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Differential Impacts of Platelet-Rich Plasma and Hyaluronic Acid on miR-132 Modulation, Inflammatory Cytokines (IL-1β and IL-6), and Functional Recovery in Knee Osteoarthritis: A Randomized Controlled Trial

Hendrian Chaniago[1,2*], Muhammad Nasrum Massi[3,4], Muhammad Andry Usman[5], Muhammad Phetrus Johan[5]

1. Department of Orthopaedic and Traumatology, Bhayangkara Hospital, Makassar, Indonesia
2. Medical Faculty of Universitas Muslim Indonesia, Makassar, Indonesia
3. Department of Clinical Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
4. Molecular Biology and Immunology Laboratory, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
3. Department of Orthopaedics, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

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***Corresponding**:
Hendrian Chaniago
Address:
[1]Department of Orthopaedic and Traumatology, Bhayangkara Hospital, Makassar, Indonesia. Medical Faculty of Universitas Muslim Indonesia, Makassar, Indonesia
E-mail:
hendrianchaniago@gmail.com

ABSTRACT

The objective of the study was to examine differences in miR-132 gene expression, cytokine levels (IL-1β and IL-6), and functional outcomes in patients with knee osteoarthritis following treatment with PRP and HA. This study employed an exploratory, randomized, open-label, parallel-group interventional research design, where 131 participants were initially recruited. The trial was conducted from January 2023 to January 2024, at Bhayangkara Hospital Makassar, the South Sulawesi Regional Police Headquarters, and the HUM-RC Laboratory, Faculty of Medicine, Hasanuddin University. The samples of peripheral blood were collected at baseline and five days after treatment. miR-132 expression RT-PCR, cytokine levels, and clinical outcomes (VAS and WOMAC scores) were evaluated. PRP significantly decreased miR-132 expression ($p = 0.000121$), whereas HA ($p = 0.775$) and controls ($p = 0.874$) showed no significant changes. Between-group analysis revealed a significant difference between the PRP and control groups ($p = 0.0105$). IL-1β significantly decreased only in the HA group ($p < 0.001$). Both treatment groups had lower IL-1β than control group on day five ($p < 0.0001$). Meanwhile, no significant within- or between-group differences were observed for IL-6. PRP ($p = 0.006$) and HA ($p < 0.001$) significantly reduced VAS scores, but only PRP improved WOMAC ($p = 0.035$). However, the functional outcomes did not surpass the minimal clinically important difference (MCID) thresholds. PRP treatment significantly reduced miR-132 expression and improved functional outcomes to a certain extent, while HA appeared to affect IL-1β modulation with minimal functional effects.

Keywords: Hyaluronic acid, platelet-rich plasma, intra-articular injection, knee osteoarthritis, miR-132, cytokines

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Introduction

Osteoarthritis (OA) is a widespread degenerative joint disorder characterized by progressive cartilage loss, chronic pain, and limited mobility (1). It is especially prevalent among older adults, with women disproportionately affected, and is strongly associated with reduced quality of life and negative impacts on mental health (2-4). Among non-surgical therapies, hyaluronic acid (HA) and platelet-rich plasma (PRP) intra-articular injections have attracted considerable interest. PRP, autologous blood-derived, is rich in cytokines and growth factors, believed to promote tissue healing and modulate inflammation (3). In contrast, HA, a naturally occurring polysaccharide within synovial fluid, enhances mobility and reduces mechanical friction in the joints by providing lubrication and joint cushioning (5). Nevertheless, their comparative therapeutic value and underlying mechanisms remain insufficiently understood (6).

One promising molecular target in OA research is micro ribonucleic acid-132 (miR-132), a micro ribonucleic acid (mRNA) implicated in inflammatory signaling and cartilage repair (7). As a regulator of inflammatory pathways and a mediator of cartilage regeneration, miR-132 is considered a potential therapeutic biomarker for alleviating OA-related joint damage and symptoms (8, 9). Alongside this, pro-inflammatory cytokines, for example, interleukin (IL)-1β and IL-6 are involved in the mechanism of accelerating joint destruction and inflammation, underscoring the need for targeted therapeutic strategies (10). Against this backdrop, the present research investigates the distinct effects of PRP and HA on both molecular markers and functional outcomes in knee OA patients.

