

Original Article

The clinical impact of joint-local administration of platelet-rich plasma together with hyaluronic acid for knee osteoarthritis management

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Abstract: Objectives: To evaluate the clinical efficacy and safety of intra-articular injection of platelet-rich plasma (PRP) combined with hyaluronic acid (HA) versus PRP or HA alone in patients with knee osteoarthritis (KOA) over a 12-month follow-up period. Methods: Patients with Grade 2-3 KOA were grouped according to the intra-articular treatment received (PRP, HA, or PRP+HA), with each regimen administered as three injections at two-week intervals. Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Knee Injury and Osteoarthritis Outcome Score (KOOS) were assessed at baseline and at 2, 6, and 12 months. Results: All groups showed significant improvements in VAS, WOMAC, and KOOS at 2 and 6 months. At 12 months, a significantly higher proportion of patients in the PRP+HA group than in the HA group achieved $\geq 35\%$ improvement from baseline in the KOOS total score (43.5% vs. 26.7%, $P = 0.012$); however, the responder rates for VAS and WOMAC did not differ significantly among groups. Serum levels of CTX-II and COMP were significantly lower in the PRP+HA group than in the other two groups at 6 months. Conclusions: Over 12 months, PRP+HA provided sustained improvement in patient-centered outcomes compared with HA alone and was associated with greater reductions in circulating cartilage-turnover markers at 6 months. These serum markers reflect systemic rather than local joint status, the findings should be regarded as exploratory and hypothesis-generating. Nevertheless, they support PRP+HA as a promising therapeutic option that warrants further mechanistic and imaging-based validation.

Keywords: Knee Osteoarthritis, platelet-rich plasma, hyaluronic acid, intra-articular injection, pain management

Introduction

Knee osteoarthritis (KOA) is a common age-related degenerative joint disease characterized by cartilage damage, joint inflammation, pain, and reduced quality of life [1]. These problems are particularly prevalent in older people [2]. Conventional therapeutic methods include physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs), and surgery; however, their effectiveness and suitability vary considerably among individuals [3].

The combination of platelet-rich plasma (PRP) and hyaluronic acid (HA) has shown promise in treating KOA owing to their complementary mechanisms of action [1]. PRP contains growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta

(TGF- β), which promote tissue repair, cellular proliferation, and collagen synthesis [2, 3]. HA is a natural polysaccharide essential for joint homeostasis; it provides lubrication and shock absorption through its viscoelastic properties and exerts anti-inflammatory effects [4, 5]. In KOA, the intra-articular environment is characterized by a deficiency of endogenous HA and an imbalance between catabolic and anabolic processes [4]. While both PRP and HA have demonstrated individual efficacy in alleviating KOA symptoms, each has limitations: PRP's analgesic effect can be inconsistent, and its preparation is complex, whereas HA alone has limited tissue-repair ability [6, 7]. Theoretically, combining PRP's regenerative potential with HA's protective and lubricating functions may synergistically address multiple facets of KOA

pathophysiology [8, 9]. Preliminary clinical studies support this notion, suggesting that PRP+HA may improve joint function and reduce symptoms more effectively than each monotherapy [10, 11].

This biological rationale is supported by a growing body of preclinical evidence. In vitro studies have demonstrated that HA-PRP therapy significantly enhances chondrocyte proliferation, promotes cartilage-specific gene expression (including SOX9, collagen type II, and aggrecan), and inhibits inflammation-induced catabolic enzymes (e.g., MMP-3 and MMP-13) [12]. Mechanistically, this synergy involves the sequential activation of CD44 and TGF- β RII receptors, followed by downstream Smad2/3 and Erk1/2 signaling pathways, ultimately upregulating the chondrogenic transcription factor SOX9 [12]. Furthermore, PRP has been shown to enhance glycosaminoglycan-mediated reduction of pro-inflammatory and degradative OA-related markers, including IL-6, NF- κ B, MMP-13, and COMP [13]. In animal models of OA, intra-articular injection of PRP has also been shown to reduce proinflammatory cytokines (IL-1, IL-6, TNF- α) and mitigate cartilage and synovial damage [13].

However, the existing clinical data are often derived from studies with small sample sizes or short follow-up periods. Consequently, a significant gap remains in understanding the long-term comparative efficacy of this combination, particularly in direct, head-to-head comparisons against established options like HA alone. This study therefore aims to systematically evaluate the clinical efficacy and safety of intra-articular PRP+HA injections compared with PRP or HA alone in patients with KOA over a 12-month period. In addition, we aim to explore accompanying changes in systemic serum biomarkers of cartilage turnover (CTX-II, COMP) and inflammation (IL-6, TNF- α) as accessible, minimally invasive surrogates intended to complement rather than replace the clinical endpoints; characterizing local joint tissue mechanisms was beyond the scope of this cohort. Therefore, this study seeks to determine whether the combination therapy provides superior pain relief, functional improvement, and quality of life benefits, while also monitoring its safety profile.

Methods

Study design and population

This retrospective study included 138 patients with KOA who were treated at the The First People's Hospital of Pingdingshan between January 2020 and December 2022. According to treatment regimen, patients were allocated into three groups: the HA group (n = 45), the PRP group (n = 47), and the PRP+HA combined group (n = 46). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The First People's Hospital of Pingdingshan (Approval No. PYLL2022111601). Given the retrospective design of the study, the requirement for informed consent was waived. The flowchart of participant selection is illustrated in **Figure 1**.

American College of Rheumatology (ACR) criteria for diagnosing KOA included both clinical and radiological features. Because treatment was administered as part of routine clinical care, participants and treating physicians were not blinded; however, outcome assessors and data analysts were blinded to group assignment during data collection and analysis.

Inclusion criteria: (1) Age 40-75 years; (2) Clinical and radiographic diagnosis of KOA according to the ACR criteria; and (3) Radiographic severity of grade II or III according to the Kellgren-Lawrence (KL) classification.

Exclusion criteria: (1) Severe cardiovascular, cerebrovascular, hepatic, or renal diseases; (2) Contraindications to intra-articular injection, such as joint infections or skin diseases at the puncture site; (3) A history of intra-articular therapy within the previous three months; (4) Confirmed allergy to hyaluronic acid, sodium citrate, or other components of the PRP formulation; (5) Poor compliance or any other reason precluding the completion of follow-up.

