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Original Research Paper

Orthopaedics

A PROSPECTIVE STUDY TO ANALYZE THE FUNCTIONAL OUTCOME FOLLOWING USE OF COMBINATION OF PLATELET RICH PLASMA [PRP] AND HYALURONIC ACID IN ANKLE OSTEOARTHRITIS

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ABSTRACT

Background: Ankle osteoarthritis (OA), though less common than knee or hip OA, significantly affects mobility and quality of life, particularly in younger, post-traumatic populations. Current non-surgical treatments offer limited long-term relief. Platelet-rich plasma (PRP) and hyaluronic acid (HA) have shown individual efficacy in OA management. This study evaluates the combined effect of intra-articular PRP and HA in patients with ankle OA. **Methods:** This prospective interventional study included 400 patients aged 30–85 years with radiographic evidence of Grade 1–3 ankle OA. Patients received a single intra-articular injection combining autologously prepared PRP (via double-spin centrifugation) and high-molecular-weight HA. Outcome measures included the Visual Analog Scale (VAS) for pain and the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score for function, assessed at baseline and at 2-, 4-, 8-, and 12-weeks post-injection. **Results:** The mean VAS score improved significantly from 8.24 at baseline to 2.47 at 12 weeks ($p < 0.0001$). The mean AOFAS score increased from 37.49 to 82.51 ($p < 0.0001$), reflecting a marked enhancement in functional outcomes. Improvements were consistent across age groups and durations of disease. No adverse events or complications were reported. **Conclusions:** Intra-articular injection of combined PRP and HA is a safe and effective treatment for ankle OA, yielding significant short-term improvements in pain and function. These results support its use as a minimally invasive alternative to surgical intervention. Further randomized controlled trials with longer follow-up are warranted.

KEYWORDS : Ankle Osteoarthritis, Platelet-Rich Plasma, Hyaluronic Acid

INTRODUCTION

Ankle osteoarthritis (OA) is a debilitating condition characterized by progressive degeneration of the articular cartilage, subchondral bone remodeling, synovial inflammation, and ultimately joint dysfunction. (1–4) Unlike knee or hip osteoarthritis, which is primarily idiopathic and associated with age-related wear and tear, ankle OA is often post-traumatic in origin, resulting from previous fractures, ligamentous injuries, or chronic instability. (1,4,5) Ankle OA affects approximately 1% of the world's population, with an estimated incidence of 30 cases per 100,000 individuals. (6,7) Despite being less prevalent than knee and hip OA, ankle OA significantly impacts patients' quality of life by limiting mobility, inducing chronic pain, and restricting daily activities. (1,6)

In recent years, intra-articular injections have gained prominence as a minimally invasive treatment modality for OA. (8) Among these, platelet-rich plasma (PRP) and hyaluronic acid (HA) are frequently used due to their biological effects on cartilage homeostasis, inflammation modulation, and joint lubrication. (9–12)

Platelet-rich plasma is an autologous concentration of platelets derived from whole blood, containing bioactive growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF). (13) These factors promote chondroprotection, tissue healing, and anti-inflammatory effects by stimulating chondrocyte proliferation and extracellular matrix synthesis while reducing inflammatory cytokines. (14,15) PRP has been shown to provide symptomatic relief in OA by enhancing cartilage repair and modulating synovial inflammation. (16)

Hyaluronic acid, a key component of synovial fluid, acts as a viscoelastic lubricant and shock absorber within the joint. (17) It exerts chondroprotective effects by binding to CD44 receptors on chondrocytes, reducing inflammatory responses, and improving the biomechanical properties of synovial fluid. (18)

The rationale for combining PRP with HA is based on their complementary mechanisms of action. While PRP enhances the biological regenerative capacity of the joint, HA provides mechanical support and sustains the chondroprotective environment. Studies in knee osteoarthritis have demonstrated superior clinical outcomes with combination therapy compared to either agent alone, suggesting a potential benefit for ankle OA as well.

The present study aims to analyze the functional outcome following the use of a combination of platelet-rich plasma (PRP) and hyaluronic acid (HA) in patients with ankle osteoarthritis.

This study has significant implications for clinical practice by providing evidence-based data on a novel, minimally invasive treatment strategy for ankle OA. By optimizing joint preservation approaches, this study contributes to the broader goal of improving long-term functional outcomes and delaying the progression of degenerative joint disease.

