), no prior surgical history (HTO, arthros-copy, internal fixation of a knee fracture, etc.), no prior pain medica-tion (NSAIDs, etc.) in the past 1month	78	28 (48knees)	30 (40knees)	20 (34knees)	20:8	20:10	15:5	57.9±4.1	56.9±4.2	57.1±3.4	0:25:23:0	0:19:21:0	0:20:14:0	①②③⑥	24months

Table 1 (continued)

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients			Gender (F:M)			Age, (years)			K-L Grade (I: II: III: IV)			Clinical outcomes	Follow-up Periods
Xu,2022[5]	RCT	The patients aged 50-75 years old, were confirmed knee degenerative changes by X-ray or MRI, were graded Grade 1-3 knee OA according to the K-L classification with knee joint pain/swelling (duration>6 months), The VAS > 4 points while normal coagulation by laboratory tests.	34	17	—	17	13:4	—	14:3	64.8±8.5	—	60.5±7.7	2:8:7:0	—	1:9:7:0	①②	6 months

Table 1 (continued)

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients			Gender (F:M)			Age, (years)			K-L Grade (I: II: III: IV)			Clinical outcomes	Follow-up Periods
Ciapini,2023[20]	RCT	The radiographic evidence of KOA (grade II-III according to the K-L classification), pain or functional limitations in patients' activity of daily living before the treatment, age between 30 and 80 years, the absence of clinical or imaging signs of articular instability.	60	20	20	20	10:10	10:10	10:10	—	—	—	—	—	—	ⓒ	6 months

Table 1 (continued)

First Author, year	Study design	Inclusion criteria	Total number of patients	Number of patients			Gender (F:M)			Age, (years)			K-L Grade (I: II: III: IV)			Clinical outcomes	Follow-up Periods
Branch,2023[29]	RCT	The ages of 30 and 80 years who had symptomatic and radiographic evidence of unilateral or bilateral OA in the tibiofemoral or patellofemoral compartment of the target knee (K-L Grades 1-4) were screened for participation in this study by members of the research team, documented diagnosis of primary OA for at least 6 weeks, as confirmed by radiographic imaging.	64	32	32	—	16:16	20:12	—	60.66±8.99	55.78±11.42	—	21:8:1:2	16:11:3:2	—	②③④⑥	24 months

RCT randomized control trail, *PRP* platelet-rid plasma, *HA* hyaluronic acid, *K-L* Kellgren-Lawrence, *KOA* knee osteoarthritis, *OA* osteoarthritis, *VAS* Visual Analogue Scale, *NSAIDs* non-steroidal anti-inflammatory drugs ①VAS scores, ②WOMAC total scores, ③KOOSs, ④IKDC scores, ⑤Lequesne index scores, ⑥Adverse events

Table 2 The details of the administration and composition of PRP + HA and HA or PRP of the included studies.

First Author, Year	Procedural Details	EXP (PRP + HA) composition	CON(PRP) Composition	CON(HA) Composition	Number of injections	Injection Interval (weeks)
Lana,2016[10]	PRP:8.5 ml of anticoagulant ACD (citric acid, sodium citrate, dextroset) added to 60 ml venous blood; centrifuged it at 300G for 5 min; PCP aspirated and transferred out, then centrifuged it again at 700G for 17 min; activation with 0.8 ml of thrombin; obtain 5 ml PRP. Manufacturer: NR Leukocyte: Rich HA:2 ml HMW (2,400 – 3,600 kDa) non-cross-linked HA, with concentration 10mg/ml, extracted from bacteria cells (Eufflexa-Ferring) HA administered first, PRP later.	PRP: 5ml HA: 2ml	5ml	2ml	3	2
Jacob,2017[16]	PRP: 20-ml venous blood added to 5-ml of citrate phosphate dextrose; centrifuged for 7 min at 3500 rpm; PCP aspirated and transferred out, then centrifuged for 5 min at 3000 rpm; yield 2.5 ml PRP Manufacturer: NR Leukocyte: Rich HA: LMW HA or HMW HA Administration details NR	PRP: NR HA: NR	2ml	–	NR	NR
Yu,2018[4]	PRP: 8ml of PRP Manufacturer: Sigma-Aldrich; Merck KGaA, Darmstadt, Germany Leukocyte: NR HA: 0.20 mg of HA (Sigma-Aldrich; Merck KGaA) PRP and HA administered together	PRP: 8ml HA: 0.2 mg	8ml	0.2mg	8	1
Barac,2019[28]	PRP:6-ml venous blood; centrifuged for 5 min at 3600 rpm; yield 3 ml PRP Manufacturer: Regen Lab SA, Le Mont sur Lausanne, Switzerland Leukocyte: Rich HA: 2 ml of ArthroVisc (2% non-cross-linked HA, 40 mg/2 ml, Regen Lab SA, Le Mont sur Lausanne, Switzerland) or OSTENIL® PLUS (2% non-cross-linked HA with mannitol, 40 mg/2 ml, TRB Chemedica, Switzerland) PRP and HA administered together	PRP: 3ml HA: 2 ml	–	2ml	3	2