Group allocation and treatment

Patients in the PRP group received three intra-articular injections of autologous PRP (4 mL per injection) at two-week intervals. PRP prepared from peripheral venous blood using a two-step centrifugation process: first at 1,600 rpm (approximately 250 g) for 10 minutes, and

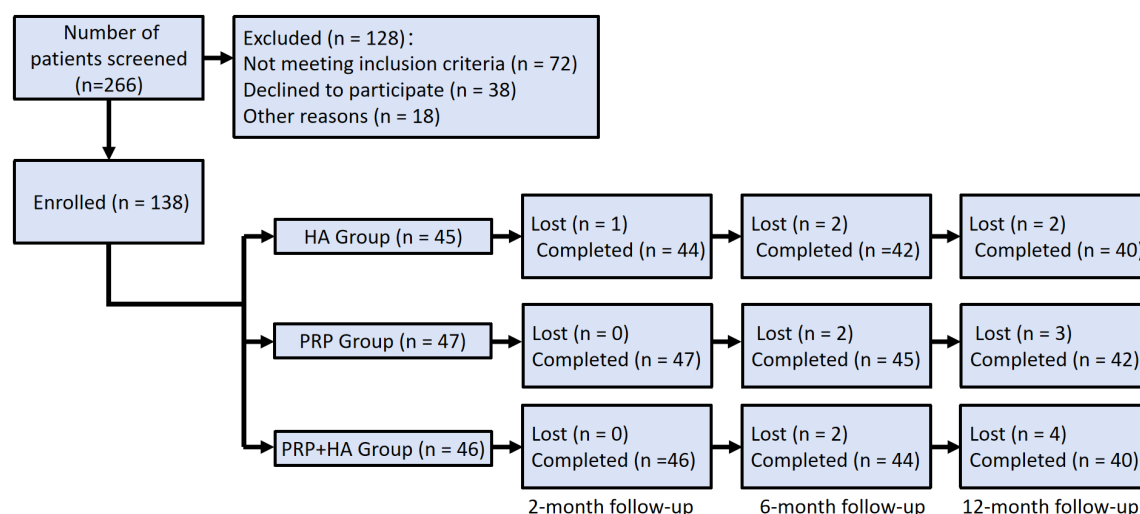


Figure 1. Flow diagram of patients selection. Flow diagram of patient screening, grouping, follow-up, and analysis. A total of 266 patients were screened for eligibility. After excluding 128 patients who did not meet the inclusion criteria (n = 72), declined to participate (n = 38), or for other reasons (n = 18), 138 patients were included and grouped according to the treatment they received: HA (n = 45), PRP (n = 47), and PRP+HA (n = 46). The numbers of patients lost to follow-up at 2, 6, and 12 months are shown for each group. All eligible patients were included in the analysis. PRP, platelet-rich plasma; HA, hyaluronic acid.

then at 3,000 rpm (approximately 900 g) for 10 minutes, both at room temperature. The prepared PRP had a median platelet concentration of $1,405 \times 10^3/\mu\text{L}$, representing an average enrichment factor of approximately 5.7 times compared with whole blood platelets. Patients in the HA groups received three intra-articular injections of 2 mL hyaluronic acid (Synvisc®; Genzyme, China) at two-week intervals. The HA used had a molecular weight of about 6,000-7,000 kDa and contained 16 mg of sodium hyaluronate per 2 mL. Patients in the PRP+HA group received a combination of 4 mL PRP and 2 mL HA (total 6 mL) per injection, also administered at two-week intervals for a total of three injections.

NSAIDs were administered for no more than 5 days after each injection to manage procedural pain, consistent with recent evidence suggesting that a short course of NSAIDs does not diminish the analgesic efficacy of PRP [14].

Functional assessment and laboratory parameter dection

Clinical outcomes: Clinical outcomes were assessed at baseline and at 2, 6, and 12 months after the final injection by two qualified orthopedic surgeons (G.M. and Z.S.) who were not involved in group allocation.

Pain visual analog rating scale (VAS): Pain severity was assessed using a 10-point VAS, ranging from 0 (no pain) to 10 (severe pain).

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [14]: The WOMAC was used to assess pain, joint stiffness, and physical function, with higher scores indicating more severe symptoms.

Knee injury and osteoarthritis outcome score (KOOS): The KOOS was used to assess knee-related pain, other symptoms, activities of daily living (ADL), and knee-related quality of life (QoL). Each subscale score was transformed to a scale ranging from 0 to 100, with higher scores indicating fewer symptoms and better knee-related function.

Adverse events: All adverse events occurring during the treatment and follow-up periods, including local pain, swelling, and infection at the injection site, were documented.

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Prior to the formal study, inter-rater reliability was assessed in a pilot sample of 30 patients.

The two surgeons independently evaluated each patient using VAS, WOMAC, and KOOS within a 48-hour interval, blinded to each other's scores. The intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs) was calculated using a two-way random-effects model with absolute agreement. The ICCs were 0.92 (95% CI: 0.85-0.96) for VAS, 0.89 (95% CI: 0.81-0.94) for WOMAC total score, and 0.87 (95% CI: 0.78-0.93) for KOOS total score, indicating good-to-excellent inter-rater reliability for all three instruments ([Supplementary Table 1](#)).

Laboratory parameter assessment: Venous blood samples (5 mL) were collected from all participants at baseline and at 2, 6 and 12 months after the final intervention. Samples were centrifuged, and the separated serum was stored at -80°C until analysis. All assays were performed in triplicates, and the mean values were used for statistical analyses. Laboratory technicians were blinded to group assignment.

Cartilage turnover markers: Serum concentrations of C-terminal cross-linked telopeptide of type II collagen (CTX-II) and cartilage oligomeric matrix protein (COMP) were quantified using enzyme-linked immunosorbent assay (ELISA) assay (Cloud-Clone Corp., Houston, TX, USA). CTX-II is a degradation product of type II collagen and serves as a marker of cartilage turnover. COMP is a matrix-associated glycoprotein indicative of joint degeneration and is associated with more severe KOA.

Inflammatory markers: Serum levels of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) were quantified using high-sensitivity ELISA kits (R&D Systems, Minneapolis, MN, USA). Elevated serum and synovial fluid levels of IL-6 and TNF- α have been consistently associated with pain severity and synovial inflammation in KOA [15].

Statistical analysis

Statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was verified using Levene's test. Continuous variables conforming to normal distribution are presented as mean $\pm$ standard deviation (SD), and categorical variables as number and per-

centage (n, %). Comparisons among groups were performed using one-way ANOVA for continuous variables and chi-square tests for categorical variables.

The main efficacy analyses included all eligible patients. Temporal changes in VAS, total WOMAC, and KOOS subscores were analyzed using two-way repeated-measures ANOVA. Sphericity was assessed using Mauchly's test; when the sphericity assumption was violated, the Greenhouse-Geisser correction was applied. In the presence of significant interactions or main effects, post-hoc pairwise comparisons were performed with Bonferroni correction. The Shapiro-Wilk test confirmed that the continuous outcome variables were approximately normally distributed (all $P > 0.05$), and Mauchly's test indicated that the sphericity assumption was met for most repeated-measures ANOVA models ($P > 0.05$). These validations support the appropriateness of the statistical models used in this study.

The proportions of patients achieving a $\geq 35\%$ improvement from baseline in KOOS total score at 12 months were compared across groups using the chi-square test with Bonferroni correction.

Missing data in the primary analyses were handled using the last observation carried forward (LOCF) approach. As a sensitivity analysis, all primary comparisons were repeated using multiple imputation for missing data, and the results were compared with those obtained using LOCF; the primary findings were unchanged, with the difference between the PRP+HA and HA groups in the KOOS responder rate remaining statistically significant.

