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Comparative study of clinical and functional outcome between the efficacy of platelet rich plasma and hyaluronic acid injection in osteoarthritis of knee joint

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Abstract
Introduction: Platelet rich plasma (PRP), a blood-derived product rich in growth factors, is a treatment for cartilage defects. PRP's use is limited due to the lack of clinical evidence. Various studies have suggested that an injection of hyaluronic acid (HA) provides better results in early osteoarthritis.
Purpose: We aimed to compare clinical and functional outcomes of using hyaluronic acid versus platelet rich plasma in the treatment of osteoarthritis of the knee joint.
Methods: 60 patients were included in the study. 30 were treated with HA and the other 30 with PRP. The patients were evaluated 6 months after the procedure. Patients were evaluated before and after the procedure using Visual Analogue Scale (VAS) and Western Ontario McMaster Universities Osteoarthritis Index (WOMAC). Range of motion was measured over time. Adverse events and patient satisfaction were also recorded.
Results: Both groups presented a clinical improvement but significantly better results were seen in the group of patients receiving PRP injections as indicated by their WOMAC and VAS scores at a 12 week and 24 week follow-up. No severe adverse events were observed. Mild pain and effusion after the injection was seen in the PRP group.
Conclusions: Our preliminary findings support the application of autologous PRP as a safe and effective method in the treatment of the initial stages of knee osteoarthritis. Significant clinical improvement was seen with 6 months of follow-up. More promising results need to be obtained in order to use it for low grade degeneration.

Keywords: osteoarthritis of knee; hyaluronic acid; platelet rich plasma

1. Introduction
Osteoarthritis (OA) is a chronic degenerative illness often associated with pain, disability, and reduction in the quality of life. It is characterized by degeneration of articular cartilage and subsequent chondral bone changes [1]. The signs include crepitus, bony enlargement due to remodelling, osteophytes, deformity, restricted ability, and stress pain [2]. The management of chondral disease is challenging due to its low regenerative potential and healing ability. The existing pharmacological therapies (NSAIDs and DMOADs) are non curative and have their own limitations. As a result, the disease not only imposes a physical disability, but also a financial burden to the individuals, family, and society at large. A study reported by Desmeules *et al.* reported a Health Related Quality of Life (HRQoL) score below the 25th percentile among patients with OA knee awaiting Total Knee Arthroplasty [3]. There is a growing need for alternate cost effective and non-invasive treatment modalities.
It has been proposed that the glycosaminoglycan-proteoglycan matrix plays a major role in the underlying pathophysiology of osteoarthritis. Therefore, Hyaluronic Acid (HA), a large viscoelastic glycosaminoglycan, has been used for therapeutic management. It has shock absorptive, traumatic energy dissipative, and lubricative properties. It also provides a protective coating for the articular cartilage surface [4]. HA injections reduce perception of pain by inhibiting inflammatory mediators, decreasing the cartilage degeneration, and promoting cartilage matrix synthesis. Therapeutic benefits in the long run were dependent on the variability of HA in terms of its molecular weight and duration of usage [5].
More recently, Platelet Rich Plasma (PRP) has been used in the treatment of osteoarthritis.

c It contains a high concentration of platelets in a small volume of plasma. It also has autologous growth factors such as PDGF, TGF-β1 and IGF [6]. It is said to stimulate proliferation and extracellular matrix metabolism in chondrocytes. Studies have shown that clinical outcomes were better with PRP in comparison to HA, especially in long term managements [7]. There are several extraneous factors involved in the clinical outcome; nevertheless, very few studies have been done in India in this line.

In this study, we aimed to compare the clinical outcomes and therapeutic benefits of HA and PRP in patients with knee osteoarthritis.

2. Materials & Methods

We conducted a randomized before and after comparative interventional study. The study population consisted of Indian patients of both genders, between 40-60 years of age, with degenerative changes in the cartilage, and an osteoarthritis of the knee joint with the grading of I or II as diagnosed by using the Kellgren & Lawrence scale. Those using tobacco or having neurological disesase, severe degenerative bone disease, presence of infection at the site, active cancer, endocrine disorders, inflammatory disorders, severe vascular diseases, traumatic knee arthritis, and unicompartmental arthritis were excluded from the study. A total of 60 patients participated in this study of which 30 patients were included in the control and intervention group. Randomization was carried out between the two groups by using block randomization. After randomization, one group would receive the HA and the other group would receive the PRP treatment.

2.1 Data collection tools: An initial screening was carried out to assess the grading of osteoarthritis using Kellgren & Lawrence OA grading [8]. There are four grades for classification of Osteoarthritis:

Grade 0 – No Radiographic features of OA are present

Grade 1 – Doubtful joint space narrowing (JSN) and possible osteophytic lipping

Grade 2 – Definite osteophytes and positive JSN on anterio posterior weight bearing radiograph

Grade 3 – Multiple osteophytes, definite JSN, sclerosis, possible bony deformity

Grade 4 – Large osteophytes, marked JSN, severe sclerosis, definite bony deformity.