Table 2 (continued)

First Author, Year	Procedural Details	EXP (PRP + HA) composition	CON(PRP) Composition	CON(HA) Composition	Number of injections	Injection Interval (weeks)
Papalia,2019[34]	PRP:8 ml of the patients' whole blood was collected and centrifuged at 3100 rpm for 9 min. Manufacturer: RegenLab THT tubes® Leukocyte: Rich HA:2 ml Hybrid HA (Sinovial HighLow, 3.2% 64 mg/2ml, IBSA) composed of 32 mg of HMW (1,100-1,400 kDa) and 32 mg of LMW (80-100 kDa) hyaluronan. Saline tamponed by HA sodium salt. Other components: NaCl, NaP and water PRP and HA administered together	PRP: 8ml HA: 2ml	8ml	2ml	3	1
Sun,2021[35]	PRP:7 mL of venous blood was collected into a PLTenus PLUS Platelet Concentrate Separator; centrifuged at a speed of 500 ~ 1200 rpm for 8 min; obtained 3 mL of leukocyte-poor PRP. Manufacturer: TCM Biotech International Corp., Taiwan Leukocyte: Poor HY AJOINT Plus is produced by microbial fermentation. PRP and HA administered together.	PRP: 3ml HA: 3ml	3	–	1	NR
Xu,2021[36]	PRP: 4ml of anticoagulant acid citate dextrose added to 36 ml venous blood; centrifuged it at 160 g for 10 min; PCP aspirated and transferred out, then centrifuged it again at 250 g for 15 min; obtain 5 ml PRP. Manufacturer: TGL–16Gr, Anting Scientific Instrument Factory, Shanghai, China Leukocyte: Rich HA: 2 ml of HA (SOFAST, 2 ml/20 mg, 2500 kDa, Shandong, China) PRP and HA administered together.	PRP: 4ml HA: 2ml	4	2	3	2
Xu,2022[5]	PRP:27 mL of venous blood added to 3-ml of 2.5% sodium citrate; centrifuged it; obtain 3 ml PRP. Manufacturer: NR Leukocyte: NR HA: 2.5 ml of SH injection. PRP and HA administered together.	PRP: 3ml HA: 2.5ml	–	2.5	EXP:2 CON:3	EXP:2 CON:1

Table 2 (continued)

First Author, Year	Procedural Details	EXP (PRP + HA) composition	CON(PRP) Composition	CON(HA) Composition	Number of injections	Injection Interval (weeks)
Ciapini,2023[20]	PRP: 8 ml of peripheral circulating blood was collected in a proper tube and centrifuged at 1500g for five minutes, obtaining 4 ml of PRP. Manufacturer: Regen Lab, Le Mont-sur-Lausanne, Switzerland Leukocyte: NR HA: 2 ml syringe containing 40mg of fermented hyaluronic acid with a molecular weight of 1550 kDa. PRP and HA administered together.	PRP: 4ml HA: 2ml	4ml	2ml	3	3 times in 2 months
Branch,2023[29]	PRP: 15 mL of whole blood was harvested; centrifuged at 1500 rpm for 5 minutes; produced 4 to 5 mL of a liquid leukocyte poor PRP Manufacturer: Arthrex ACP System and Centrifuge (Arthrex, Inc.) Leukocyte: Poor HA: 3 mL high molecular weight hyaluronic acid (Hymovis, Fidia Pharma) for the first 2 injections PRP administered first, HA later.	PRP: 4~5ml HA: 3ml	4~5ml	–	3	1

HA hyaluronic acid, *HMW* high molecular weight, *LMW* low molecular weight, *PRP* platelet-rich plasma, *SH* sodium hyaluronate, *EXP* the experimental group, *CON* the control group, *NR* not reported

number of studies included in the analysis and the exclusion of non-RCTs. Finally, the combined therapy exhibited a safer profile than PRP- or HA-alone therapies. This information will assist orthopedic surgeons and patients with early-to mid-stage KOA or older patients unable to undergo surgery due to physical limitations in making informed choices about conservative treatments.

