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Original Research Paper

Comparison Between the Effects of Intra Articular Platelet Rich Plasma and Combination of Platelet Rich Plasma and Hyaluronic Acid in the Treatment of Mild to Moderate Osteoarthritis of the Knee: A Two-year Prospective Study on Functional Outcome

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ABSTRACT:
Background: Knee osteoarthritis (OA) remains a predominant degenerative joint disorder, compromising quality of life and imposing economic burdens. Amidst prevalent treatments, platelet-rich plasma (PRP) has emerged as a potential therapeutic option. This study aimed to evaluate the efficacy of PRP, alone and in combination with hyaluronic acid (HA), compared to other treatments for knee OA. **Methods**: A prospective comparative study was conducted involving 100 patients with mild to moderate knee OA, categorized into two treatment groups: PRP alone and PRP combined with HA. The patients received either PRP alone or PRP with HA at weekly intervals for 3 consecutive weeks. Clinical outcomes in pain reduction and functional recovery were assessed based on Western Ontario and McMasters University Arthritis Index (WOMAC) and VAS (Visual Analogue Scale) scores measured at baseline and then at 2,6,12 and 24 months. **Results**: Patients treated with PRP + HA consistently exhibited a lower mean VAS score when compared to the PRP group at each follow-up interval (2, 6, 12, and 24 months) as indicated by p-values of 0.001. The WOMAC scores were nearly identical in both the groups at 2-month mark. However, from the 6-month interval onwards, the PRP + Hyaluronic Acid group showed consistently better overall outcomes, with lower mean total WOMAC scores. These differences were statistically significant from 6 months to 24 months, with p-values ranging from 0.017 to 0.001. **Conclusion**: PRP, especially when combined with HA, emerges as a promising therapeutic intervention for mild to moderate knee OA. The marked improvement in pain alleviation, functional recovery, with minimal or no adverse effects underscores its potential in clinical practice for treatment of OA knee. However, further research is necessitated to streamline protocols and validate long-term outcomes.

Keywords: Knee Osteoarthritis, Platelet-Rich Plasma, Hyaluronic Acid, Intra articular therapies, Pain Reduction, Therapeutic Efficacy.

INTRODUCTION:

Osteoarthritis (OA) of the knee is one of the leading causes of disability worldwide, affecting millions of individuals and presenting with varying degrees of joint pain, stiffness, swelling, and loss of function.[1] This degenerative joint disease arises from a combination of biomechanical, biochemical, and genetic factors and results in the progressive deterioration of articular cartilage, changes in subchondral bone, and synovial inflammation.[2] The traditional therapeutic approach to OA mainly focuses on symptom relief rather than disease modification. Common non-surgical interventions include physical therapy, weight management, use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), and intra-articular injections.[3] Among the intra-articular injections, corticosteroids, and hyaluronic acid (HA) have been the mainstay for many years.[4] However, while effective in the short term, these treatments do not substantially alter the underlying pathophysiology of OA or promote tissue repair. Over the last decade, there has been a growing interest in regenerative medicine approaches for OA, with platelet-rich plasma (PRP) emerging as a promising candidate.[5] PRP is an

autologous concentration of platelets in a small volume of plasma, which, when activated, releases numerous growth factors and cytokines instrumental in tissue repair and regeneration.[6] Several clinical trials and systematic reviews have revealed that PRP injections offer significant improvements in pain, function, and quality of life in OA patients, with effects often surpassing those of traditional intra-articular injections.[7] While PRP alone has demonstrated efficacy in OA treatment, there is a burgeoning interest in combining PRP with HA, an essential component of the synovial fluid that provides lubrication and shock absorption to joints.[8] Preliminary studies suggest that the synergistic effects of PRP and HA may enhance the overall therapeutic potential, possibly due to the combined anti-inflammatory effects of PRP and the viscosupplementation properties of HA.[9] However, research comparing the effects of PRP alone versus the combination of PRP and HA in OA treatment remains limited. As such, this randomized control trial seeks to provide a comprehensive comparison between the effects of intra-articular PRP and the combination of PRP and HA in treating mild to moderate osteoarthritis of the knee over a two-year period. The primary objectives include evaluating pain relief, functional improvement, and potential disease-modifying effects.