Participants who fell in grade I and II were included in the study. Following this grading, an interview schedule was used to collect the data in our study. It comprised of two components-

1. Questions relating to the background characteristics of the patient such as the age, gender, and side of the diseased knee joint.
2. Questions relating to the assessment of clinical and functional outcomes. This was performed using Visual Analog Scale score [9]: This tool was used as a self-assessment tool for pain with a score ranging from 0 – 10.

Interpretation of the score

0- No pain

1-3 – Low pain distress score

4-6 – Moderate pain distress score

7-10 – High pain distress score.

This score was measured for both HA and PRP groups prior to intervention. It was also measured on the 6th, 12th, and 24th week following intervention.

The Western Ontario and McMaster Universities Arthritis score (WOMAC) was also utilized [10]. This tool consists of evaluating pain, stiffness and physical function by rating over a scale of 5, where 0 is none and 4 is extremely difficult. The final score is computed by the formula: total score/ 96 (in %). This score was measured for both HA and PRP groups prior to intervention. It was also measured on the 6th, 12th, and 24th week following intervention.

2.2 Data collection

This study was carried out in the Orthopaedics Department of Vydehi Institute of Medical Sciences. This study was carried out as a single blind trial with two intervention groups, namely the HA and PRP groups. It was done as a randomized before and after comparative interventional study among a total of 60 participants, with 30 in each group. Any patient with clinical symptoms of osteoarthritis was screened based on inclusion and exclusion criteria. Patients with grade I or II Osteoarthritis based on Kellgren & Lawrence grading were taken up for the study. They were randomly allocated into either HA group or PRP group using block randomization technique. After obtaining informed consent, a structured interview schedule was administered to both the groups to obtain information on their background characteristics, clinical and functional outcome of Osteoarthritis using VAS and WOMAC tools. Following this, the intervention was done. The procedure for both the groups is given below:

2.2.1 HA group: The participant was made to lie down supine on the examination couch, with the affected knee flexed at the joint. The knee was scrubbed with Povidone-iodine solution. After this, 5 ml of Hyaluronic Acid was injected in either lateral or medial joint line. This was followed by performing active range of movement exercise on that knee joint. Same procedure is repeated after 1 week in the same knee.

2.2.2 PRP group: Initially, 30 ml of venous blood was drawn from the participant's median cubital vein. This was centrifuged at 2100 rotations for the first 9 minutes followed by 1500 rotations for the next 6 minutes. After this, the Plasma Rich Platelets were separated in a special container. The participant was made to lie down supine on the examination couch, with the affected knee flexed at the joint. The knee was scrubbed with Povidone-iodine solution. After this, 5 ml of Platelet Rich Plasma was injected in either lateral or medial joint line. This was followed by performing of active range of movement exercise on that knee joint.

The clinical and functional outcomes of the interventions were assessed at 6, 12, and 24 weeks after the procedure using VAS and WOMAC scores.

2.3 Statistical analysis

Data was entered in Microsoft Excel Spreadsheet. Statistical analysis was carried out using SPSS software ver.15. The background characteristics were expressed in percentages. Mean and SD were computed for VAS and WOMAC scores at different durations of assessment: prior to intervention and 6, 12, and 24 weeks after the intervention. Paired t test was used to compare the treatment outcomes at each period, for each group separately. Independent t test was used to compare the outcome mean scores between both the groups. Chi square test was used to compare the percentages of VAS scores between both the groups.

3. Results

This study was carried out among 60 participants, of which 30 were in HA group and 30 were in Platelet Rich Plasma (PRP) group. Table 1 shows the background particulars of the study population.

Table 1: Background particulars of the study participants

S. no	Particulars	HA group		PRP group	
		Frequency	Percentage	Frequency	Percentage
1.	**Age (in years)**				
	35-40	13	43.4	11	36.6
	40-45	7	23.3	7	23.3
	45-50	10	33.3	10	33.3
	50-55	0	0	2	0.06
2.	**Sex**				
	Male	14	46.7	18	60.0
	Female	16	53.3	12	40.0
3.	**Side of the limb**				
	Left	15	50.0	13	43.3
	Right	15	50.0	17	56.7
4.	**Grading of Osteoarthritis (Kellgren and Lawrence)**				
	Grade I	20	66.7	15	50.0
	Grade II	10	33.3	15	50.0

Table 2 shows the mean scores for VAS and WOMAC in HA group. The mean VAS score was 5.03±0.615 prior to intervention, while at 24th week it was 3.10±0.923. Similarly, prior to intervention, WOMAC score was 29.83±2.069 and the same at 24th week was 25.57±2.528.