In this meta-analysis, we also increased the minimal clinically important difference (MCID) concept to assess the disparity between the PRP + HA and HA-alone groups: VAS scores [37] and WOMAC total scores [38]. Although the WOMAC total scores did not achieve the MCID (9 points) in this study, the PRP + HA group exhibited significant improvement over the HA group in VAS scores, with a decrease of 1.00 at 1 month, 1.87 at 6 months and 2.07 at 12 months; two of them were above the MCID in VAS scores (1.37). This indicates the clinical superiority of the PRP + HA treatment group in alleviating midterm pain compared to the HA group.

Standardization of combination therapy

Different preparations of PRP and HA can lead to variations in the treatment outcomes in patients with KOA. Currently, there are no standardized definitions for the preparation of PRP and HA, and various studies have used their own methods to prepare PRP, different concentrations of HA, varying injection doses, frequencies, and intervals for experimentation. For example, in an RCT conducted by Jacob et al. [16], the PRP injection dose was 2 ml, whereas in a trial conducted by Yu et al. [4], the PRP injection dose was 8 ml. HA is present in different concentrations and types [39–41], as reported in the relevant literature, and HA products injected into joints with a molecular weight of 3×10^3 kDa or higher, especially those derived from biological fermentation processes, have proven to be more effective and safer [40]. In the included studies, almost all utilized HA molecules with molecular weights lower than