Although intra-articular PRP and HA injections have shown clinical effectiveness in knee OA, their differential impact on molecular processes and patient outcomes remains unclear. No prior studies have directly compared their influence on miR-132 expression, levels of pro-inflammatory cytokines (IL-1β and IL-6), and clinical measures such as the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). As PRP has been shown to exert anti-inflammatory and analgesic activities (11, 12), PRP is expected to decrease miR-132 expression and inflammatory cytokines as well as and improve clinical outcomes more efficacious than HA. Thus, this study aimed to compare the changes in miR-132 gene expression, cytokine levels (IL-1β and IL-6), and functional outcomes in patients with knee osteoarthritis following intra-articular injections of PRP and HA.

Methods

Study Design

This study was conducted as an exploratory, randomized, open-label, parallel-group interventional study to compare the effects of intra-articular PRP and HA on miR-132 gene expression, IL-1β and IL-6, and clinical outcomes measured by VAS and WOMAC in patients with knee OA. A group of healthy individuals was included as a reference for normative comparison.

Participants were blinded to group allocation, while the principal investigator was aware of the treatment assignments. To minimize bias, a coding system was created by the principal investigator using an Excel spreadsheet. The analysists responsible for measuring miR-132 expression dan cytokines levels, as well as the clinicians performing the injections and functional assessments were blinded to the treatment. Ethical clearance was obtained from the Hasanuddin University Medical Ethics Commission (protocol number: 23/UN4.6.5.31/PP36/2023), aligning with Declaration of Helsinki, International Council for Harmonization (ICH) guideline, Good Clinical Practice (GCP) standards, Council for International Organizations of Medical Sciences (CIOMS) standards, World Health Organization (WHO) standards and operational Guidelines for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, Ethics Committee/Institutional Review Board Standard Operating Procedures, and Local Regulation and Standards in Ethical Review. The trial was conducted between January 2023 and January 2024 at Bhayangkara Makassar Hospital, Indonesia.

The study population consisted of patients presenting with knee pain who were diagnosed with knee OA based on Kellgren–Lawrence grades 0 to 2 at the Orthopedic Polyclinic of Bhayangkara Hospital Makassar. Written informed consent was obtained from each participant prior to conducting the study, and patient data were treated with confidentiality. Eligible participants had not previously received PRP or HA injections and fulfilled all inclusion, exclusion, and

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dropout criteria. Recruitment followed a consecutive sampling method, in which patients were enrolled according to their order of admission until the study period concluded.

The required sample size for this study was determined using the following calculation (13):

$$n = 2(Z\alpha + Z[1-\beta])^2 x \frac{SD^2}{d^2}$$

Assuming a minimal clinically relevant difference of 12.5 for the WOMAC score, with 5% alpha error and 80% power, the number of samples required for this study is:

$$n = 2(1.96 + 1.28)^2 x \frac{13.5^2}{12.5^2} = 19$$

Additional participants were recruited to account for potential dropouts.

Eligibility

Participants were screened by a trained research assistant under the supervision of the principal investigator. Eligible subjects were adults aged ≥50 years with knee osteoarthritis classified as Kellgren–Lawrence (KL) grade 0 to 2. Radiographic grading criteria were as follows: Grade 0, no radiographic evidence of osteoarthritis; Grade 1, possible osteophyte formation with questionable joint space narrowing; and Grade 2, definite osteophytes with potential joint space narrowing.

Exclusion criteria included the presence of other rheumatic conditions, recent corticosteroid or non-steroidal anti-inflammatory drugs (NSAIDs) use, knee infections, prior lower limb surgery, tumors, hemoglobin levels <12 g/dL, or platelet counts <150,000/mL. A control group of healthy adults (≥50 years, BMI ≥25 kg/m², and normal knee radiographs) was included to establish baseline biomarker values and did not receive any treatment. Eligible participants were randomly assigned to PRP or HA groups.

Randomization

To minimize selection bias, participants were randomly allocated into PRP and HA. Sequence generation was performed using using a computer-generated randomization method with allocation ratio of 1:1. Allocation concealment was maintained by applying coding system prepared by the principal investigator, whereby each consecutive participant was assigned to either PRP or HA treatment group.

Parameter Measurements

Baseline parameters—including hematology, biochemistry, body mass index (BMI), age, sex, and OA grade—were recorded one week prior to injection. For miR-132 expression quantification, the has-miR-132-5p miRCURY® LNA® miRNA polymerase chain reaction (PCR) Assay (QIAGEN, Germany) was used, while serum cytokine concentrations of IL-6 and IL-1β were measured with enzyme-linked immunosorbent assay (ELISA) kits (Human Interleukin IL-1β and IL-6, Mybiosource®, USA). Functional outcomes, which were the primary outcomes, were assessed using the VAS and the WOMAC. All the parameters were measured again five days after injection.