MATERIALS AND METHODS

Study Design

This was a prospective interventional study conducted at the Department of Orthopaedics, Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur, from April 2023 to July 2025. Ethical approval was obtained from the Institutional Ethics Committee (IEC/2023/7335-151). Informed consent was obtained from all participants prior to enrollment.

Participants

A total of 400 patients diagnosed with ankle osteoarthritis (Grade I–III based on modified Kellgren-Lawrence criteria) were included. Inclusion criteria were: age between 30 and 85 years, chronic ankle pain >3 months, radiological evidence of OA, and failure of prior conservative treatments. Exclusion criteria included: previous ankle surgery, active infection, systemic inflammatory arthritis, coagulopathy, malignancy, or hypersensitivity to HA.

Intervention

Each patient received a single intra-articular injection of 2 mL

of autologous PRP combined with 4 mL of high-molecular-weight hyaluronic acid. PRP was prepared using a double-spin centrifugation technique (first spin at 1500 rpm for 15 minutes, second at 3500 rpm for 10 minutes), producing leukocyte-poor PRP. Injections were administered under aseptic conditions with patients in the supine position and ankle in neutral dorsiflexion.

Outcome Measures

Pain was assessed using the Visual Analog Scale (VAS), and functional status was evaluated using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score. Both scores were recorded at baseline and at follow-up visits at 2-, 4-, 8-, and 12-weeks post-injection.

Statistical Analysis

Data were analyzed using SPSS software trial version 26.0. Repeated-measures ANOVA was used to compare VAS and AOFAS scores over time. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 400 patients were included, comprising 290 males (72.5%) and 110 females (27.5%) [Table 1, Figure 1]. The mean age of the cohort was 57.95 ± 12.80 years (range, 23–76 years) [Table 2]. Table 3 [Figure 2] evaluates pain reduction over time using the Visual Analog Scale (VAS). The mean VAS score at presentation was 8.24 ± 0.71, signifying severe pain. At two weeks, the score reduced to 6.97 ± 0.85; at four weeks, it further dropped to 5.95 ± 0.87; at eight weeks, it was 5.08 ± 0.71; and by the end of three months, the score significantly decreased to 2.47 ± 0.51. Post hoc analysis using the Wilcoxon test demonstrated a statistically significant reduction in pain at each time point compared to the previous one ($p < 0.0001$), and the overall Friedman test was also highly significant ($F = 147.029$; $p < 0.001$). Table 4 [Figure 3] assesses functional improvement using the AOFAS Ankle-Hindfoot Score. The baseline score was 37.49 ± 1.85, indicating poor function. At two weeks, the score improved to 59.10 ± 3.26; at four weeks, it increased to 65.13 ± 4.40; by eight weeks, it reached 75.67 ± 6.20; and at three months, the mean AOFAS score peaked at 82.51 ± 3.72. All pairwise comparisons using the Paired t-test showed statistically significant improvement at each time point ($p< 0.0001$), and the repeated measures ANOVA confirmed overall significance ($F= 106.366$; $p < 0.001$).

Subgroup Analysis

Improvement in VAS and AOFAS scores was observed across all age groups and OA grades. Patients with Grade I and II OA showed a more pronounced functional improvement compared to those with Grade III disease. No statistically significant difference was found between male and female outcomes ($p > 0.05$).

Safety

No adverse events, including infection, joint stiffness, or allergic reactions, were reported during the study period.

Table-1: Gender Distribution of Study Participant

Gender	Frequency	Percentage (%)
Male	290	72.5
Female	110	27.5
Total	400	100.0

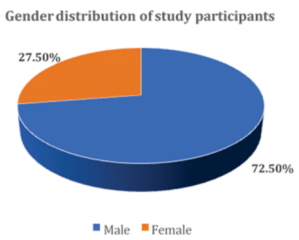

Figure 1: Gender Distribution of Study Participants

Table-2: Age Distribution of the Study Participants

Age	Min	Max	Mean±S.D
	23	76	57.95±12.80

Table-3: Pain Reduction Over Time Using the Visual Analog Scale (VAS) Among Study Participants

VAS Score	Mean ± S.D	Post hoc analysis using Wilcoxon test				
Presentation	8.24±0.71	-	2 weeks	4 weeks	8 weeks	3 months
2 weeks	6.97±0.85	Presentation	<0.0001	<0.0001	<0.0001	<0.0001
4 weeks	5.95±0.87	2 weeks		<0.0001	<0.0001	<0.0001
8 weeks	5.08±0.71	4 weeks			<0.0001	<0.0001
3 months	2.47±0.51	8 weeks				<0.0001