The correlation between biochemical markers and clinical outcomes was assessed using Spearman's rank correlation coefficient. These biomarker analyses were exploratory and hypothesis-generating; no adjustment for multiple testing was applied, and the result should be interpreted accordingly. A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 138 subjects were allocated into three groups: HA ($n = 45$), PRP ($n = 47$) and

Table 1. Comparison of baseline demographics and functional assessment findings among groups

Characteristic	HA (n = 45)	PRP (n = 47)	PRP+HA (n = 46)	Test statistic (df)	P-value
Baseline characteristics					
Age (years)	61.25 ± 5.32	59.67 ± 5.85	60.41 ± 5.03	F (2, 135) = 0.982	0.376
Sex (male/female)	11/34	15/32	12/34	χ^2 (2) = 0.654	0.721
Pain duration (months)	4.18 ± 2.31	4.52 ± 2.67	4.09 ± 2.15	F (2, 135) = 0.411	0.664
BMI (kg/m ²)	27.85 ± 2.54	27.58 ± 2.38	28.02 ± 2.71	F (2, 135) = 0.354	0.703
Outcome measures					
Kellgren-Lawrence grade				χ^2 (2) = 0.178	0.915
II	24	26	25		
III	21	21	21		
WOMAC Pain	9.45 ± 1.68	9.62 ± 1.55	9.81 ± 1.72	F (2, 135) = 0.539	0.584
WOMAC Stiffness	2.55 ± 1.18	2.68 ± 1.35	2.62 ± 1.22	F (2, 135) = 0.132	0.876
WOMAC Function	30.82 ± 8.45	29.51 ± 7.82	29.13 ± 7.35	F (2, 135) = 0.614	0.543
WOMAC Total	42.82 ± 10.83	41.81 ± 9.76	41.56 ± 9.28	F (2, 135) = 0.221	0.802
VAS	7.95 ± 1.25	7.72 ± 1.38	8.05 ± 1.31	F (2, 135) = 0.770	0.465

Notes: PRP, Platelet-rich Plasma; HA, Hyaluronic acid; WOMAC, Western Ontario and McMaster Universities Arthritis Index; SD, Standard Deviation.

Table 2. Comparison of baseline serum biochemical markers among groups

Marker	HA Group (n = 45)	PRP Group (n = 47)	PRP+HA Group (n = 46)	F (df)	P-value
CTX-II (pg/mL)	695.2 ± 138.5	702.1 ± 145.3	698.0 ± 144.9	F (2, 135) = 0.115	0.892
COMP (µg/mL)	8.09 ± 2.38	8.15 ± 2.51	8.11 ± 2.47	F (2, 135) = 0.024	0.976
IL-6 (pg/mL)	4.61 ± 1.42	4.52 ± 1.35	4.55 ± 1.39	F (2, 135) = 0.112	0.894
TNF-α (pg/mL)	5.19 ± 1.62	5.27 ± 1.71	5.22 ± 1.68	F (2, 135) = 0.055	0.947

Notes: PRP, Platelet-rich Plasma; HA, Hyaluronic acid; CTX-II, serum biomarkers of cartilage turnover; COMP, cartilage oligomeric matrix protein.

PRP+HA (n = 46). The baseline characteristics were well balanced among the three groups (all $P > 0.05$; **Table 1**). The mean ages of patients in the HA, PRP, and PRP+HA groups were 61.25 ± 5.32 years, 59.67 ± 5.85 years, and 60.41 ± 5.03 years, respectively, with no significant difference among groups ($P = 0.376$). The proportions of male patients were 24.4% (11/45), 31.9% (15/47), and 26.1% (12/46), respectively ($P = 0.721$). The duration of knee pain at baseline was comparable among the three groups: 4.18 ± 2.31 months in the HA group, 4.52 ± 2.67 months in the PRP group, and 4.09 ± 2.15 months in the PRP+HA group ($P = 0.664$). Body mass index (BMI) values were also similar across groups, with means of 27.85 ± 2.54, 27.58 ± 2.38, and 28.02 ± 2.71 kg/m², respectively ($P = 0.703$). The distribution of K-L grades were comparable among the three groups ($P = 0.915$).

Baseline outcome measures did not differ significantly among groups. The mean WOMAC

total scores were 42.82 ± 10.83 in the HA group, 41.81 ± 9.76 in the PRP group, and 41.56 ± 9.28 in the PRP+HA group ($P = 0.802$). Baseline VAS scores were 7.95 ± 1.25, 7.72 ± 1.38, and 8.05 ± 1.31, respectively ($P = 0.465$). These results confirm that the three groups were well balanced at baseline and suitable for subsequent efficacy assessment.

Comparison of baseline biochemical markers among groups

As shown in **Table 2**, baseline serum levels of CTX-II, COMP, IL-6, and TNF-α showed no significant differences among the three groups (all $P > 0.05$), confirming baseline comparability for biochemical markers.

Comparison of PRP cellular composition between PRP and PRP+HA groups

The cellular composition of PRP in the PRP+HA group (after HA addition) was compared with

Table 3. Comparison of PRP components among the three groups

PRP components	PRP (n = 47)	PRP+HA (n = 46)	t (df)	P-value
PLT Count ($\times 10^3/\mu\text{L}$)	1328.56 $\pm$ 348.21	1265.43 $\pm$ 310.57	T (91) = 0.936	0.352
PRP/Blood PLT Ratio	5.43 $\pm$ 1.08	5.19 $\pm$ 0.94	T (91) = 1.162	0.248
WBC Count ($\times 10^3/\mu\text{L}$)	2.35 $\pm$ 0.42	2.28 $\pm$ 0.39	T (91) = 0.842	0.401
Leukocyte Differential Count				
Lymphocyte ($\times 10^3/\mu\text{L}$) (%)	1942.17 $\pm$ 356.84 (82.63 $\pm$ 1.71)	1885.63 $\pm$ 329.45 (82.81 $\pm$ 1.68)	T (91) = 0.636	0.527
Neutrophil ($\times 10^3/\mu\text{L}$) (%)	258.52 $\pm$ 50.17 (11.05 $\pm$ 0.92)	252.49 $\pm$ 47.83 (11.18 $\pm$ 0.85)	T (91) = 0.410	0.684
Monocyte ($\times 10^3/\mu\text{L}$) (%)	149.31 $\pm$ 48.26 (6.32 $\pm$ 1.95)	141.88 $\pm$ 44.79 (6.01 $\pm$ 1.88)	T (91) = 0.779	0.438

Notes: PRP, Platelet-rich Plasma; HA, Hyaluronic acid; PLT, platelet; WBC, white blood cell.

that in the PRP monotherapy group. No significant differences were observed for any cellular parameter between the two groups (all $P > 0.05$; **Table 3**).

The mean platelet count was $1328.56 \pm 348.21 \times 10^3/\mu\text{L}$ in the PRP group and $1265.43 \pm 310.57 \times 10^3/\mu\text{L}$ in the PRP+HA group ($P = 0.352$). The ratio of PRP platelet concentration to whole blood platelet concentration was similar between the two groups (5.43 ± 1.08 vs. 5.19 ± 0.94 , $P = 0.248$). Of note, in the PRP+HA group, an equal volume of HA was added to the PRP immediately before injection, increasing the total delivery volume from 4 mL (PRP only) to 6 mL (PRP+HA), and thus, the final platelet density was proportionally reduced. The platelet counts reported in **Table 3** reflect this dilution, as samples were taken from the final mixture.