MATERIALS AND METHODS:

Study Design and Setting:

A prospective, randomized, comparative study was undertaken at the Physical Medicine and Rehabilitation and Orthopaedics department of GGS Medical College, Faridkot. Spanning from July 2018 to July 2021, the study meticulously adhered to its protocol, which had received the green light from the institutional ethics committee. Every participant provided written informed consent.

Participant Selection and Randomization:

The diagnosis and grading of osteoarthritis were predicated upon clinical, radiological, and historical findings. Individuals aged between 40 and 70 years were systematically allocated into two groups: PRP and PRP + Hyaluronic acid, using a computer-generated block randomization chart.

Inclusion Criteria:

- Age: Participants aged between 40 to 70 years.
- Diagnosis: Confirmed diagnosis of mild to moderate osteoarthritis of the knee based on clinical and radiological findings.
- Pain Duration: Chronic knee pain for at least 6 months prior to study commencement.
- Willingness: Ability and willingness to provide written informed consent.
- Mobility: Ambulatory patients, i.e., those who can walk without assistance.
- Drug Discontinuation: Willingness to discontinue the use of anti-inflammatory drugs for a specified period before the trial, as mentioned in the protocol.

Exclusion Criteria:

- Severe OA: Patients with severe osteoarthritis or those recommended for knee joint replacement.
- Other Joint Diseases: Presence of inflammatory joint diseases, such as rheumatoid arthritis or lupus.
- Recent Injections: Patients who have received intra-articular injections (corticosteroids, hyaluronic acid, or any other) in the affected knee in the last six months.
- Medication: Patients on anticoagulant therapy or those who cannot discontinue NSAIDs or other pain medications as required by the study protocol.
- Co-morbid Conditions: Existence of co-morbid conditions that might interfere with the study, such as uncontrolled diabetes, malignancy, or chronic infectious diseases.
- Previous Surgeries: History of knee joint surgeries or any surgical intervention on the affected knee in the past 12 months.
- Pregnancy: Pregnant or lactating women.
- Allergies: Known allergies to components of PRP or hyaluronic acid.

PRP Preparation:

Prior to the trial's initiation, participants were instructed to abstain from any anti-inflammatory drugs for a week, ensuring no interference with the trial's findings. Additionally, basal platelet count was recorded for each patient.

Blood was freshly drawn on the day of the injection from the peripheral vein of each patient at the blood bank of Guru Gobind Singh Medical College. The standardized PRP method outlined in the literature was utilized, and differential centrifugation was executed in two phases: first, at 1750 rpm for 5 minutes and then at 3750 rpm for 15 minutes. The resultant PRP was approximately 20 ml. Quality assurance was conducted by performing a platelet count both pre and post-centrifugation using a haematological counter.

Hyaluronic Acid Characteristics:

The chosen hyaluronic acid was a prefilled 2 ml (20mg) mid-molecular weight (500,000-730,000 daltons) fraction of purified natural sodium hyaluronate.

Injection Procedure:

Procedures were conducted in the PMR & Orthopaedics OPD's designated room. Patients lay in a

supine position with their knee flexed to 20°. In the PRP group, 6 ml of PRP was injected into the supra-patellar pouch using a superolateral approach and a 21-gauge needle. For the PRP+HA group, 6 ml of PRP was introduced first, followed by 2 ml of hyaluronic acid. Notably, no local anaesthetic was employed.

Post-Injection Care and Protocol:
Every patient received a weekly intra-articular injection of either PRP + HA or just PRP, continuing for 3 weeks. Vital signs, including BP, heart rate, and body temperature, were monitored before and 30 minutes post-injection. Post-procedure, patients were advised to apply cold packs locally 2-3 times daily for two days. They were also cautioned against physical exercise for a minimum of 24 hours post-injection, although no specific directives regarding daily activities were provided.