Preparation and Interventions

PRP preparation followed the protocol described by Buendía-López, Medina-Quirós and Fernández-Villacañas Marín (14). Venous blood (34 mL) was collected into acid citrate dextrose (ACD) gel tubes, with an additional 3 mL of ethylenediaminetetraacetic acid (EDTA). The first centrifugation (1000 rpm for 15 minutes) separated red blood cells from plasma, which then underwent a second centrifugation (2000 rpm for 10 minutes) to yield 5 mL of PRP. The PRP was subsequently activated with 1 mL of $CaCl_2$. For the HA group, a single intra-articular injection of 2.5 ml of solution containing 25 mg of sodium hyaluronate (OSFLEX®, Novel Pharmaceutical Laboratories, Jakarta, Indonesia) was administered. The average molecular of sodium hyaluronate used was 0.7–1.4 × 10 Da.

Intra-articular injections of PRP or HA were performed under strict aseptic and sterile conditions using a 21–23G needle via the anterolateral approach to the inferolateral soft tissue of the knee joint, with the knee flexed at 90°–110°. All procedures were carried out by the same senior orthopedic surgeon at the hospital. Paracetamol and ice packs were permitted for pain control. Only the more symptomatic knee was included in the analysis. All interventions were overseen and performed by the principal investigator.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics version 22.0. Within-group changes were assessed

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using paired sample t-tests for normally distributed variables, while non-normally distributed data were evaluated using the Wilcoxon signed-rank test. On the other hand, between-group changes were analyzed using one-way analysis of variance (ANOVA) for normally distributed variables, while non-normally distributed data were evaluated using the Kruskal-wallis test. Statistical significance was set at $p < 0.05$. These statistical analyses ensured reliable data interpretation and strengthened the validity of findings related to the biological mechanisms underlying knee OA treatment.

Results

From 131 screened patients (92 women, 39 men), 55 met inclusion criteria and were randomized into PRP (n = 27) and HA (n = 28) groups (Figure 1). Healthy subjects were also recruited as normative control (n = 22). Each participant, except the healthy subjects, received a single-dose intra-articular injection, and efficacy was compared across groups over five days.