Leukocyte concentrations were similar between the two groups (2.35 ± 0.42 vs. $2.28 \pm 0.39 \times 10^3/\mu\text{L}$, $P = 0.401$). The distribution of leukocytes, including percentages and absolute counts of lymphocytes, neutrophils, and monocytes, also showed no significant differences between the two groups (all $P > 0.05$). These results indicate that, apart from the expected dilution, the cellular components of the PRP preparation were preserved after the addition of HA.

Changes in outcome measures from baseline to 2 and 6 months

At 2 and 6 months after the final injection, we assessed changes in the primary outcome measures (**Table 4**). A significant group $\times$ time interaction was found for WOMAC total score ($P = 0.041$) and the KOOS Activities of Daily Living (ADL) subscale ($P = 0.041$). Subsequent

pairwise comparisons of WOMAC total scores showed that the reduction in the PRP+HA group was significantly greater than that in the HA group at both 2 months ($P = 0.030$) and 6 months ($P = 0.014$); however, no significant difference was observed between the PRP and PRP+HA groups at either time point (both $P > 0.05$). For KOOS ADL scores, pairwise comparisons showed a significant difference between the PRP+HA and HA groups at 6 months ($P = 0.026$), but not at 2 months ($P = 0.862$); No significant difference was found between the PRP+HA and PRP groups at 6 months ($P = 0.128$).

For all other outcome measures in which the group $\times$ time interaction was not significant ($P \geq 0.05$), including WOMAC Pain, Stiffness, and Function subscales, VAS, and the KOOS Pain, Symptom, and Quality of Life subscales, all three treatment groups showed clinically meaningful improvements from baseline at both 2 and 6 months. As shown in **Table 4**, most within-group evaluations had P values ranging from 0.001 to 0.049, with several comparisons (e.g., WOMAC Pain in the PRP+HA group at 2 and 6 months, WOMAC Function in the PRP+HA group at 2 months, and VAS across all groups at both times) showing $P < 0.001$. No significant between-group differences were observed for these outcomes at any time point.

In short, PRP, HA and combined therapy all significantly alleviated pain and stiffness and improved mobility and overall well-being in patients with KOA in the short to medium term. Although each treatment showed advantages, the PRP+HA combination showed specific advantages over HA alone in two areas: greater reduction in WOMAC total score at 2 and 6

PRP and HA for knee osteoarthritis

Table 4. Changes in outcome measures

Parameter	Group	Baseline	2 Months	P (vs. baseline)	6 Months	P (vs. baseline)	Group × Time F (df)	Group × Time P	Post-hoc (2 months)	Post-hoc (6 months)
WOMAC Pain	PRP+HA	9.81 ± 1.72	4.52 ± 1.63	< 0.001	4.18 ± 1.79	< 0.001	F (4, 270) = 2.28	0.058	PRP+HA vs. PRP: MD = 0.51, P = 0.387 PRP+HA vs. HA: MD = 0.99, P = 0.092 PRP vs. HA: MD = 0.48, P > 0.999	PRP+HA vs. PRP: MD = 0.94, P = 0.224 PRP+HA vs. HA: MD = 2.60, P = 0.069 PRP vs. HA: MD = 1.66, P > 0.999
	PRP	9.62 ± 1.55	5.03 ± 1.79	0.001	5.12 ± 1.88	0.002				
	HA	9.45 ± 1.68	5.51 ± 1.61	0.003	6.78 ± 1.72	0.008				
	PRP+HA	2.62 ± 1.22	1.22 ± 0.98	0.002	1.92 ± 0.95	0.019	F (4, 270) = 0.58	0.672	Not applicable	Not applicable
	PRP	2.68 ± 1.35	1.15 ± 1.19	0.001	1.48 ± 1.21	0.007				
	HA	2.55 ± 1.18	0.68 ± 1.05	0.002	1.08 ± 0.99	0.004				
WOMAC Function	PRP+HA	29.13 ± 7.35	18.22 ± 6.43	< 0.001	15.98 ± 6.52	0.001	F (4, 270) = 1.22	0.304	Not applicable	Not applicable
	PRP	29.51 ± 7.82	17.96 ± 6.38	< 0.001	16.51 ± 7.89	0.001				
	HA	30.82 ± 8.45	21.13 ± 7.02	0.004	20.38 ± 7.15	0.007				
WOMAC Total	PRP+HA	41.56 ± 9.28	23.96 ± 7.91	< 0.001	22.08 ± 8.25	0.001	F (4, 270) = 2.53	0.041	PRP+HA vs. PRP: MD = 0.18, P = 0.198 PRP+HA vs. HA: MD = 3.36, P = 0.030 PRP vs. HA: MD = 3.18, P > 0.999	PRP+HA vs. PRP: MD = 1.03, P = 0.462 PRP+HA vs. HA: MD = 6.16, P = 0.014 PRP vs. HA: MD = 5.13, P > 0.999
	PRP	41.81 ± 9.76	24.14 ± 8.44	0.001	23.11 ± 10.32	0.002				
	HA	42.82 ± 10.83	27.32 ± 8.93	0.003	28.24 ± 9.47	0.006				
VAS	PRP+HA	8.05 ± 1.31	3.24 ± 1.12	< 0.001	4.15 ± 1.26	< 0.001	F (4, 270) = 1.09	0.362	Not applicable	Not applicable
	PRP	7.72 ± 1.38	2.58 ± 1.15	< 0.001	2.81 ± 1.34	< 0.001				
	HA	7.95 ± 1.25	3.01 ± 1.18	< 0.001	3.92 ± 1.44	< 0.001				
KOOS Pain	PRP+HA	28.15 ± 12.03	18.92 ± 10.85	0.002	12.78 ± 11.52	0.001	F (4, 270) = 2.31	0.056	PRP+HA vs. PRP: MD = 1.94, P = 0.365 PRP+HA vs. HA: MD = 0.97, P = 0.099 PRP vs. HA: MD = 2.91, P > 0.999	PRP+HA vs. PRP: MD = 1.24, P = 0.289 PRP+HA vs. HA: MD = 0.13, P = 0.075 PRP vs. HA: MD = 1.11, P > 0.999
	PRP	28.42 ± 13.21	20.86 ± 12.14	0.005	14.02 ± 14.36	0.002				
	HA	28.78 ± 13.45	17.95 ± 11.82	0.001	12.91 ± 11.73	0.001				
KOOS Symptom	PRP+HA	32.95 ± 13.88	28.82 ± 12.56	0.038	16.28 ± 11.15	< 0.001	F (4, 270) = 0.59	0.668	Not applicable	Not applicable
	PRP	33.21 ± 11.25	31.05 ± 13.48	0.049	18.97 ± 12.03	0.001				
	HA	33.58 ± 11.89	28.74 ± 12.39	0.031	16.35 ± 11.22	< 0.001				
KOOS ADL	PRP+HA	27.15 ± 11.38	33.42 ± 11.05	< 0.001	16.98 ± 10.67	0.001	F (4, 270) = 2.53	0.041	PRP+HA vs. PRP: MD = 0.16, P > 0.999 PRP+HA vs. HA: MD = 0.13, P = 0.862 PRP vs. HA: MD = 0.29, P = 0.735	PRP+HA vs. PRP: MD = 4.34, P = 0.128 PRP+HA vs. HA: MD = 0.13, P = 0.026 PRP vs. HA: MD = 4.47, P = 0.441
	PRP	27.42 ± 10.67	33.58 ± 12.88	< 0.001	21.32 ± 14.05	0.009				
	HA	27.68 ± 10.92	33.29 ± 11.18	< 0.001	16.85 ± 10.54	< 0.001				
KOOS QOL	PRP+HA	24.18 ± 10.05	19.82 ± 9.21	0.014	12.58 ± 9.15	< 0.001	F (4, 270) = 1.10	0.355	Not applicable	Not applicable
	PRP	24.55 ± 10.44	23.15 ± 9.86	0.044	23.08 ± 13.52	0.032				
	HA	24.89 ± 10.62	19.91 ± 9.33	0.008	12.71 ± 9.08	< 0.001				