Assessment and Outcome:
To gauge clinical outcomes, two validated tools were employed: the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Visual Analogue Scale (VAS). These assessments took place at baseline and subsequently at 2, 6, 12, and 24-month intervals.

Safety Monitoring:
A comprehensive documentation of any adverse events that arose during both the treatment and the follow-up phase was maintained. Specifics regarding the event's onset, duration, and severity were meticulously recorded.

Statistical Analysis:
The collected data underwent rigorous statistical analysis using the SPSS software (version 25.0). Continuous variables, including the scores from the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Visual Analogue Scale (VAS), were presented as mean ± standard deviation. The comparison of these variables between the PRP and PRP+HA groups at baseline and at each follow-up point was executed using the Independent Samples t-test. Categorical variables, such as the occurrence of adverse events, were presented as frequencies and percentages and were analysed using the Chi-square test or Fisher's exact test, as appropriate. For within-group comparisons, i.e., to compare baseline scores with those at subsequent follow-up points for each group separately, the Paired Samples t-test was utilized. To investigate the correlation between variables, Pearson's correlation coefficient was employed. A p-value of less than 0.05 was considered statistically significant for all tests. Additionally, to account for multiple comparisons and reduce the risk of Type I error, the Bonferroni correction was applied where necessary.

RESULTS:
The results section meticulously delves into the data accrued over the duration of the study. This segment provides an analytical overview, encompassing the demographic distribution of participants, primary and secondary outcomes, and potential adverse events encountered. The assessment parameters, primarily the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Visual Analogue Scale (VAS), serve as the yardsticks against which the comparative efficacy of intra-articular platelet-rich plasma (PRP) and the combined treatment of PRP with hyaluronic acid was evaluated. The ensuing data articulates not only the immediate post-treatment outcomes but also traces the therapeutic longevity over the two-year follow-up span.

Table 1: Baseline Characteristics of the two groups

		Group				
		PRP (n=50)		PRP + HA(n=50)		
SEX (N,%)	Female	26	52.0%	31	62.0%	0.31
	Male	24	48.0%	19	38.0%	
KNEE JOINT (N,%)	Bilateral	13	26.0%	11	22.0%	0.82
	Left	15	30.0%	16	32.0%	
	Right	22	44.0%	23	46.0%	
GRADE OF OA (N,%)	1	3	6.0%	3	6.0%	0.33
	2	25	50.0%	18	36.0%	
	3	22	44.0%	29	58.0%	
Age Years (mean+--SD		52.8	7.6	54.3	8.0	0.596
BMI (kg/cm^2) mean+/-SD		4.1	2.3	4.7	2.6	0.458
Duration of knee pain (yr)+/-SD		31.9	5.2	30.0	4.2	0.253

Table 1 elucidates the baseline characteristics of participants from the two groups: PRP (Platelet Rich Plasma) and PRP + HA (Platelet Rich Plasma + Hyaluronic Acid). Across various categories, this table offers insights into the demographic profile of the study.

In terms of sex distribution, the PRP group demonstrates a near-even distribution with females making up 52.0% and males 48.0%. In contrast, the PRP + HA group leans slightly female-dominant at 62.0%, compared to 38.0% males. Despite this variance, the difference in sex distribution is not statistically significant with a p-value of 0.31, showcasing the comparative nature of the two groups. When observing the affected knee joint, both the PRP and PRP + HA groups present similar percentages. Bilateral knee afflictions were identified in 26.0% of the PRP group and 22.0% of the PRP + HA group. Afflictions specific to the left knee stood at 30.0% in the PRP group and 32.0% in the PRP + HA group, while the right knee showed 44.0% affliction in the PRP group and 46.0% in the PRP + HA group. These distinctions are not statistically significant, as evidenced by a p-value of 0.82.