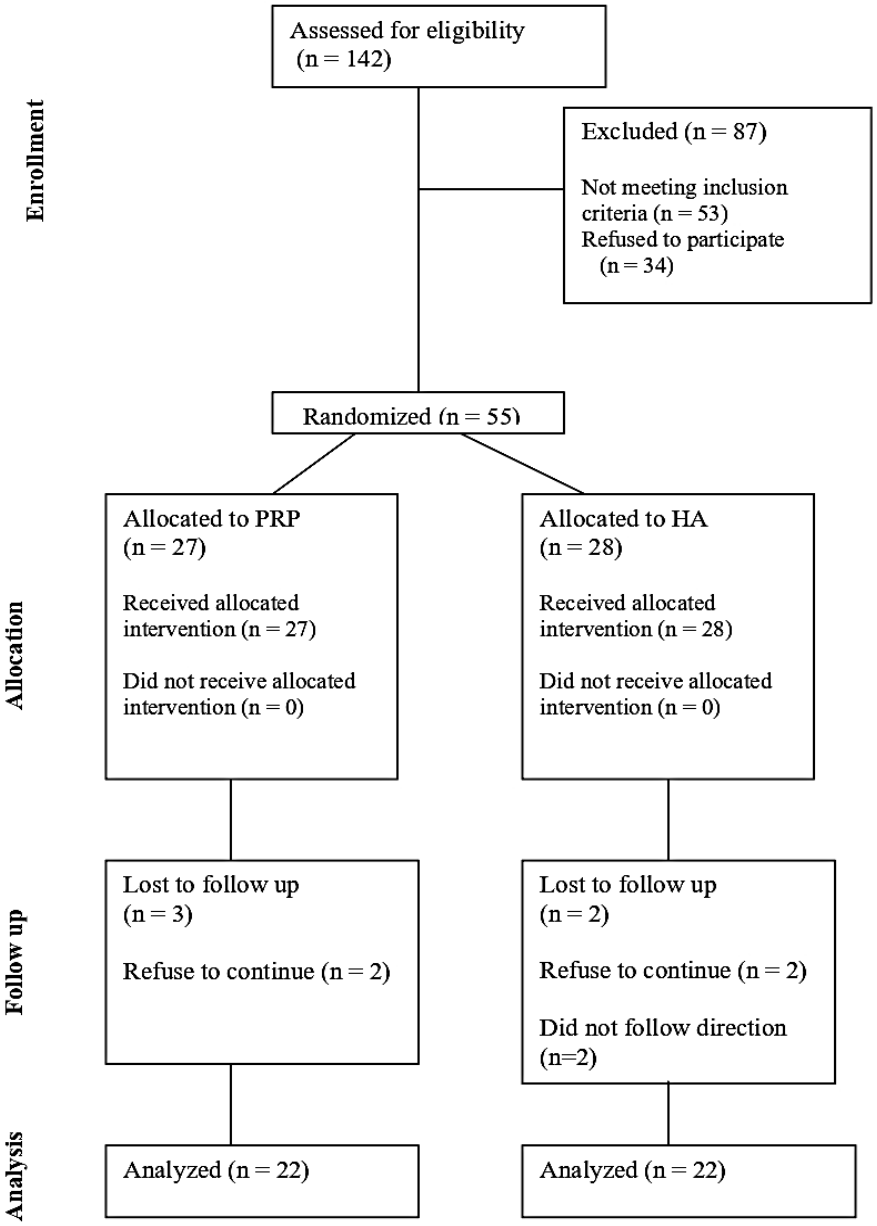

Figure 1. Flow diagram of the study. N: number of patients; PRP: platelet-rich plasma; HA: hyaluronic acid

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Data Characteristics

A total of 131 participants were screened, with 87 excluded due to not meeting exclusion criteria (n = 53) and 34 declining participations. Following participant dropouts, the final sample analyzed included 22 participants per group (PRP, HA, and control) (Figure 1). The study population comprised 15 males (22.73%) and 51 females (77.27%) (Table 1).

The mean age was 60 years in the PRP group (range: 56-76), 59.4 years in the HA group (range: 50-70), and 53.5 years in the control group (range: 50-71). Gender distribution within each group was comparable. Baseline differences among groups were assessed using one-way ANOVA for continuous variables and chi-square tests for categorical variables.

miR-132 Expression Levels

The data obtained were not normally distributed, thus changes in miR-132 expression were analyzed using Wilcoxon signed-rank test for within-group comparisons and Kruskal-wallis test for between-group differences. Within-group comparisons with 95% confidence level showed that PRP treatment significantly reduced miR-132 expression ($p = 0.000121$), whereas HA and control groups showed no significant changes ($p = 0.775$ and $p = 0.874$, respectively) (Table 2).

Table 1. Demographic characteristics of respondents and comparison of groups

Characteristics	Group PRP n = 22	Group HA n = 22	Control Group n = 22	TOTAL
Men (frequency and percentage)	6 (27.27)	3 (13.64)	6 (27.27)	15 (22.73)
Women (frequency and percentage)	16 (72.73)	19 (86.36)	16 (72.73)	51 (77.27)
Age, mean (range)	60 (56-76)	59.4 (50-70)	53.5 (50-71)	

Table 2. Analysis of changes in miR-132 expression by group

Parameters	Group	H-0 (Pre) Mean ± SD (95% CI)	H-5 (Post) Mean ± SD (95% CI)	Mean Difference	P-value for Within-Group Analysis
miR-132 expression	PRP	5.18 ± 9.25 (1.08 – 9.28)	0.95 ± 0.59 (0.69 – 1.21)*	-4.23	< 0.000121
	HA	4.92 ± 10.5 (0.26 – 9.57)	0.52 ± 0.23 (0,42 – 0,62)	-4.40	0.775
	Control	3.61 ± 7.38 (0.34 – 6.88)	0.39 ± 0.36 (0,23 – 0.55)	-3.32	0.874
Note: Within-group analysis was performed using Wilcoxon test while between-group analysis was performed using Kruskal-wallis test. * $p < 0.05$ using Kruskal-wallis test compared to control group; SD refers to standard deviation; CI stands for confidence interval					

PRP therapy decreased miR-132 expression from 5.18 to 0.95, while HA treatment showed a smaller reduction from 4.92 to 0.52 (Figure 2). Following between-group analysis, statistical significance was observed only between PRP and control groups ($p = 0.0105$), indicating PRP effectiveness. Nonetheless, no significant difference was observed between PRP and HA 5 days after treatments ($p = > 0.9999$). These findings suggest PRP may influence miR-132 regulation more effectively than HA.

Cytokine Analysis

IL-1β levels significantly decreased in the HA group ($p < 0.001$, Wilcoxon signed-rank test), while

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PRP and control groups showed no significant changes (p = 0.308 and p = 0.723) (Table 3 and Figure 3). Nonetheless, five days after treatment, the IL-1β levels on both treatment groups were statistically significant compared to the control group (p = < 0.0001). No significant change was observed between both treatment groups on day 5 (p = > 0.9999).