Notes: Data are presented as mean ± SD. *P*-values for within-group comparisons (vs. baseline) are from repeated-measures ANOVA. The group × time interaction *P*-value is from two-way repeated-measures ANOVA. Post-hoc pairwise comparisons with Bonferroni adjustment were performed only for parameters with a significant group × time interaction (*P* < 0.05, shown in bold: WOMAC Total and KOOS ADL). For parameters without a significant interaction, pairwise comparisons were not formally tested; within-group changes over time were assessed by repeated-measures ANOVA. PRP, platelet-rich plasma; HA, hyaluronic acid; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee Injury and Osteoarthritis Outcome Score; VAS, Visual Analogue Scale.

PRP and HA for knee osteoarthritis

Table 5. Changes in serum biochemical markers over time

Marker	Group	Baseline	2 Months	6 Months	Group × Time F (df)	Group × Time P	Post-hoc (PRP+HA vs. HA)
CTX-II (pg/mL)	PRP+HA	698.0 ± 144.9	475.2 ± 118.3*	410.5 ± 105.7*	F (4, 270) = 4.15	0.002	MD = 127.8, 95% CI: 52.3 to 203.3, P = 0.001
	PRP	702.1 ± 145.3	490.5 ± 125.6*	445.8 ± 112.4*			
	HA	695.2 ± 138.5	558.9 ± 130.7*	538.3 ± 128.1*			
COMP (µg/mL)	PRP+HA	8.11 ± 2.47	5.85 ± 1.72*	5.21 ± 1.55*	F (4, 270) = 3.68	0.006	MD = 1.17, 95% CI: 0.38 to 1.96, P = 0.004
	PRP	8.15 ± 2.51	5.98 ± 1.78*	5.43 ± 1.62*			
	HA	8.09 ± 2.38	6.72 ± 1.95*	6.38 ± 1.88*			
IL-6 (pg/mL)	PRP+HA	4.55 ± 1.39	2.08 ± 0.75*	2.21 ± 0.85*	F (4, 270) = 4.22	0.003	2 months: MD = 0.77, 95% CI: 0.32 to 1.22, P < 0.001; 6 months: MD = 0.58, 95% CI: 0.18 to 0.98, P = 0.002
	PRP	4.52 ± 1.35	2.21 ± 0.81*	2.35 ± 0.89*			
	HA	4.61 ± 1.42	2.85 ± 0.98*	2.79 ± 0.95*			
TNF-α (pg/mL)	PRP+HA	5.22 ± 1.68	2.95 ± 1.05*	3.02 ± 1.08*	F (4, 270) = 3.45	0.009	MD = 0.53, 95% CI: 0.14 to 0.92, P = 0.008
	PRP	5.27 ± 1.71	3.05 ± 1.10*	3.11 ± 1.12*			
	HA	5.19 ± 1.62	3.42 ± 1.18*	3.55 ± 1.21*			

Notes: Data are presented as mean ± SD. *Indicates a significant difference compared with baseline within the same group, P < 0.001 (repeated-measures ANOVA). The group × time interaction P-value is from two-way repeated-measures ANOVA. Pairwise comparisons were performed with Bonferroni correction. IL-6 showed significant differences between the PRP+HA and HA groups at both 2 months (P < 0.001) and 6 months (P = 0.002), while the other biomarkers showed significant differences at 6 months. No post-hoc comparisons between the PRP+HA and PRP groups were significant for any biomarker at any time point (all P > 0.05).

Table 6. Comparison of proportion of patients with $\geq 35\%$ reduction in VAS, WOMAC or KOOS scores after 12 months among groups

12 Months Follow-Up Data					
Parameter	PRP+HA Number (%)	PRP Number (%)	HA Number (%)	χ^2 (df)	P
WOMAC Total	27 (58.7)	25 (53.2)	23 (51.1)	χ^2 (2) = 0.54	0.763
VAS	35 (76.1)	32 (68.1)	30 (66.7)	χ^2 (2) = 1.59	0.451
KOOS Total	20 (43.5)	15 (31.9)	12 (26.7)	χ^2 (2) = 6.48	0.04
Additional Comparisons for 12 Months Follow-Up					
	Comparison	χ^2 (df)	P		
VAS	PRP+HA vs. PRP	χ^2 (1) = 0.13	0.721		
	PRP+HA vs. HA	χ^2 (1) = 0.98	0.323		
	PRP vs. HA	χ^2 (1) = 0.00	> 0.999		
WOMAC	PRP+HA vs. PRP	χ^2 (1) = 0.00	> 0.999		
	PRP+HA vs. HA	χ^2 (1) = 1.67	0.197		
	PRP vs. HA	χ^2 (1) = 0.31	0.576		
KOOS Total	PRP+HA vs. PRP	χ^2 (1) = 2.24	0.133		
	PRP+HA vs. HA	χ^2 (1) = 6.34	0.012		
	PRP vs. HA	χ^2 (1) = 0.60	0.437		

Notes: PRP, Platelet-Rich Plasma; HA, Hyaluronic acid; WOMAC, Western Ontario and McMaster Universities Arthritis Index; KOOS, Knee Injury and Osteoarthritis Outcome Score.

months, and more pronounced improvement in KOOS ADL at 6 months.

Changes in biochemical markers

As shown in **Table 5**, serum levels of CTX-II, COMP, IL-6 and TNF- α were all significantly lower than baseline at both 2 months and 6 months in all three groups (all within-group comparisons: $P < 0.001$). Two-way repeated-measures ANOVA showed a significant group $\times$ time interaction for all four biomarkers ($P = 0.002$ for CTX-II, $P = 0.006$ for COMP, $P = 0.003$ for IL-6, and $P = 0.009$ for TNF- α), indicating that the temporal changes differed among the three treatment groups.

Post-hoc pairwise comparisons with Bonferroni correction showed that at 6 months, the levels of CTX-II (410.5 ± 105.7 pg/mL) and COMP (5.21 ± 1.55 μ g/mL) in the PRP+HA group were significantly lower than those in the HA group (CTX-II: 538.3 ± 128.1 pg/mL, $P = 0.001$; COMP: 6.38 ± 1.88 μ g/mL, $P = 0.004$). IL-6 decreased more significantly in the PRP+HA group than in the HA group at 2 months (2.08 ± 0.75 pg/mL vs. 2.85 ± 0.98 pg/mL, $P < 0.001$), and the difference remained significant at 6 months ($P = 0.002$). TNF- α levels were also significantly lower in the PRP+HA

group than in the HA group at 6 months (3.02 ± 1.08 vs. 3.55 ± 1.21 pg/mL, $P = 0.008$). No statistically significant differences were found between the PRP and PRP+HA groups for any biomarker at any time point (all $P > 0.05$). In an exploratory analysis, serum CTX-II showed a positive correlation with the WOMAC total score (Spearman's $P = 0.38$, $P = 0.012$).