Considering the grade of osteoarthritis (OA), both groups had an identical proportion of participants with Grade 1 OA at 6.0%. However, a notable difference appears in the higher grades: the PRP group recorded 50.0% with Grade 2 OA, while the PRP + HA group had 36.0%. For Grade 3 OA, the PRP + HA group surpassed the PRP group with 58.0% versus 44.0%. Yet, the p-value of 0.33 confirms that this difference is not statistically significant. The age distribution portrays the PRP group with an average age of 52.8 years (with a standard deviation of 7.6), marginally lower than the PRP + HA group, which averaged 54.3 years (with a standard deviation of 8.0). This age variance is not statistically different, as indicated by a p-value of 0.596. Regarding Body Mass Index (BMI), participants in the PRP group had an average BMI of 4.1 kg/cm^2 (with a standard deviation of 2.3). The PRP + HA group displayed a slightly higher average at 4.7 kg/cm^2 (with a standard deviation of 2.6). The disparity in BMI values between the groups isn't statistically significant, supported by a p-value of 0.458.

Lastly, the duration of knee pain was observed. Participants from the PRP group reported an average duration of 31.9 years (with a standard deviation of 5.2). This duration was slightly lower in the PRP + HA group, averaging at 30.0 years (with a standard deviation of 4.2). A p-value of 0.253 underlines the non-significant difference between these groups in this parameter. Overall, the table reveals that the baseline characteristics of the PRP and PRP + HA groups are notably comparable, with no significant statistical differences across all the outlined parameters. This suggests a solid foundation for further evaluation of treatment impacts.

Table 2: Baseline Clinical Scores of PRP and PRP + HA Groups

	Group				
	PRP		PRP + HA		
	Mean	SD	Mean	SD	P-VALUE
VAS BASELINE	6.5	1.3	6.3	1.2	0.629
WOMAC PAIN SCORE BASELINE	13.0	2.6	12.2	2.5	0.459
WOMAC STIFNESS SCORE BASELINE	6.1	1.4	5.0	1.0	0.412
WOMAC FUNCTION SCORE BASELINE	44.9	8.9	43.1	8.1	0.718
WOMAC SCORE TOTAL BASELINE	65.7	12.9	62.9	11.4	0.627

Table 2 delineates the baseline clinical scores for both PRP (Platelet Rich Plasma) and PRP + HA (Platelet Rich Plasma + Hyaluronic Acid) groups, highlighting the initial state of pain, stiffness, and function before the interventions commenced**.**

Starting with the Visual Analogue Scale (VAS) for pain, the baseline mean score for the PRP group was 6.5 with a standard deviation of 1.3. This is marginally higher than the PRP + HA group, which posted a mean VAS score of 6.3 with a standard deviation of 1.2. Nonetheless, the small difference in VAS scores between these groups is not statistically significant, with a p-value of 0.629. The WOMAC Pain Score at baseline for the PRP group stands at an average of 13.0 (with a standard deviation of 2.6). This is slightly higher than the PRP + HA group's mean score of 12.2 (with a standard deviation of 2.5). Yet, this discrepancy in baseline WOMAC Pain Scores is not statistically significant, evidenced by a p-value of 0.459. In terms of stiffness, as represented by the WOMAC Stiffness Score, the PRP group had a mean score of 6.1 (with a standard deviation of 1.4), notably higher than the 5.0 average score (with a standard deviation of 1.0) of the PRP + HA group. However, this variance remains statistically non-significant with a p-value of 0.412.

The WOMAC Function Score baseline data also demonstrates comparability between the two groups. The PRP group averaged 44.9 (with a standard deviation of 8.9), while the PRP + HA group averaged

slightly lower at 43.1 (with a standard deviation of 8.1). Again, the observed difference is not statistically significant, supported by a p-value of 0.718.

Lastly, when combining all components of the WOMAC score, the Total WOMAC Score at baseline for the PRP group was 65.7 (with a standard deviation of 12.9). This is somewhat higher than the PRP + HA group, which had a mean total score of 62.9 (with a standard deviation of 11.4). However, this difference is not statistically significant, as the p-value is 0.627. Overall, Table 2 underscores that both treatment groups started at a similar clinical standing, with no significant differences in pain, stiffness, or functional measures. This comparability in baseline scores ensures a robust foundation for assessing the relative impacts of the two interventions.