There were no significant changes in IL-6 levels between baseline and five days after treatment in all the groups (p > 0.05, Wilcoxon signed-rank test). Similarly, IL-6 levels did not notably differ across all groups (p > 0.05, Kruskal-Wallis test), indicating limited treatment impact on IL-6 modulation.

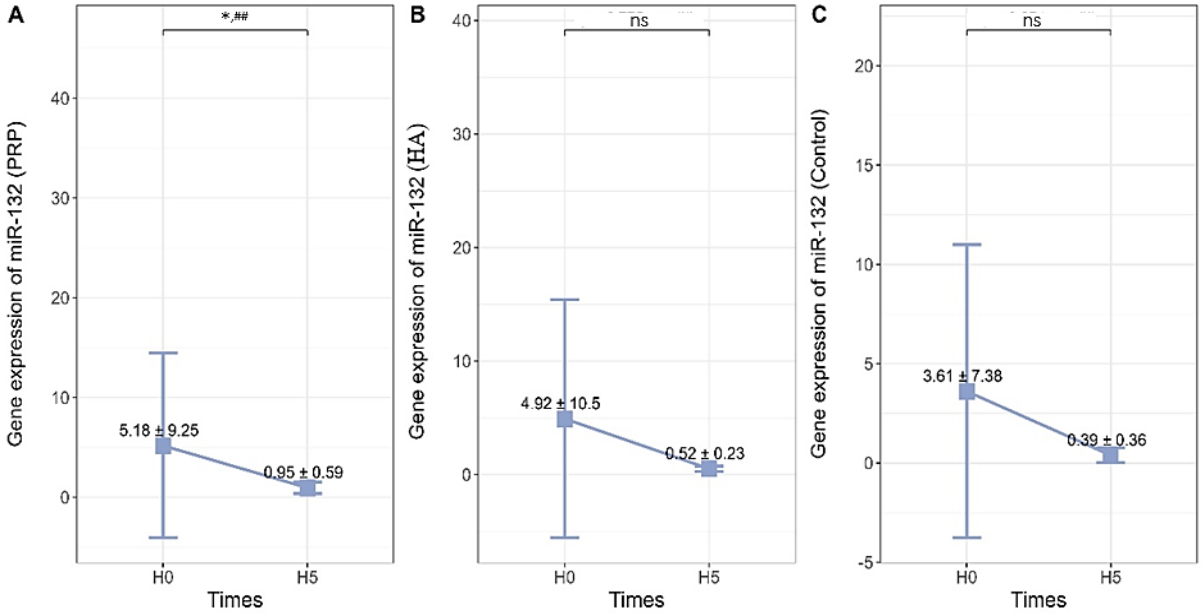

Figure 2. Error plot of changes in miR-132 expression in the treatment groups. Data are presented as mean ± standard deviation (n = 22). * p < 0.05 using Kruskal-wallis test compared to control group; ## p < 0.001 using Wilcoxon test; ns: not significant.