Friedman test F value 147.029; p-value <0.001(s)

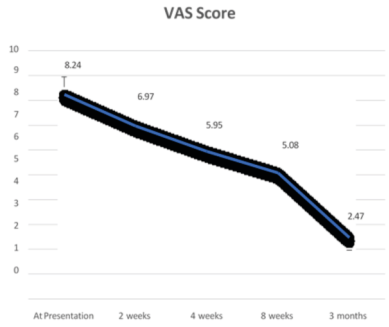

Figure 2: Pain Reduction Over Time Using the Visual Analog Scale (VAS)

Table-4: Functional Improvement Using the AOFAS Ankle-Hindfoot Score Among Study Participants

AOFAS SCORE	Mean±S.D	Post hoc analysis using Paired t test				
Presentation	37.49±1.85	-	2 weeks	4 weeks	8 weeks	3 months
2 weeks	59.10±3.26	Presentation	<0.0001	<0.0001	<0.0001	<0.0001
4 weeks	65.13±4.40	2 weeks		<0.0001	<0.0001	<0.0001
8 weeks	75.67±6.20	4 weeks			<0.0001	<0.0001
3 months	82.51±3.72	8 weeks				<0.0001

Repeated measure ANOVA value 106.366; p-value <0.001(s)

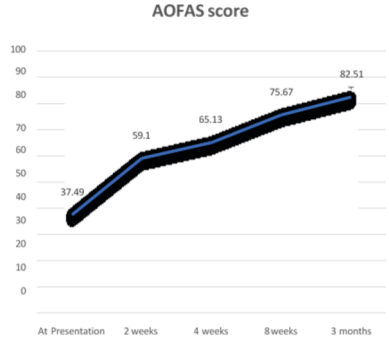

Figure 3: Functional Improvement Using the AOFAS Ankle-Hindfoot Score

DISCUSSION

In present study, the age of the participants ranged from 23 to 76 years, with a mean of 57.95 ± 12.80 years, indicating a predominance of ankle osteoarthritis in middle-aged to elderly individuals. This aligns with the findings by Howlader

MAA (2023) (19), who reported participant age ranges between 46.2 to 62 years across multiple studies. Similarly, Zhang Q et al. (2022) (22) noted participant ages between 40–60 years. (22) Huang HY et al. (2022) (21) and Sun SF et al. (2021) (23) included participants with mean ages of approximately 58.4 ± 8.1 and 60.6 ± 8.4 years, respectively, while Yu W et al. (2018) (9) enrolled participants aged 22–72 years with a mean age of 48 years. These findings suggest that osteoarthritis commonly affects the middle-aged to elderly population, consistent with our cohort.

Our study cohort comprised 72.5% males and 27.5% females, showing a distinct male predominance in ankle osteoarthritis. This gender distribution contrasts with that reported by Howlader MAA (2023) (19), who noted a predominance of females in studies on knee osteoarthritis. Zhou B et al. (2022) (20) and Zhao J et al. (2020) (10) reported a near-equal distribution between genders (e.g., 33 males and 21 females in one arm; $p = 0.576$ in Zhou B's study), indicating gender was not significantly associated with treatment outcomes.

Our study showed a significant reduction in VAS scores from 8.24 ± 0.71 at baseline to 2.47 ± 0.51 at 12 weeks ($p < 0.0001$), indicating substantial pain relief. These results are consistent with findings from Howlader MAA (2023) (19), where VAS reduction in PRP+HA groups ranged from 1.94 to 5.9, and control groups from 0.2 to 5.3. Sun SF et al. (2021) (23) observed VAS reductions with greater short-term improvement in PRP-alone at 1 month (−5.6mm, $p = 0.017$), but superior long-term pain relief with PRP+HA at 6 months (+7.9 mm, $p = 0.020$). Similarly, Zhou B et al. (2022) (20) demonstrated significantly lower post-treatment VAS in the PRP+HA group ($p < 0.001$).

Zhang Q et al. (2022) (22) reported VAS mean difference (MD) of −0.65 at 1 month ($p = 0.05$), with no significant differences at later time points, although the improvements did not exceed the minimum clinically important difference (MCID = 1.16). Zhao J et al. (2020) (10) confirmed mid-term (6-month) VAS superiority in the PRP+HA group (SMD = −0.31; $p = 0.01$), while Aw AAL et al. (2021) (25) observed significant early (4–6 weeks) and late (12 months) reductions with PRP+HA (SMD = −1.55 and −1.45, respectively; $p < 0.00001$). These findings support our observation of early and sustained pain relief with combination therapy.

