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Original Article PM & R

Comparative analysis of single-dose platelet-rich plasma and hyaluronic acid therapies in knee osteoarthritis: A 12-week follow-up study

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ABSTRACT

OBJECTIVE: Osteoarthritis (OA) is a prevalent and disabling joint condition that affects millions worldwide, particularly in the knee joint, and it presents limited therapeutic options. Platelet-rich plasma (PRP) and hyaluronic acid (HA) have emerged as promising intra-articular treatments. This study aimed to compare the effects of single-dose PRP and HA on pain, functionality, and stiffness in patients with knee OA over a 12-week follow-up period.

METHODS: A retrospective analysis was conducted on 64 patients who underwent single-dose intra-articular HA or PRP treatment for knee OA between December 2021 and June 2022. Pain and functional outcomes were assessed using the Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. Patient satisfaction was evaluated using a Likert scale. Appropriate statistical analyses were performed to compare treatment outcomes and $p<0.05$ was considered statistically significant.

RESULTS: Both PRP and HA treatments led to significant improvements in pain, functionality, and stiffness over the 12-week follow-up period. VAS pain scores decreased significantly in both groups, but a greater reduction was observed in the HA group. Additionally, the HA group exhibited superior improvement in the WOMAC physical function score at the 4-week mark ($p=0.047$).

CONCLUSION: This study is another novel contribution to the growing literature on treatment of PRP and HA treatments for knee OA, where we highlighted the potential benefits of single-dose HA in alleviating pain and enhancing physical function.

Keywords: Hyaluronic acid; knee osteoarthritis; platelet-rich plasma.

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Osteoarthritis (OA) is the most common chronic joint disease [1], currently affecting an estimated 250 million individuals worldwide [2]. It is one of the leading causes of disability [2] and exerts a significant socioeconomic burden, accounting for 1 to 2.5% of the gross domestic product in high-income nations [3].

The knee is the most commonly affected joint by OA, contributing to approximately 85% of the global OA burden [2, 4–6]. The hallmark manifestation of this disease is pain, typically characterized by its insidious onset [7]. Over time, this pain may become apparent during periods of rest or nocturnal hours [7]. Additionally, morning stiffness or discomfort following prolonged rest is a common feature [7]. The diagnostic process of individuals for OA primarily relies on a patient's medical history and findings from physical examinations, often supplemented by radiological imaging modalities [7].

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Numerous therapeutic approaches have been exhaustively investigated by a multitude of researchers over the years. Regrettably, as of now, there is no approved treatment regimen available that can modify the trajectory of OA and hinder its advancement [2]. One promising approach in this regard involves the intra-articular administration of platelet-rich plasma (PRP) into the knee joint. To elucidate, PRP constitutes an autologous biologic therapy derived by the centrifugation of peripheral blood obtained through venesection [8]. This preparation contains growth factors and bioactive proteins known to influence the regenerative processes within joint structures [9]. On the other hand, another prominent intra-articular therapy for knee OA is hyaluronic acid (HA). HA is a glycosaminoglycan molecule naturally present in the knee joint, which provides viscoelastic properties to the synovial fluid [10].

Within the framework of the present investigation, we scrutinized the effects of a single dose of PRP and HA on pain, stiffness, and functional outcomes in patients with knee OA over a 12-week follow-up period. To the best of our knowledge, this study is one of the pioneering original studies comparing single-dose PRP and HA treatments in patients with knee OA.

Highlight key points

- In patients with knee osteoarthritis, both PRP and HA led to improvements in pain, functionality, and stiffness measures at 12-week follow-up.
- The HA group experienced a greater decrease in pain scores, as measured by the VAS, compared to the PRP group.
- HA demonstrated superior improvement in physical function scores, as measured by WOMAC, at the 4-week mark in comparison to PRP.

Table 1. Inclusion and exclusion criteria for patients

Inclusion criteria	Age ≥18 years
	Kellgren-Lawrence grade 2-3
	Written informed consent
Exclusion criteria	Coagulation disorders
	Pregnancy or breastfeeding
	Malignancy
	Inflammatory disease
	Systemic infectious in the past 2 weeks
	Local infection at the site of the procedure
	Patients undergone intra-articular injection but did not come to the 4th and 12th week follow-ups on time

MATERIALS AND METHODS

This is a retrospective study conducted at the tertiary care rehabilitation hospital. This research adhered to the principles outlined in the World Medical Association Declaration of Helsinki, and it received approval from the Istinye University Human Research Ethics Committee (date: 22.09.2023, number: 23/213). A total of 64 patients who underwent single-dose intra-articular HA or PRP treatment for knee OA between December 2021 and June 2022 were considered. Knee OA diagnosis for all patients was clinically established and supported by anterior-posterior knee radiographs. Staging of knee OA was performed using the Kellgren-Lawrence radiographic grading scale and recorded as in [11]. The inclusion and exclusion criteria are listed in Table 1. Baseline patient characteristics including age, sex, and body mass index (BMI) were collected from the hospital database.