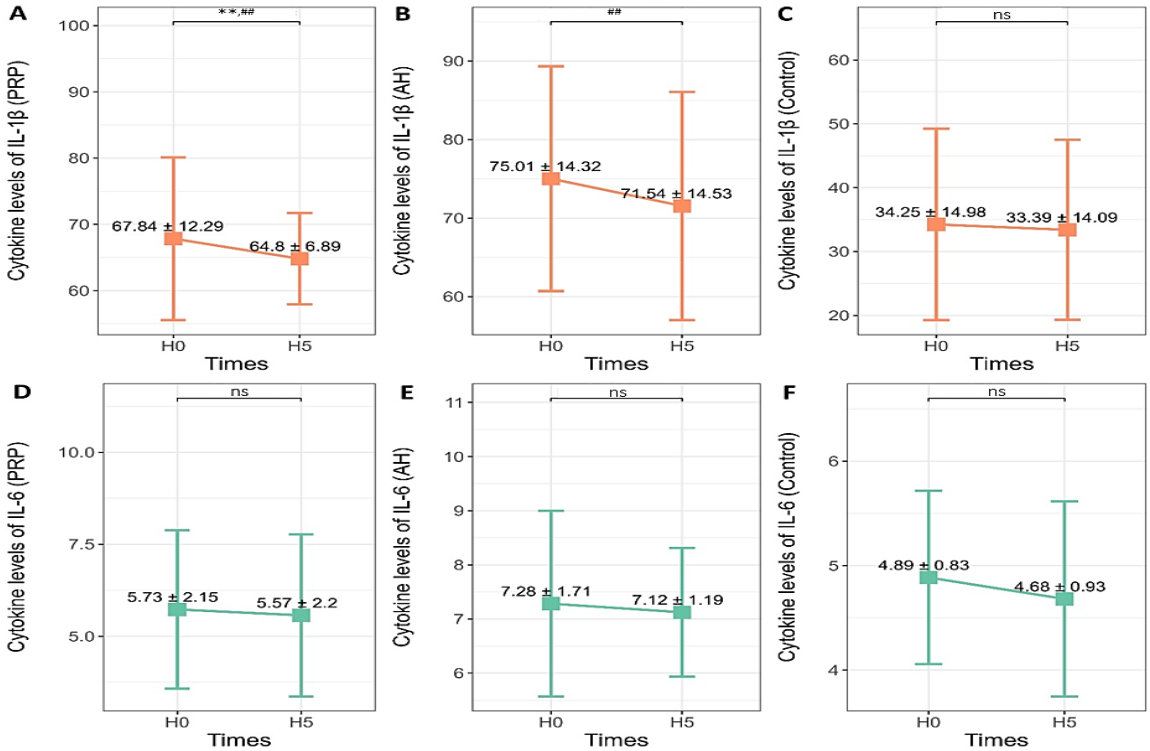

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Figure 3. Error plot of changes in cytokine levels in the treatment groups. Data are presented as mean ± standard deviation (n = 22). ** p < 0.0001 using Kruskal-wallis test compared to control group; ## p < 0.001 using Wilcoxon test; ns: not significant.

Table 3. Analysis of changes in cytokine levels in groups

Parameters	Groups	H-0 (Pre) Mean ± SD (95% CI)	H-5 (Post) Mean ± SD (95% CI)	Mean Difference	P-value for Within-Group Analysis
IL-1β cytokine level	PRP	67.84 ± 12.29 (62.39 – 73.28) pg/mL	64.8 ± 6.89** (61.75 – 67.86) pg/mL	-3.04	0.308
	HA	75.01 ± 14.32 (68.66 – 81.36) pg/mL	71.54 ± 14.53** (65.09 – 77.98) pg/mL	-3.47	< 0.001
	Control	34.25 ± 14.98 (27.61 – 40.89) pg/mL	33.39 ± 14.09 (27.14 – 39.64) pg/mL	-0.86	0.723
IL-6 cytokine level	PRP	5.73 ± 2.15 (4,78 – 6.68) pg/mL	5.57 ± 2.2 (4.59 – 6.55) pg/mL	-0.16	0.784
	HA	7.28 ± 1.71 (6.52 – 8.04) pg/mL	7.12 ± 1.19 (6.60 – 7.65) pg/mL	-0.16	0.703
	Control	4.89 ± 0.83 (4.52 – 5.25) pg/mL	4.68 ± 0.93 (4.27 – 5.10) pg/mL	-0.21	0.204

Note: Within-group analysis was performed using Wilcoxon test while between-group analysis was performed using Kruskal-wallis test. ** p < 0.0001 using Kruskal-wallis test compared to control group; PRP: platelet-rich plasma; HA: hyaluronic acid; SD: standard deviation; CI: confidence interval.

Pain and Functional Outcomes

VAS scores were analyzed using paired t-tests, showing significant improvements in PRP (p = 0.006) and HA (p < 0.001) groups (Table 4), suggesting effective pain reduction.

Table 4. Analysis of changes in VAS and WOMAC by group

Parameters	Group	H-0 (Pre) Mean ± SD	H-5 (Post) Mean ± SD	Mean Difference	P-value for Within-Group Analysis
VAS	PRP	1.68 ± 0.48	1.32 ± 0.48	-0.36	0.006
	HA	1.86 ± 0.35	1.36 ± 0.49	-0.5	0.001
WOMAC	PRP	1.27 ± 0.46	1.09 ± 0.29	-0.18	0.035
	HA	1.09 ± 0.29	1.05 ± 0.21	-0.05	0.773

Note: analysis was performed using paired t-test. PRP: platelet-rich plasma; HA: hyaluronic acid; SD: standard deviation.

PRP reduced VAS from 1.68 to 1.32, while HA reduced it from 1.86 to 1.36. WOMAC scores significantly improved only in the PRP group (p = 0.035, paired t-test), indicating better functional improvement compared to HA (p = 0.773) (Figure 4). Effect sizes (Cohen's d) suggest PRP had a stronger impact on joint function than HA. These results indicate PRP may offer better functional benefits, though both treatments reduce pain. Further investigations into larger samples are required to validate these findings. No adverse events were observed in any group during the follow-up period.