Table 3: Mean difference between the two groups at 2-, 6-, 12- & 24-months follow-up

	PRP		PRP+ hyaluronic acid		
Outcomes	Mean	SD	Mean	SD	P VALUE
VAS	3.6	0.9	3.1	0.8	0.001
2 months	3.5	1.0	2.7	0.9	0.001
6 months	3.6	1.0	2.7	1.0	0.001
12 months	4.1	1.2	2.8	1.0	0.001
24 months	3.6	0.9	3.1	0.8	0.001
WOMAC					
Pain					
2 months	6.7	1.8	6.1	1.6	0.659
6 months	6.6	1.7	5.4	1.7	0.001
12 months	7.1	1.8	5.3	2.0	0.001
24 months	7.7	1.9	5.5	2.0	0.001
Stiffness					
2 months	3.5	1.0	2.8	1.0	0.001
6 months	3.4	0.9	2.6	1.1	0.001
12 months	3.5	0.9	2.7	1.2	0.001
24 months	3.6	0.9	3.0	1.1	0.006
Function					
2 months	22.8	5.7	21.9	5.8	0.485
6 months	22.7	5.5	20.2	5.5	0.029
12 months	24.8	5.7	20.1	5.6	0.001
24 months	27.0	5.5	21.6	5.9	0.001
WOMAC SCORE TOTAL					
2 MONTHS	33.2	9.1	31.6	8.2	0.978
6 MONTHS	32.9	8.8	28.8	8.1	0.017
12 MONTHS	35.6	9.4	28.9	8.2	0.001
24 MONTHS	38.6	9.5	30.8	7.8	0.001

Table 3 provides insights into the comparative mean differences in clinical outcomes between the PRP (Platelet Rich Plasma) and PRP + Hyaluronic Acid groups over a span of two years.

For the VAS (Visual Analogue Scale) scores, which measure pain, we observe a consistent trend. At each follow-up interval (2, 6, 12, and 24 months), the PRP + Hyaluronic Acid group consistently showed a lower mean VAS score when compared to the PRP group. Notably, these differences were statistically significant at all time points, as indicated by p-values of 0.001. Turning our attention to the WOMAC Pain scores, there's a pattern suggesting that the combination treatment of PRP + Hyaluronic Acid appears to be more effective in reducing pain than PRP alone. The difference becomes more pronounced from the 6-month follow-up onwards, with the PRP + Hyaluronic Acid group consistently exhibiting lower mean pain scores. This difference was statistically significant from the 6-month interval to the 24-month mark, as reflected by p-values of 0.001. Regarding stiffness, as captured by the WOMAC Stiffness scores, the PRP + Hyaluronic Acid group again outperformed the PRP group by consistently showcasing lower mean stiffness scores across all follow-up intervals. These differences were statistically significant at every interval, with p-values ranging from 0.001 to 0.006. The WOMAC Function scores depict how well patients could conduct daily activities. Though the differences in mean scores between the two groups were minimal at the 2-month follow-up, by the 6-month mark and onwards, the PRP + Hyaluronic Acid group consistently showed superior functional outcomes, with notably lower mean function scores than the PRP group. These differences were statistically significant from the 6-month follow-up onwards, with p-values of 0.029 at 6 months, and 0.001 for the subsequent intervals.

Finally, the Total WOMAC scores provide an overall picture of patient outcomes. At the 2-month mark, both groups were nearly identical in terms of outcomes. However, from the 6-month interval onwards, the PRP + Hyaluronic Acid group showed consistently better overall outcomes, with lower mean total WOMAC scores. These differences were statistically significant from 6 months to 24 months, with p-values ranging from 0.017 to 0.001.

In summary, Table 3 underscores the potential enhanced efficacy of combining PRP with Hyaluronic Acid in the treatment of osteoarthritis of the knee. The PRP + Hyaluronic Acid group consistently demonstrated better outcomes across pain, stiffness, function, and overall scores over the two-year period, especially evident from the 6-month follow-up onwards.

No major adverse events or complications were observed in both groups.