Treatment

The HA group received Monovisc (Anika Therapeutics; lightly cross-linking sodium hyaluronate 88 ng/4 mL). For PRP, a manual preparation technique was utilized. A 24 ml venous blood sample was taken from each patient and divided into 3 tubes containing anticoagulant citrate dextrose. The material was first centrifuged at 1,195 rpm for 20 minutes, then the first two layers obtained were re-centrifuged at 1,890 rpm for 15 minutes. The platelet-rich layer was separated and used. 3 ml of PRP was used for each patient, and the remaining sample was sent to the laboratory for counting to be sure of the platelet count.

Outcome Measures

The patients' Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores [12], and at rest, nocturnal and during activity Visual Analogue Scale (VAS) pain scores [13] were recorded from the hospital database. WOMAC is a multidimensional questionnaire consisting of total 24 questions; 5 in the sub-heading of pain, 2 in the sub-heading of stiffness, and 17 in the sub-heading of physical function, administered in patients with hip or knee OA [12]. It has also Turkish validity and reliability [14]. Further, patient satisfaction

Table 2. Demographic and clinical features of patients

	PRP (n=32)	HA (n=32)	p
Age (year), mean±SD	58.71 ±7.53	61.43±8.21	0.173
Gender (female/male), n	28/4	29/3	0.689
BMI (kg/m^2), mean±SD	29.97±3.56	31.72±4.39	0.107
Symptom duration (month), median (IQR 25–75)	24.0 (12.0–64.5)	14.0 (9.75–36.0)	0.154
Affected part (right/left), n	18/14	20/12	0.611
K-L grading scale (grade 2/3), n	19/13	15/17	0.316

BMI: Body mass index; HA: Hyaluronic acid; IQR: Interquartile range; K-L: Kellgren Lawrence; N: number; PRP: Platelet-rich plasma; SD: Standard deviation.

that was evaluated according to the Likert scale (1, very dissatisfied; 2, dissatisfied; 3, neutral; 4, satisfied; 5, very satisfied) was recorded from the hospital database. The WOMAC and VAS scores were evaluated before the injection, 4 weeks after the injection, and 12 weeks after the injection, while the Likert scale was evaluated at the end of the 12 weeks.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences 23.0 version (IBM, Armonk, NY, USA). Discrete variables were represented as numbers (%) while continuous variables were expressed through either mean±standard deviation or median with the interquartile range (25–75). The normal distribution compliance of the data was assessed through the utilization of the Kolmogorov-Smirnov test and the examination of histograms. Differences between groups in discrete variables were examined using the Chi-square test. For normally distributed data, pairwise group comparisons were conducted with Student's t-test, while Mann-Whitney U test was applied for data not adhering to normal distribution. Within groups showing abnormal distribution, pairwise comparisons were carried out using the Wilcoxon-signed-rank t-test. Significance level was accepted as $p<0.05$.

RESULTS

The mean age of the patients in the PRP group was 58.71±7.53, while in the HA group, it was 61.43±8.21 (p=0.173). The majority of patients in both groups were women, with 28 (87.5%) in the PRP group and 29 (90.6%) in the HA group. Comparisons between the two groups regarding age, gender, BMI, symptom duration, affected side, and Kellgren-Lawrence grading scale staging revealed no statistical differences (p=0.173, p=0.689, p=0.107, p=0.154, p=0.611, p=0.316, respectively). The patients' demographic and clinical data are detailed in Table 2.

Pain scores measured by VAS decreased significantly in both PRP and HA groups at the 4th and 12th weeks compared to pre-treatment, this decrease was statistically significantly higher in the HA group than in the PRP group. VAS values and statistical findings are presented in Table 3.

A statistically significant decrease in WOMAC scores was observed in both the PRP and HA groups at the 4th and 12th weeks compared to pre-treatment. When comparing WOMAC score changes between the groups, the HA group showed a greater decrease in the physical function score than the PRP group at the 4th week (p=0.047). This was the only statistically significant difference observed between the PRP and HA groups in WOMAC scores. Detailed WOMAC scores and statistical findings are included in Table 4. Additionally, Likert scale assessments are listed in Table 5.