12-month outcomes

We examined the proportion of patients in each group who achieved a clinically meaningful improvement ($\geq 35\%$ reduction in VAS and WOMAC scores, and $\geq 35\%$ increase in KOOS total score) after 12 months. The WOMAC total score: 58.7% of patients in the PRP+HA group, 53.2% in the PRP group, and 50.0% in the HA group met or exceeded this threshold, with no significant difference among groups ($P = 0.763$). For VAS score, 76.1% of patients in the PRP+HA group, 68.1% in the PRP group, and 63.8% in the HA group showed a $\geq 35\%$ reduction, with no significant difference ($P = 0.451$). For the KOOS total score, 43.5% of the PRP+HA group, 31.9% of the PRP group, and 26.7% of the HA group achieved the 35% improvement threshold, with a statistically significant difference among the three groups ($P = 0.04$) (**Table 6**).

Table 7. Comparison of adverse events among groups

Adverse Event	HA Group (n = 45)	PRP Group (n = 47)	PRP+HA Group (n = 46)	χ^2 (df)	P
Any Adverse Event, n (%)	8 (17.8)	13 (27.7)	10 (21.7)	χ^2 (2) = 1.33	0.514
Transient injection site pain	6 (13.3)	11 (23.4)	8 (17.4)	χ^2 (2) = 1.77	0.412
Transient injection site swelling	3 (6.7)	5 (10.6)	4 (8.7)	χ^2 (2) = 0.49	0.782
Skin redness	1 (2.2)	2 (4.3)	1 (2.2)	χ^2 (2) = 0.46	0.795
Warmth at the joint	0 (0)	1 (2.1)	0 (0)	χ^2 (2) = 2.01	0.365
Serious Adverse Event, n (%)	0 (0)	0 (0)	0 (0)	-	N/A

Notes: PRP, Platelet-Rich Plasma; HA, Hyaluronic acid.

Pairwise comparisons of the responder proportions showed no significant differences for VAS (PRP+HA vs. PRP, $P = 0.721$; PRP+HA vs. HA, $P = 0.323$; PRP vs. HA, $P > 0.999$) or for WOMAC (PRP+HA vs. PRP, $P > 0.999$; PRP+HA vs. HA, $P = 0.197$; PRP vs. HA, $P = 0.576$). For the KOOS total score, the proportion of patients achieving $\geq 35\%$ improvement at 12 months was significantly higher in the PRP+HA group than in the HA group ($P = 0.012$), whereas the PRP+HA and PRP groups did not differ significantly ($P = 0.133$), nor did the PRP and HA groups ($P = 0.437$) (**Table 6**).

Adverse events

Intra-articular administration was safe, with only mild, self-limiting adverse events reported (**Table 7**). The most prevalent events included transient pain (13.3%-23.4%) and mild swelling (6.7%-10.6%) at the injection site. All symptoms resolved spontaneously within 72 hours without intervention. Importantly, no serious adverse events occurred in any patient.

Discussion

All three treatments (PRP, HA, and PRP+HA) significantly improved pain, stiffness, functional status (WOMAC scores), and patient-reported outcomes (VAS and KOOS) at 2 and 6 months after treatment. All cohorts showed a decrease in discomfort indicators (VAS and WOMAC Pain) at both 2 and 6 months. However, the magnitude of pain relief was similar among the three groups, with no significant group $\times$ time interaction for pain-related outcomes. For most primary outcome measures - including VAS, WOMAC pain, stiffness, and function subscales - the temporal improvements were comparable across groups, and no significant group $\times$ time interactions were observed.

Nevertheless, PRP+HA combination demonstrated significant advantages in certain domains. Specifically, the PRP+HA group showed a greater reduction in WOMAC total scores and a more pronounced improvement in KOOS Activities of Daily Living (ADL) compared with the HA group. At 6 months, pairwise comparisons revealed a significant difference in KOOS ADL scores between the PRP+HA and HA groups ($P = 0.026$), while the difference between PRP+HA and PRP groups was not significant ($P = 0.128$). WOMAC subscale scores also improved from baseline within each group, with the most pronounced improvements observed in the PRP+HA group.

After 12 months, the proportion of patients achieving a clinically meaningful improvement ($\geq 35\%$ increase) in KOOS total score was significantly higher in the PRP+HA group than in the HA group (43.5% vs. 26.7%). However, no significant differences were found between the PRP+HA and PRP groups for any outcome measure at this time point, and responder rates for VAS and WOMAC did not differ significantly among the three groups. These findings suggest that the combined intervention may offer some specific and sustained benefits for patient-reported knee health and overall life quality (as reflected by KOOS) compared to HA alone, rather than selectively improving pain or functional impairment alone. The fact that this benefit did not translate into significant differences in VAS or WOMAC scores at 12 months indicates that the added value of PRP+HA over HA alone may be more evident in global quality-of-life domains than in individual symptom-specific measures.

These observations are consistent with recent studies [16, 17] demonstrating that PRP+HA improves outcomes in KOA. Some prior studies

have reported that both HA and PRP provide sustained pain relief and symptom improvement, although the durability of PRP's effect is shorter-lived [16-18]. Based on the favorable efficacy and safety profile observed in the current study, PRP+HA appears to be an option for patients with moderate-to-severe KOA, particularly for those who prioritize overall life quality improvement over symptom-specific relief.

This study is among the few to examine the separate and combined effects of PRP and HA on serum markers of cartilage turnover and inflammation in patients with KOA. Reduced concentrations of CTX-II and COMP were observed in all groups after 2 and 6 months of treatment; therefore, it is proposed that intra-articular administration may suppress the catabolic activity of osteoarthritic tissues. More significantly, at 6 months, CTX-II had decreased by 41.2% from baseline in the PRP+HA group (from 698.0 to 410.5 pg/mL), compared with 22.6% in the HA group (695.2 to 538.3 pg/mL). As CTX-II is a systemic marker of type II collagen degradation, this difference suggests a greater reduction in cartilage catabolism in the PRP+HA group. However, it cannot demonstrate structural modification of the joint, which would require imaging or histological assessment [18]. However, because these measurements were derived from serum biomarkers rather than synovial fluid, they provide indirect evidence only. Direct evidence of cartilage protection would require synovial fluid analysis or imaging-based assessments (e.g., MRI) in future studies. This biochemical pattern is consistent with preclinical reports in which PRP-derived growth factors and the lubricating and anti-inflammatory properties of HA acted synergistically to limit type II collagen degradation and matrix catabolism [14, 19]; the present clinical dataset, however, cannot verify this mechanism, and this interpretation therefore remains hypothetical.