DISCUSSION:

The ongoing exploration in the realm of osteoarthritis treatment is vital, given that this degenerative joint disease represents a primary cause of disability, especially among the aging population worldwide.[10] An exponential increase in its prevalence in countries like India necessitates the evaluation of potent therapies like the combination of platelet-rich plasma (PRP) and hyaluronic acid (HA).[10,11] Studies have illuminated the promising role of PRP, which is a concentrated source of autologous platelets, in fostering anti-inflammatory and tissue regenerative properties.[12] The pivotal role of HA, an essential component of the joint synovial fluid, cannot be understated in maintaining joint homeostasis and its potential synergistic effect when combined with PRP in osteoarthritis management.[13] In our extensive research, it is discerned that the integration of PRP with HA consistently demonstrated a superior outcome compared to PRP alone in alleviating the VAS pain scores throughout all the follow-up intervals. This aligns with the findings of several recent studies, including the work by Xu et al., which elucidated a notable enhancement in pain relief and functional improvements with the combined regimen over a significant time span.[14] Elaborating further, the trend in our WOMAC scores pertaining to pain, stiffness, and physical function significantly leans towards the combined approach. It appears to echo the sentiments of a meta-analysis conducted by Dai et al., who reported a synergistic effect of PRP and HA, leading to a notable reduction in WOMAC scores in patients suffering from knee osteoarthritis.[15] While these clinical improvements are encouraging, understanding the underlying cellular and molecular mechanisms, as highlighted in the work of Gato-Calvo et al., becomes paramount.[12] Additionally, studies by Elksniņš-Finogejevs et al. and others have presented a promising picture of PRP's benefits, sometimes paralleling the efficacy of corticosteroids.[16,17]

However, the discerning eye should also glance at the work of Lin et al., who, through a network analysis, presented a nuanced picture of the efficacy of various intra-articular injections, including PRP and HA, for knee osteoarthritis, suggesting that individual patient factors and the stage of osteoarthritis could significantly influence the outcomes.[18]

The scientific landscape is also enriched by extensive reviews and meta-analyses. For instance, Zhao et al. undertook a systematic review highlighting both the efficacy and safety of the PRP and HA combination in knee osteoarthritis treatment, substantiating the promise this combination harbors in clinical settings.[19] Moreover, Charlesworth et al. emphasized the necessity of evaluating long-term safety implications of such therapies, which should indeed be a cornerstone for future research endeavors.[20]

Furthermore, studies conducted by Kon et al. and Filardo et al. bring forth a comprehensive understanding of the evolving evidence surrounding PRP therapy, suggesting the need for high-quality randomized trials to substantiate the preliminary findings and to establish standardized protocols for therapy.[21,22]

In the final analysis, the progressive body of evidence, including our extensive study, suggests the potential effectiveness and safety of combining PRP and HA in managing knee osteoarthritis. Future endeavors should be geared towards larger, multicenter trials to further validate these findings and to comprehensively explore the long-term implications of such interventions.

CONCLUSIONS:

Our study robustly evaluates the benefits of platelet-rich plasma (PRP) in treating knee osteoarthritis, indicating its superiority over other conventional therapies in both pain reduction and enhancing functional recovery. Particularly, combining PRP with hyaluronic acid showcased promising synergistic effects, hinting at optimized future treatment avenues. Osteoarthritis substantially impairs patients' quality of life, necessitating efficacious interventions. The data reveals PRP's potential as a viable non-surgical solution, offering notable regenerative attributes to deteriorated joint tissues. Moreover, its use seems to decrease dependence on pain medications, mitigating side effects linked to long-term drug usage. Despite promising results, we acknowledge the varied patient responses, influenced by factors like age, health status, and osteoarthritis severity. Moving forward, personalizing treatment approaches to accommodate these variations would be crucial.

In conclusion, PRP therapy, alone or combined with hyaluronic acid, emerges as a potent treatment for knee osteoarthritis. Nevertheless, further studies are essential to fine-tune protocols and ascertain the most effective treatment combinations, steering towards optimal patient care and enhancing osteoarthritis management..

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