DISCUSSION

Both PRP and HA applications resulted in up to 12 weeks of improvement in pain, functionality, and stiffness in patients with knee OA. In our study, a greater decrease in VAS pain scores was observed throughout the follow-up period in patients who received HA injections. Additionally, the HA group demonstrated better improvement in the WOMAC physical function score during the first 4 weeks. However, no statistically significant difference was found in other WOMAC scores between the groups.

Table 3. VAS rest pain, VAS nocturnal pain and VAS movement pain scores

	PRP (n=32)	HA (n=32)	p**
VAS, median (IQR 25–75)			
Rest			
Baseline	4.5 (1.0–8.0)	6.0 (2.5–8.5)	0.632
4 week	2.0 (0.0–6.0)	1.5 (0.0–4.0)	0.343
12 week	3.0 (1.0–6.0)	2.0 (0.0–6.0)	0.468
Baseline -4 week	0.0 (0.0–3.0)	3.0 (0.75–5.0)	**0.023**
Baseline -12 week	0.0 (0.0–1.75)	2.0 (0.0–4.0)	**0.049**
p*	**0.001**	<**0.001**	
Nocturnal			
Baseline	5.5 (1–10)	5 (2–10)	0.734
4 week	2 (0–6)	2 (0–4.25)	0.426
12 week	3.5 (0–7)	2 (0–6)	0.562
Baseline -4 week	0 (0–3)	4 (0.5–7)	**0.010**
Baseline -12 week	0 (0–2)	3 (0–5)	**0.022**
p*	**0.001**	<**0.001**	
Movement			
Baseline	7.5 (6–10)	9.5 (8–10)	0.067
4 week	3 (1–7)	2.5 (1.75–6.25)	0.814
12 week	5 (1–9)	3 (2–7)	0.713
Baseline -4 week	5 (0–6)	7 (2–8)	**0.035**
Baseline -12 week	2 (0–5.75)	5 (1–7)	**0.035**
p*	<**0.001**	<**0.001**	

VAS: Visual Analogue Scale; IQR: Interquartile range; SD: Standard deviation. *: It indicates the difference between pre-treatment and post-treatment measurements within the same group at 12 weeks. **: It indicates the difference between the PRP and HA groups at the 12-week mark.

In our literature review, we found numerous studies, including meta-analyses, on the use of PRP and HA in knee OA patients [15–17]. A closer examination of these meta-analyses revealed significant heterogeneity in PRP and HA preparation and application, also noted as limitations in these studies [15–17]. Most studies focused on multiple injections. We found very few studies comparing single doses of PRP and HA, one such study by Buendia-Lopez et al. [18] claimed that PRP was superior to HA in all measurable parameters such as pain, stiffness, and physical function. However, these results contradicted our findings. To explain these discrepancies, we consider three factors. First, our study had a 12-week follow-up period, whereas Buendia-Lopez et al.'s study [18] lacked data at 4 and 12 weeks. Second, our study included patients with stages 2 and 3 according to the Kellgren-Lawrence classification, while their manuscript included patients with stages 1 and 2. Lastly, differences in PRP and HA content and preparation may contribute to the variations between the two studies.

Another study on single-dose PRP and HA belongs to Gormeli et al. [19], they found no significant difference in outcome measures between the two treatments, although both groups showed improvement. They used EuroQol VAS and International Knee Documentation Committee (IKDC) subjective scores for comparison. Given that the IKDC and WOMAC scales both assess functionality and symptoms and that we observed no significant difference in WOMAC scores at 12 weeks between HA and PRP groups in our study, in this sense, Gormeli et al.'s study [19] is partially consistent with ours.

Table 4. Western Ontario and McMaster Universities Arthritis Index (WOMAC) evaluations