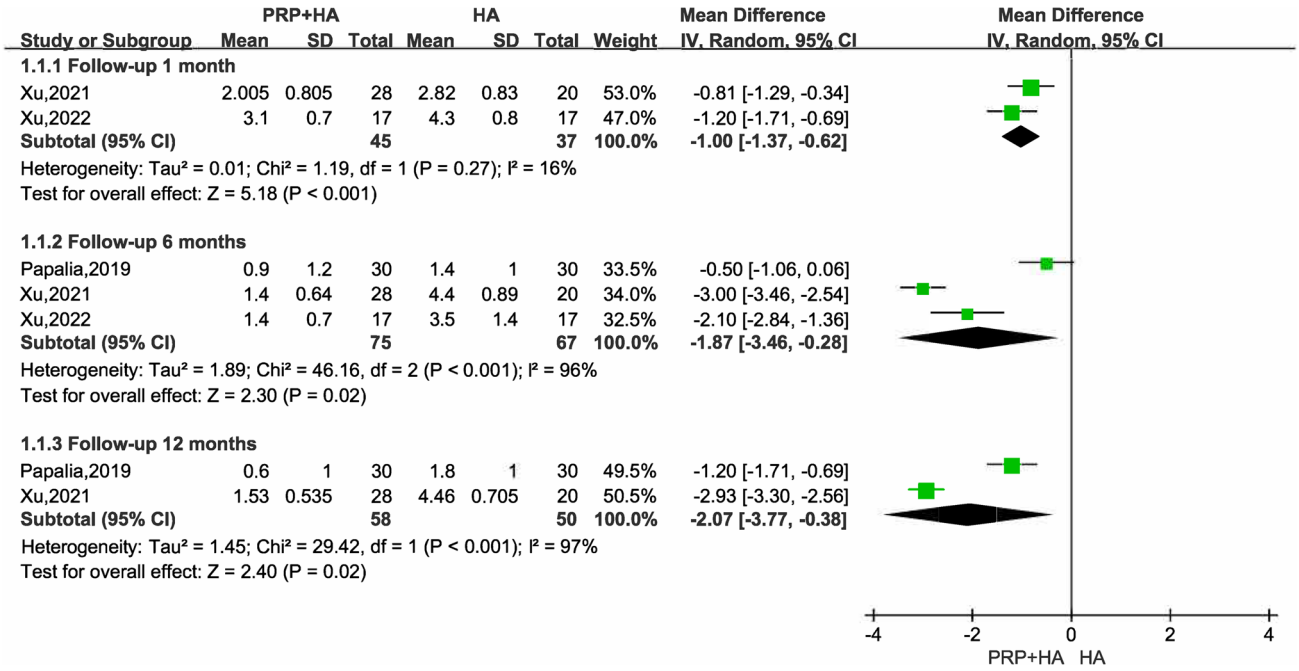

Fig. 2 Forest plot comparing the VAS scores at 1-, 6-, and 12-months between PRP + HA and HA after treatment. (CI, confidence interval; SD, standard deviation; IV, inverse variance.)

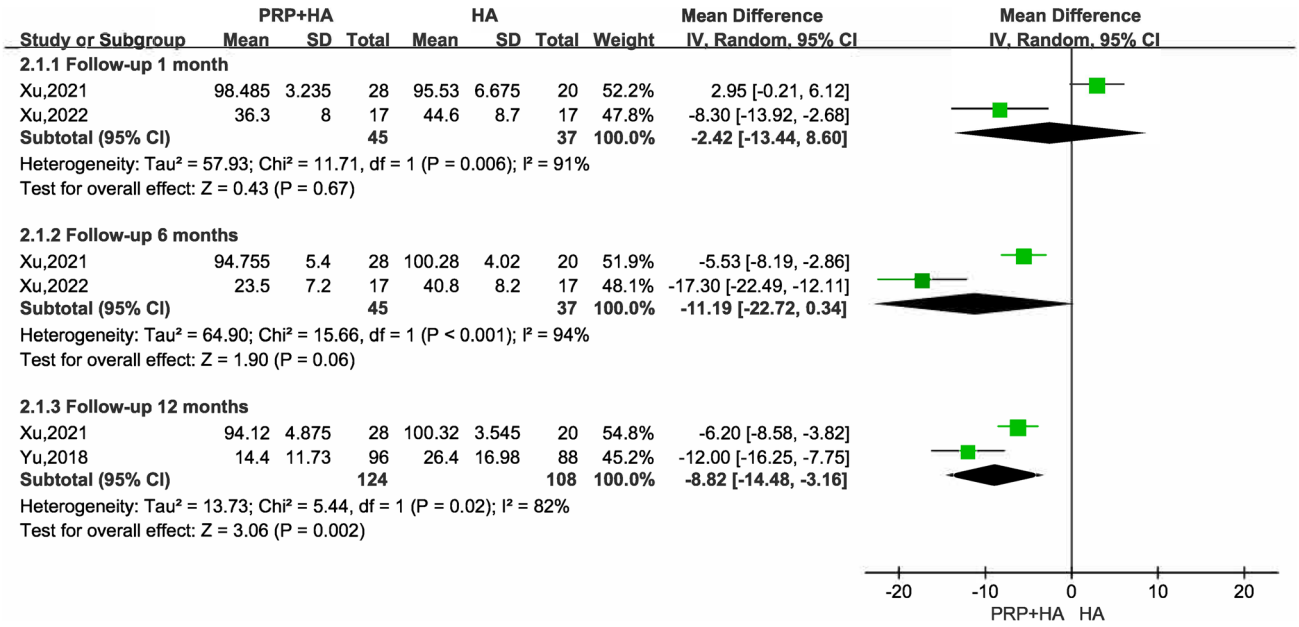

Fig. 3 Forest plot comparing the WOMAC total scores at 1-, 6-, and 12-months between PRP + HA and HA after treatment. (CI, confidence interval; SD, standard deviation; IV, inverse variance.)

those mentioned above. This may have led to an increase in the number of AEs in the HA group, thereby affecting the reliability of the results. A systematic review suggested that repeated intra-articular HA injections are effective and safe for treating KOA [42], while multiple HA injections may increase the risk of infection during future TKA procedures [43, 44]. Therefore, conservative treatment aims not only to improve immediate symptoms but also to consider potential long-term complications that may occur in patients with KOA.