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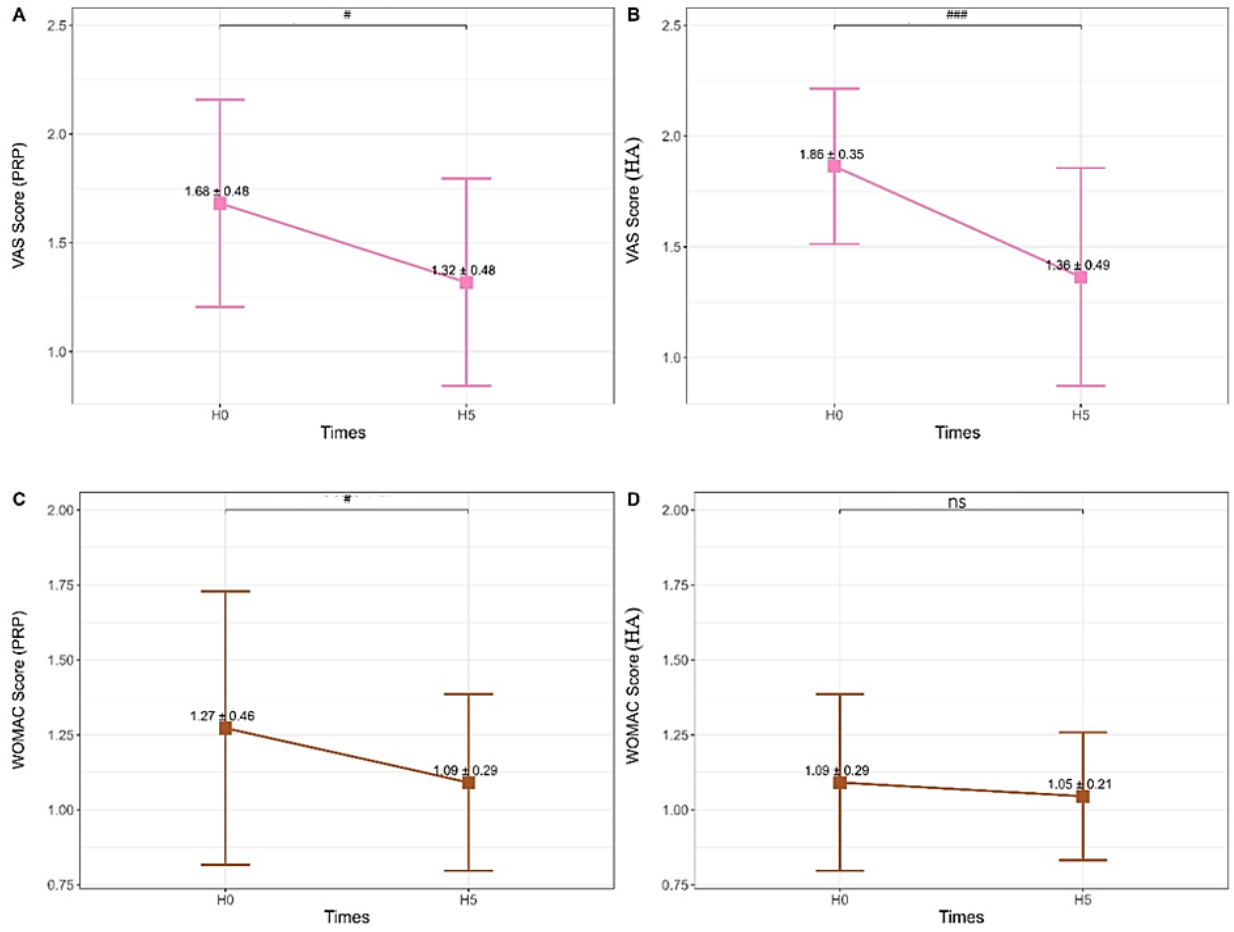

Figure 4. Error plot of changes in VAS and WOMAC in the treatment groups. Data are presented as mean ± standard deviation (n = 22). # p < 0.05 using Wilcoxon test; ## p < 0.001 using Wilcoxon test; ### p < 0.005 using Wilcoxon test; ns: not significant.

Discussion

A key finding is the significant reduction in miR-132 expression in the PRP group (5.18 to 0.95; $p < 0.000121$), highlighting PRP's potential to modulate molecular pathways in OA. In line with this, PRP treatment significantly reduced miR-132 expression compared to the control group ($p = 0.0105$). Previous research documented increased miR-132 expression levels in patients with OA, suggesting its role in OA progression (15, 16). As such, the miR-132 expression reduction is expected to be beneficial. However, others reported decreased miR-132 expression levels in OA patients (17, 18).