Functional recovery, as measured by AOFAS in our study, improved significantly from 37.49 ± 1.85 at baseline to 82.51 ± 3.72 at 12 weeks ($p < 0.0001$). Yu W et al. (2018) (9) observed the greatest improvement in WOMAC scores in the combination group (mean total score improvement = 23.69 ± 13.28; $p < 0.01$ vs PRP or HA). Zhou B et al. (2022) (20) reported higher Lysholm Knee Scores in the PRP+HA group ($p < 0.01$), and Sun SF et al. (2021) (23) found improvements in WOMAC pain, stiffness, and function domains (all $p < 0.001$), with the PRP+HA group showing a better trend at 6 months.

Nonetheless, our functional gains were statistically robust and clinically significant, demonstrating a clear benefit of PRP+HA in ankle OA.Several potential mechanisms could explain the observed benefits of combining HA and PRP without inhibiting their individual actions.

HA provides structural support and lubrication while PRP delivers bioactive factors: HA's role in providing increased joint lubrication and acting as a supportive scaffold for the extracellular matrix can create a more conducive environment for the growth factors and cytokines released by PRP to exert their regenerative and anti-inflammatory effects. (24)

PRP may enhance HA production: Research has indicated that PRP, with its potent mixture of growth factors and cytokines, has been shown to increase the production of HA from native synoviocytes. This suggests a potential additive effect where PRP not only contributes its own therapeutic benefits but may also stimulate the endogenous production of HA. (24)

Dissimilar biological mechanisms leading to synergistic effects: The combination of HA and PRP may leverage their different biological mechanisms to address various aspects of OA pathology. HA primarily acts through visco-supplementation and influencing the extracellular matrix, while PRP modulates the inflammatory response and promotes tissue healing through growth factors. These distinct actions, when combined, can have a synergistic impact on pain reduction, functional improvement, and potentially cartilage regeneration. The study by Lana et al. (2016) suggests that the combination of HA+PRP showed synergic effects in their potential regenerative and anti-inflammatory properties compared to HA or PRP alone. This association can influence inflammatory cytokines in the chondrocyte degeneration process and promote cartilage regeneration while inhibiting inflammation in OA. The observed improvement in WOMAC physical activity scores between 30-90 days after combination therapy aligns with the timeframe for these cellular and molecular modifications. (24). The findings of our study strongly align with the majority of existing literature on PRP+HA combination therapy in osteoarthritis, particularly regarding pain reduction, functional improvement, and safety. While prior studies focused predominantly on the knee joint, our results extend the clinical utility of this modality to ankle osteoarthritis, highlighting consistent efficacy across joints. Differences in gender distribution and disease duration are likely attributable to anatomical, demographic, and sociocultural factors rather than treatment response variability. Future research should incorporate larger cohorts, imaging-based outcomes, and inflammatory marker analysis to further validate the utility of PRP-HA therapy in ankle OA.

CONCLUSION

Intra-articular injection of a combination of platelet-rich plasma (PRP) and hyaluronic acid (HA) demonstrated significant short-term improvements in pain relief and functional outcomes in patients with ankle osteoarthritis. The therapy was well tolerated, with no adverse events observed during the follow-up period. These findings suggest that PRP-HA combination therapy is a safe and effective non-surgical treatment option for early to moderate stages of ankle OA.

Given the minimally invasive nature and biological potential of this treatment, it may serve as a valuable joint-preserving intervention, especially for younger, active individuals with post-traumatic OA. Further large-scale randomized controlled trials are warranted to confirm these outcomes, assess long-term efficacy, and compare the combination therapy against monotherapies and placebo.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. No financial support was received for this study.

Ethics Statement

This study was conducted in accordance with the ethical standards of the institutional and national research committee. Approval was obtained from the Institutional Ethics Committee of Netaji Subhash Chandra Bose Medical College, Jabalpur (Approval No.: IEC/2023/7335-151). Written informed consent was obtained from all participants prior to inclusion.

Author Contributions

Dr. Nitin Kumar Sahu: Conceptualization, patient selection, data collection, analysis, manuscript drafting.
Dr. Shamikh Raza (Co-author): Study design, supervision, methodology guidance, critical revision of manuscript.

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