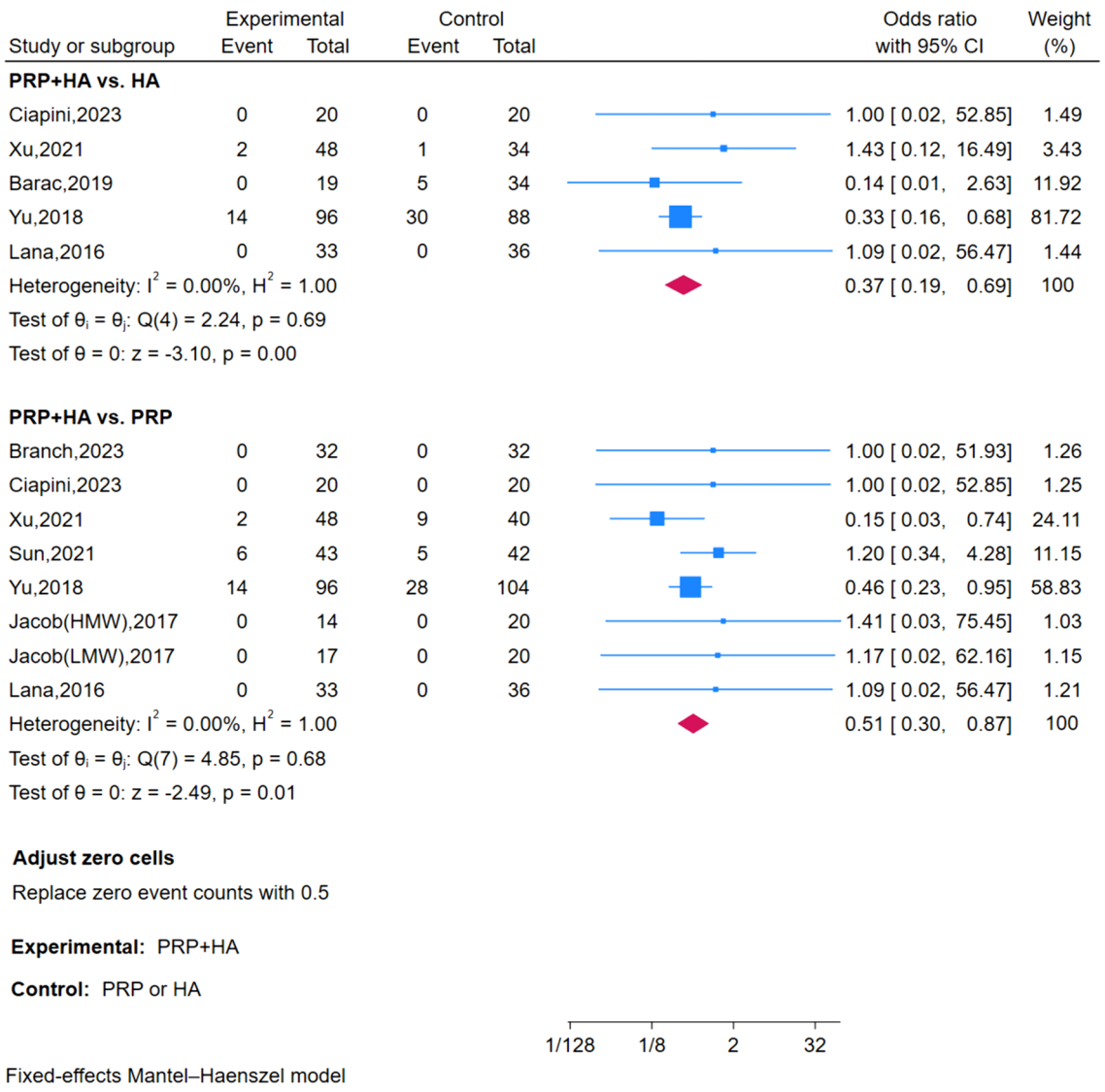

Fig. 4 Forest Plot comparing the incidence of adverse events between PRP + HA and HA or PRP. (CI, confidence interval.)