This conflicting result possibly reflects the complex roles that miR-132 plays in OA progression. In contrast, the HA group, despite a larger numerical decrease (4.92 to 0.52), exhibited high variability, rendering the miR-132 expression reduction statistically insignificant ($p = 0.775$). The high standard deviation in the HA group suggests inconsistent responses, whereas PRP demonstrated a more predictable effect on miR-132 expression. These findings align with previous research suggesting PRP's bioactive proteins contribute to its anti-inflammatory properties (19-21).

Regarding inflammatory markers, IL-1β levels statistically significant decreasing only in the HA group ($p < 0.001$), suggesting its role in synovial fluid enhancement. However, between group analyses showed that following PRP and HA treatment, the IL-1β levels of the treatment groups significantly reduced compared to the control group ($p = < 0.0001$). These findings indicate that both treatments can affect IL-1β to a certain extent. Conversely, neither PRP nor HA significantly affected IL-6 levels ($p > 0.05$), consistent with findings that systemic inflammation may not be the primary therapeutic target in OA (22). Given IL-1β's role in cartilage degradation and inflammatory signaling via Janus kinase/signal transducer and

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activator of transcription (JAK/STAT) and mitogen-activated protein kinase (MAPK) pathways, its reduction is clinically relevant (23-25).

Clinical outcomes reinforce PRP's therapeutic advantages. Both PRP and HA notably reduced pain (VAS: PRP, $p = 0.006$; HA, $p < 0.001$), but PRP demonstrated better functional improvements (WOMAC: $p = 0.035$). PRP's regenerative effects may be attributed to sustained growth factor release, promoting cellular repair and angiogenesis (26, 27). HA primarily functions as a joint lubricant, alleviating pain but lacking PRP's reparative potential. Despite the functional outcome improvements, the observed changes did not exceed the Minimal Clinically Important Difference (MCID) threshold scores of 12.5 and 2.25 established for WOMAC and VAS, respectively (28). This may suggest that the improvement lacks clinically meaningful change.

Overall, the PRP outcomes obtained in this study demonstrated only limited improvement in patients with OA. These findings differ from those of Duymus, Mutlu, Dernek, Komur, Aydogmus and Kesiktas (29), who reported that PRP provided superior joint improvement compared to the symptomatic relief offered by HA. Several reports, however, have not clearly identified which treatment is more effective. This may be due to PRP variability, attributed to protocol differences, patient comorbidities, and individual platelet concentrations, underscoring the need for optimized preparation techniques and PRP standardization (30). PRP's efficacy is linked to high platelet counts (>1,500,000/µl) and growth factor concentrations that promote tissue regeneration and modulate inflammation with minimal immune risk (22, 29). Patient-specific factors such as OA severity, age, and comorbidities should be considered to refine protocols. Combination therapies, integrating PRP's regenerative properties with HA's lubricating effects, warrant further investigation. PRP's clinical adoption is hindered by insufficient high-quality evidence on long-term structural benefits (31, 32). However, its rising utilization in OA treatment suggests growing acceptance. A meta-analysis indicates PRP-HA combinations may enhance outcomes without increasing adverse effects (33). Future long-term studies are necessary to validate these findings and refine therapeutic strategies.

The current study has several limitations that need to be considered. First, the relatively small sample size may have limited the statistical power to detect smaller but clinically meaningful differences, particularly in molecular outcomes such as miR-132 expression and cytokine levels which tend to have high variability. Consequently, the findings should be interpreted with caution and have limited generalizability. Second, this study only employed a short follow up period of 5 days, which was selected based on earlier study by Dilley, Bello, Roman, McKinley and Sankar (34) who reported that inflammatory responses peaked at 5 to 7 days following impact. Therefore, a long-term follow-up period, such as one year, would be highly valuable in determining the benefit of PRP and HA since OA is a chronic disease. Third, we did not determine PRP concentration nor conduct quality control, which may contribute to PRP variability. Lastly, the current study lacks placebo, making it impossible to determine if both treatments are more effective than placebo effects. As a result, the study results may be less reliable.

This study demonstrates that PRP treatment significantly reduces miR-132 expression and results in functional outcomes improvements, albeit the functional improvements do not exceed the MCID threshold. On the other hand, HA works possibly through IL-1β regulation with limited improvement in functional outcome. Future studies with much larger sample sizes and longer monitoring periods, implementing standardized PRP preparation and quality control, should be done to compare the benefits of PRP and HA treatments or evaluate their combination.

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