	PRP (n=32)	HA (n=32)	p**
WOMAC, median (IQR 25–75)			
Pain			
Baseline	16.0 (13.25–17.75)	13.0 (10.0–16.0)	0.207
4 week	6.5 (4.0–15.75)	5 (2.0–8.5)	0.051
12 week	9.5 (4.25–16)	8 (2–13.0)	0.097
Baseline -4 week	6.5 (0–10.75)	8.5 (6.5–11.0)	0.146
Baseline -12 week	2.5 (0–7.5)	8.0 (3.0–10.0)	0.058
p*	**<0.001**	**<0.001**	
Stiffness			
Baseline	5.0 (3.25–6.75)	4.0 (3.0–7.0)	0.808
4 week	2.0 (1.0–4.0)	1.5 (0–3.0)	0.264
12 week	2.5 (1.25–4.75)	2.0 (1.0–5.0)	0.356
Baseline-4 week	2.5 (0–4.0)	3.0 (1.75–4.0)	0.462
Baseline -12 week	1.5 (0–3.75)	2.0 (0–4.0)	0.559
p*	**<0.001**	**0.001**	
Function			
Baseline	49.5 (39.75–57.75)	49.0 (43.0–57.0)	0.956
4 week	26.0 (15.25–42.75)	21.0 (10.0–29.75)	0.123
12 week	35.5 (19.0–49.0)	27.0 (15.0–47.0)	0.353
Baseline-4 week	24.0 (0–33.75)	30.0 (24.0–35.0)	**0.047**
Baseline -12 week	10.0 (0–27.0)	24.0 (8.0–31.0)	0.072
p*	**<0.001**	**<0.001**	
Total			
Baseline	66.5 (59.5–80.0)	67.0 (57.0–77.0)	0.66
4 week	37.0 (19.5–60.25)	26.0 (14.5–43.75)	0.094
12.hafta	47.5 (24.75–67.25)	33.0 (20.0–62.0)	0.244
Baseline-4 week	33.0 (0–48.5)	42.5 (30.75–49.0)	0.073
Baseline -12 week	14.0 (0–37.0)	35.0 (12.0–43.0)	0.077
p*	**<0.001**	**<0.001**	

WOMAC: Western Ontario and McMaster Universities Arthritis; IQR: Interquartile range; SD: Standard deviation. *: It indicates the difference between pre-treatment and post-treatment measurements within the same group at 12 weeks. **: It indicates the difference between the PRP and HA groups at the 12-week mark.

In a study conducted by Louis et al. [20], there was no difference in WOMAC scores between the HA and PRP groups at the 3rd and 6th month follow-ups, and similarly, Park et al. in [21] did not observe any WOMAC difference between the groups at the 3rd month follow-up. For the study comparing cross-linked HA and PRP with a 6th month follow-up, in [22], they found that there was no statistically significant difference in WOMAC scores between the HA and PRP groups. Although it is similar to our study and the studies mentioned above, the only significant change in the HA group was the WOMAC pain score at the 1st and 3rd months [22]. This may due to the material used in HA group or the difference in study population.

Furthermore, none of the studies mentioned above investigated nocturnal pain, which affects sleep. In our study, nocturnal pain was included as an outcome measure [23]. We found that both PRP and HA provide relief from nocturnal pain, with a statistically significant

TABLE 5. Likert scale scores

Likert Scale, 12 week, (%)	PRP (n=32)	HA (n=32)	Total (n=64)
Very satisfied	21.9	46.9	34.4
Somewhat satisfied	40.6	37.5	39.1
Neither satisfied nor dissatisfied	9.4	15.6	12.5
Somewhat dissatisfied	25.0	0	12.5
Very dissatisfied	3.1	0	1.6

PRP: Platelet-rich plasma; HA: Hyaluronic acid; n: Number.

decrease in the HA group. However, it's important to acknowledge the limitations of our study, such as its retrospective design, the relatively small number of patients involved, and the use of a single-dose PRP protocol. While single-dose PRP treatment has shown promise, it deviates from the more commonly used multi-dose protocols. This could potentially impact the comparative efficacy observed between PRP and HA treatments and should be considered when interpreting our findings.

Conclusion

In conclusion, this study underscores the potential benefits of single-dose PRP and HA treatments in patients with OA. Both PRP and HA demonstrated improvements in pain, functionality, and stiffness over a 12-week follow-up period. Notably, HA treatments appeared to result in a more significant reduction in VAS pain scores at 12-week follow-up period and a greater improvement in the WOMAC physical function score during the initial 4 weeks. However, no substantial differences were observed between the groups in other WOMAC scores. In our study, unlike other studies, nocturnal pain was also investigated and the effectiveness of HA and PRP on nocturnal pain was also demonstrated. Nonetheless, the lack of standardization in PRP and HA applications poses a challenge, leading to varied results across studies. Future research should focus on multi-center studies with standardized methods and extended follow-up periods.

Ethics Committee Approval: The Istinye University Human Research Ethics Committee granted approval for this study (date: 22.09.2023, number: 23/213).

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