The effectiveness of different types of PRP [45], known as leukocyte-rich platelet-rich plasma (LR-PRP) and leukocyte-poor platelet-rich plasma (LP-PRP), for treating KOA has been debated with no clear agreement in the scientific community [46]. This prevailing understanding suggests that LP-PRP is linked to anti-inflammatory effects, whereas LR-PRP is associated with pro-inflammatory effects [19, 46]. Although a meta-analysis suggested that adverse reactions were prevalent in PRP treatments regardless of leukocyte concentration [47], recent studies comparing LR-PRP with LP-PRP for KOA treatment indicated that LP-PRP resulted in lower pain levels during intra-articular injections [2, 19, 48]. Of the 10 RCTs included in this meta-analysis, five used LR-PRP, two used LP-PRP, and three did not report relevant information. Hence, the varying occurrence of AEs in PRP groups across studies may have reduced the reliability of the combined results. Previous literature reports recommend that PRP treatment for patients with KOA between K-L grades 1 and 3 is typically administered in two to four sessions, spaced 2–4 weeks apart [9, 49]. This is consistent with the frequencies used in most of the included studies. Recent studies have shown that multiple PRP injections administered over several years are more effective than a single injection [50–53]. However, a recent meta-analysis found that multiple injections did not always provide significant pain relief or functional improvement [54]. This finding suggests that further research is required to confirm the optimal number of PRP injections. This difference resulted in considerable heterogeneity in the pooled results. In future studies, it will be essential to establish a standardized approach for combination therapy to improve reporting consistency.

Comparison with other studies

Previously, five meta-analyses investigated the effects of PRP + HA therapy: Zhang [6], Karasavvidis [25], Aw [24], Zhao [26] and Qiao [27]. The meta-analyses conducted by Zhang et al. [6], AW et al. [24], and Zhao et al. [26] demonstrated that PRP + HA therapy resulted in significantly greater improvement in VAS scores and WOMAC total and function scores compared to PRP-alone therapy in the short to medium term, while according to Qiao et al. [27], PRP-alone therapy outperformed PRP + HA therapy in WOMAC total and function scores. However, this meta-analysis revealed no significant differences in VAS scores at 1- or 6-months and in WOMAC total scores at 1-, 3-, 6-, 12-, and 24-months. The differences in these results may be related to the previous meta-analysis, which included non-RCTs [6, 24–26] and limited studies [27]. Furthermore, both Zhang et al. [6] and AW et al. [24] reported better IKDC scores in the PRP + HA therapy group than in the PRP-alone therapy group at the 6-month mark. In our analysis, we found no significant heterogeneities at 4–6 weeks and 6-month time points. The results reported by Karasavvidis et al. [25] and Qiao et al. [27] showed that superior improvement in pain and function with the combination therapy of PRP and HA compared to HA-alone therapy in terms of VAS scores at 3-, 6-, and 12-months. These findings align with the results of our meta-analysis of VAS scores at 6- and 12-months. Additionally, Zhao et al. [26] suggested that the combination therapy of PRP with HA did not show a significant difference in AEs compared to PRP- or HA-alone therapy. In addition, Qiao et al. [27] revealed that PRP-alone therapy was safer than PRP + HA therapy. In contrast, Zhang et al. [6] and AW et al. [24] demonstrated that dual therapy was generally safer than PRP-alone, which was consistent with our findings. Hence, this meta-analysis offers a comprehensive reassessment of the contentious findings from prior studies.

Limitations

This study included all recently published RCTs to eliminate potential selection bias introduced by non-RCTs. Therefore, the quality of evidence in the major subgroup analyses was moderate or above. In addition, we presented mean differences instead of standardized mean differences to make the results more accessible and understandable. Furthermore, this analysis provides valuable reference information on the short- and long-term efficacy of KOA treatment.

Nevertheless, the limited number of enrolled RCTs in this meta-analysis and the formulations of PRP and HA, were not consistent across trials, resulting in a restricted pool of studies for each outcome indicator. Notably, regarding WOMAC-related indicators, disparities in values have been observed in certain studies owing to varying threshold settings [36]. Furthermore, the relatively small sample sizes of certain RCTs could limit the statistical validity of the study [5, 28]. Lastly, owing to the limited number of RCTs included in the study, we were unable to conduct additional subgroup analyses related to different doses and frequencies of PRP interventions, as well as the K-L grades of KOA.

Conclusion

The findings of this study suggest that the combination of PRP and HA demonstrates promising clinical safety in patients with KOA. PRP + HA therapy exhibited a higher level of safety than the administration of PRP or HA alone. In symptomatic patients with KOA, the combined therapy of PRP and HA showed superior improvements in pain and function compared with patients treated solely with HA injections.

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Data availability Additional Information Explanation for why data not available: Prof. Zuo and Prof. Zhang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

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