Concurrent decrease in serum levels of IL-6 and TNF- α were also observed, likely reflecting underlying changes in systemic inflammatory status. Two months after treatment, the decline in IL-6 was more pronounced in the PRP+HA group than in the HA-only group, suggesting that PRP may augment the early anti-inflammatory effect of HA. This difference persisted at 6 months, though the magnitude was small-

er, indicating an attenuating rather than a persistent advantage over time. Given that these findings are based on systemic serum markers, they should be interpreted as indicative of systemic inflammatory modulation rather than definitive evidence of local joint anti-inflammatory effects. Future studies measuring synovial fluid cytokine levels would provide more direct evidence.

In an exploratory correlation analysis, higher CTX-II levels were associated with higher WOMAC scores, indicating that greater cartilage turnover accompanied poorer clinical status. This association is consistent with previous reports linking changes in cartilage degradation biomarkers with adverse changes in the disease state [21].

It should be pointed out that no significant differences were observed in any of the four biomarkers between the PRP monotherapy group and the PRP+HA combined-treatment group at any time point. Therefore, although PRP+HA showed advantages over HA alone in certain clinical and biochemical measures, no additional biochemical benefit of PRP+HA over PRP alone was detected in these serum markers. This comparison was not powered as a primary endpoint, and a clinically relevant difference cannot be excluded based on these data. Extended follow-up and direct cartilage imaging (e.g., MRI) would be required to confirm these biochemical findings.

Importantly, the molecular mechanisms invoked to explain PRP- and HA-mediated effects, including enhancement of chondrocyte anabolism through CD44 and TGF- β RII engagement, downstream Smad2/3 and ERK1/2 signaling, upregulation of SOX9, and suppression of catabolic enzymes (MMP-3, MMP-13) and pro-inflammatory mediators (IL-6, NF- κ B) are derived from previous in vitro and animal investigations and were not directly interrogated in the present work [14, 19-21]. For example, in vitro studies on osteoarthritic chondrocytes have shown that adding PRP to HA enhances chondrocyte proliferation and extracellular-matrix (glycosaminoglycan) synthesis [19], whereas a rodent osteoarthritis model demonstrated that an engineered HA/PRP-based hydrogel suppressed cartilage-matrix degradation and joint inflammation in vivo [14]. Our dataset comprises clinical outcome scores and system-

ic serum biomarkers only; no cell-based assays, animal models, synovial fluid analyses, joint histopathology, or MRI-based cartilage assessments were performed. Accordingly, the biomarker changes reported here should be interpreted as systemic, indirect correlates that are consistent with-but do not by themselves establish a local chondroprotective or anti-inflammatory mechanism of PRP+HA.

Limitations

Several limitations to this study should be acknowledged. First, as a retrospective study, selection and indication bias cannot be completely excluded. Furthermore, the absence of a placebo control group (e.g., saline injection or sham procedure) limited our ability to distinguish the specific therapeutic effects of PRP and HA from the nonspecific effects of the intra-articular injection procedure itself - a procedure known to exert a substantial placebo response in KOA. The decision not to include a placebo group was primarily based on ethical considerations, as withholding active treatment from patients with symptomatic KOA for a 12-month follow-up period was deemed unacceptable in our institutional practice. Second, the biochemical markers analyzed in this study were derived from peripheral blood serum rather than from synovial fluid. While serum markers provide a systemic overview of cartilage turnover and inflammation, they may not fully reflect local pathophysiological changes within the articular microenvironment following intra-articular injections. Synovial fluid collection in routine clinical follow-up is challenging: the fluid volume in non-effused KOA knees is often insufficient for reliable analysis, and the invasive nature of the procedure, combined with infection risk, significantly limits patient acceptance and compliance - particularly when repeated aspirations at three follow-up time points would be required. Moreover, the study did not incorporate knee joint imaging (e.g., MRI) to directly evaluate changes in cartilage structure. Consequently, mechanistic insights derived from serum biomarkers alone are inherently limited and should be interpreted as indirect evidence rather than definitive proof of structural modification. Third, although PRP preparation followed a standardized two-step centrifugation protocol, batch-to-batch variability in platelet and growth factor content is inherent to autologous blood products and may

have contributed to heterogeneous treatment responses among patients. Similarly, despite a standardized injection protocol performed by experienced orthopedic surgeons, minor differences in injection technique or needle placement could not be entirely eliminated and may have influenced the local bioavailability of the therapeutic agents. Fourth, the follow-up period was limited to 12 months. While this duration is longer than that of many prior studies on PRP and HA injections (which often report outcomes at 3 to 6 months), it remains insufficient to fully assess the long-term durability of the therapeutic effects, the potential slowing of cartilage structural progression, or the occurrence of delayed adverse reactions. Whether the observed improvements in pain, function, and biochemical markers translate into sustained clinical benefit beyond 12 months, and whether the combination therapy truly modifies the long-term trajectory of cartilage degeneration, remains to be determined.

Fifth, the economic and practical feasibility of PRP+HA therapy should be considered in practice. Although PRP and HA are available in medical institutions, their widespread adoption has been limited by relatively high treatment costs, the need for specialized equipment, and the requirement for multiple sessions. Insurance reimbursement for PRP therapy varies greatly, and thus many patients may not have access to this treatment in resource-limited settings.

Finally, and most pertinent to the interpretation of the present findings, this study did not include any bench-level mechanistic experiments or direct assessment of local joint pathology, such as in vitro chondrocyte or synoviocyte assays, in vivo animal osteoarthritis models, synovial fluid analysis for local inflammatory and cartilage-degradation markers, synovial or cartilage histopathology, and knee MRI for quantifying cartilage wear and synovial hyperplasia. Consequently, all cartilage-protective and anti-inflammatory inferences in this report rest on systemic serum markers and prior preclinical evidence; the local mechanism of action can be established only by future studies that integrate these complementary approaches.

Future research directions

Although PRP+HA combination therapy showed encouraging clinical benefit and favorable sys-

temic biomarker trends, the underlying local mechanisms remain to be established. Because the present study was confined to clinical scores and peripheral-blood markers, future work should be designed specifically to bridge the gap between systemic observations and joint-level pathology. First, controlled in vitro experiments using human chondrocytes and synoviocytes, together with in vivo animal osteoarthritis models, are needed to elucidate the molecular basis of the PRP-HA synergy (e.g., CD44 and TGF- β RII signaling, Smad2/3 and ERK1/2 axes, SOX9-driven chondrogenesis, and suppression of MMP-3, MMP-13, IL-6, and NF- κ B). Second, clinical studies should incorporate paired synovial-fluid analysis to capture local inflammatory and cartilage-degradation markers alongside serum indices, allowing direct comparison of systemic and intra-articular responses. Third, longitudinal quantitative MRI (e.g., T2 or T2* mapping, cartilage thickness and volume, and semiquantitative synovitis scoring) should be used to objectively quantify cartilage wear and synovial hyperplasia and to test whether the biochemical changes observed here translate into measurable structural preservation. Finally, adequately powered, multicenter, placebo-controlled randomized trials with extended follow-up (e.g., 2-5 years) and standardized PRP preparation are warranted to confirm long-term efficacy, durability, and safety and to identify the patient subgroups most likely to benefit from the combination therapy.

Conclusion

HA, PRP, and PRP+HA combination therapy all significantly improved clinical outcomes in patients with mild-to-moderate KOA in the short to medium term (up to 6 months). At 12 months after treatment, the three cohorts showed comparable pain relief (VAS) and disease-related symptoms (WOMAC); however, the PRP+HA group demonstrated a significantly higher proportion of patients achieving a clinically meaningful improvement ($\geq 35\%$) in the KOOS total score compared with the HA group. These findings suggest that the combination treatment may be associated with sustained functional and quality-of-life benefits for up to 12 months. Given that this was a retrospective, non-randomized comparison and that the biomarker data reflect systemic rather than local joint sta-

tus, these observations should be regarded as exploratory. Prospective, adequately powered trials with direct assessment of joint tissue are warranted to confirm these findings and to identify which patient subgroups are most likely to benefit from this combined treatment.

Disclosure of conflict of interest

None.

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References

- [1] Qiao X, Yan L, Feng Y, Li X, Zhang K, Lv Z, Xu C, Zhao S, Liu F, Yang X and Tian Z. Efficacy and safety of corticosteroids, hyaluronic acid, and PRP and combination therapy for knee osteoarthritis: a systematic review and network meta-analysis. *BMC Musculoskelet Disord* 2023; 24: 926.
- [2] Martin SD, Eberlin CT, Kucharik MP and Cheri-an NJ. Harvest and application of bone marrow aspirate concentrate to address acetabular chondral damage during hip arthroscopy. *JBJS Essent Surg Tech* 2023; 13: e22.00010.
- [3] Zhou B, Feng H, Lei B and Zhang P. Effect of autologous platelet-rich plasma combined with sodium hyaluronate on clinical efficacy and serum inflammatory factors in patients with knee osteoarthritis. *Am J Transl Res* 2022; 14: 8724-8732.
- [4] Glinkowski WM and Tomaszewski W. Intra-articular hyaluronic acid for knee osteoarthritis: a systematic umbrella review. *J Clin Med* 2025; 14: 1272.
- [5] Bruyère O, Alokail M, Al-Daghri N, Reginster JY and Sabico S. Effects of intra-articular hyaluronic acid injections on pain and function in patients with knee osteoarthritis: an umbrella review of systematic reviews and meta-analyses of randomized placebo-controlled trials. *Maturitas* 2025; 203: 108779.
- [6] Glinkowski WM, Gut G and Śladowski D. Platelet-rich plasma for knee osteoarthritis: a comprehensive narrative review of the mechanisms, preparation protocols, and clinical evidence. *J Clin Med* 2025; 14: 3983.
- [7] Zhou Q, Chen J, Yu W, Cao D, Ye Y and Shen J. A critical overview of systematic reviews and meta-analyses of intra-articular injection of platelet rich plasma versus hyaluronic acid for

- knee osteoarthritis. *Clin Rheumatol* 2025; 44: 547-571.
- [8] Karm MH, Kwon HJ, Kim CS, Kim DH, Shin JW and Choi SS. Cooled radiofrequency ablation of genicular nerves for knee osteoarthritis. *Korean J Pain* 2024; 37: 13-25.
- [9] Vassallo V, Di Meo C, D'Agostino A, La Gatta A, Cimini D, Toro G, Iolascon G, Mastrogiacomo M and Schiraldi C. Biomechanical and biological features of hyaluronic acid in combination with chondroitin and platelet rich plasma for regenerative medicine applications. *Front Bioeng Biotechnol* 2025; 13: 1607469.
- [10] Wu YT, Li TY, Lee KC, Lam KHS, Chang CY, Chang CK and Chen LC. Efficacy of a novel intra-articular administration of platelet-rich plasma one-week prior to hyaluronic acid versus platelet-rich plasma alone in knee osteoarthritis: a prospective, randomized, double-blind, controlled trial. *J Clin Med* 2022; 11: 3241.
- [11] Gilat R, Haunschild ED, Knapik DM, Evuarherhe A Jr, Parvaresh KC and Cole BJ. Hyaluronic acid and platelet-rich plasma for the management of knee osteoarthritis. *Int Orthop* 2021; 45: 345-354.
- [12] Chiou CS, Wu CM, Dubey NK, Lo WC, Tsai FC, Tung TDX, Hung WC, Hsu WC, Chen WH and Deng WP. Mechanistic insight into hyaluronic acid and platelet-rich plasma-mediated anti-inflammatory and anti-apoptotic activities in osteoarthritic mice. *Aging (Albany NY)* 2018; 10: 4152-4165.
- [13] Chen WH, Lo WC, Hsu WC, Wei HJ, Liu HY, Lee CH, Tina Chen SY, Shieh YH, Williams DF and Deng WP. Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy. *Biomaterials* 2014; 35: 9599-9607.
- [14] Zhou T, Ran J, Xu P, Shen L, He Y, Ye J, Wu L and Gao C. A hyaluronic acid/platelet-rich plasma hydrogel containing MnO₂ nanozymes efficiently alleviates osteoarthritis in vivo. *Carbohydr Polym* 2022; 292: 119667.
- [15] Leung YY, Huebner JL, Haaland B, Wong SBS and Kraus VB. Synovial fluid pro-inflammatory profile differs according to the characteristics of knee pain. *Osteoarthritis Cartilage* 2017; 25: 1420-1427.
- [16] Karasavvidis T, Totlis T, Gilat R and Cole BJ. 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. *Arthroscopy* 2020; 37: 1277-1287, e1.
- [17] Zhang Q, Liu T, Gu Y, Gao Y and Ni J. Efficacy and safety of platelet-rich plasma combined with hyaluronic acid versus platelet-rich plasma alone for knee osteoarthritis: a systematic review and meta-analysis. *J Orthop Surg Res* 2022; 17: 499.
- [18] Garcia-Motta H, Carvalho C, Guilherme EM, de Oliveira MPB and Rossi KNZP. Effects of intra-articular injection of platelet-rich plasma on the inflammatory process and histopathological characteristics of cartilage and synovium in animals with osteoarthritis: a systematic review with meta-analysis. *Adv Rheumatol* 2024; 64: 24.
- [19] Russo F, D'Este M, Vadalà G, Cattani C, Papalia R, Alini M and Denaro V. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: rheological and biological evaluation. *PLoS One* 2016; 11: e0157048.
- [20] van Buul GM, Koevoet WL, Kops N, Bos PK, Verhaar JA, Weinans H, Bernsen MR and van Osch GJ. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. *Am J Sports Med* 2011; 39: 2362-70.
- [21] Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P and Desiderio MA. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-κB inhibition via HGF. *J Cell Physiol* 2010; 225: 757-66.

PRP and HA for knee osteoarthritis

Supplementary Table 1. Inter-rater reliability for VAS, WOMAC, and KOOS scores (n = 30)

Outcome Measure	ICC (2, 1)	95% Confidence Interval	Reliability Level
VAS	0.92	0.85-0.96	Excellent
WOMAC Total	0.89	0.81-0.94	Good
KOOS Total	0.87	0.78-0.93	Good

Notes: ICC, intraclass correlation coefficient; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee Injury and Osteoarthritis Outcome Score. ICC (2, 1) was calculated using a two-way random-effects model for absolute agreement.