Table 2: Mean scores of VAS and WOMAC for HA group

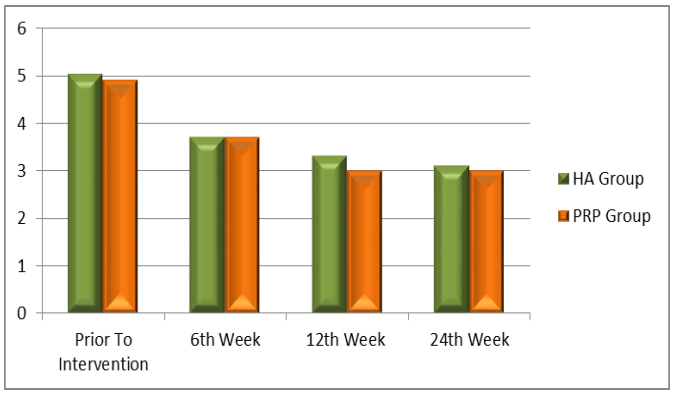
S. No	Duration	N	VAS		WOMAC	
			Mean	SD	Mean	SD
1.	Prior to intervention	30	5.03	0.615	29.83	2.069
2.	6th Week	30	3.70	1.119	27.67	2.090
3.	12th Week	30	3.33	.884	26.57	2.300
4.	24th Week	30	3.10	.923	25.57	2.528

Table 3 shows the mean scores for VAS and WOMAC in PRP group. The mean VAS score was 4.87±0.860 prior to intervention, while at 24th week it was 3.00±0.643. Similarly, prior to intervention, WOMAC score was 31.67±2.963 and the same at 24th week was 23.63±1.217.

Table 3: Mean Scores of VAS and WOMAC for PRP Group

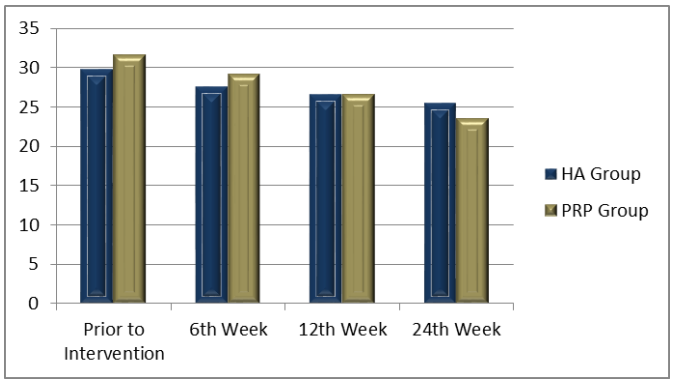
S. No	Duration	N	VAS		WOMAC	
			Mean	SD	Mean	SD
1.	Prior to intervention	30	4.87	0.860	31.67	2.963
2.	6th Week	30	3.70	.651	29.23	2.223
3.	12th Week	30	3.00	.830	26.77	1.960
4.	24th Week	30	3.00	.643	23.63	1.217

Graph 1 shows the comparison between the mean VAS scores between the HA & PRP group,



Graph 1: Comparison of Mean VAS Scores Between HA & PRP Group

Graph 2 shows the comparison of the mean WOMAC scores between the HA group and PRP group.



Graph 2: Comparison of Mean WOMAC Scores Between HA Group and PRP Group

The VAS Score was graded as high (7-10), moderate (4-6) and low (1-3). The score for HA group is given in table 4. It was found that prior to the intervention, 100% of the study population belonged to moderate score, while at the 24th week, 80% of the study population have progressed to low score, which shows the effect of treatment.

Table 4: Percentage of scores for VAS for HA group

S. No	Duration of intervention	High		Moderate		Low	
		N	%	N	%	N	%
1.	Prior to intervention	0	0	30	100	0	0
2.	6th week	0	0	17	56.7	13	43.3
3.	12th week	0	0	14	46.7	16	53.3
4.	24th week	0	0	6	20.0	24	80.0

The VAS Score for PRP group is given in table 5. It was found that prior to the intervention, 93.3% of the study population belonged to moderate score, while at the 24th week, 80% of the study population have progressed to low score, which shows the effect of treatment.

Table 5: Percentage of scores for VAS for PRP group

S. No	Duration of intervention	High		Moderate		Low	
		N	%	N	%	N	%
1.	Prior to intervention	0	0	28	93.3	2	6.7
2.	6th week	0	0	18	60.0	12	40.0
3.	12th week	0	0	8	26.7	22	73.3
4.	24th week	0	0	6	20.0	24	80.0

The mean WOMAC scores between prior and post intervention in HA group were compared in table 6. There was a significant difference in the means as the duration increased. A statistically significant difference was seen between prior to the intervention and at 6th week (t=4.563, p<0.0005), 12th week (t=6; p<0.0005) and 24th week (t=6.579; p<0.0005).

Table 6: Comparison of means for HA group between pre and post intervention for WOMAC

S. No	Factor	Mean Difference	Standard Error	t value	95% CI		p value
					lower	Upper	
1.	Prior to intervention Vs. 6th week	2.167	.475	4.563	1.195	3.138	.0001
2.	Prior to intervention Vs. 12th Week	3.267	.544	6.000	2.153	4.380	.0001
3.	Prior to intervention Vs. 24th week	4.267	.648	6.579	2.940	5.593	.0001

The mean WOMAC scores between pre and post intervention in PRP group were compared in table 7. There was a significant difference in the means as the duration increased. A statistically significant difference was seen between prior to the intervention and at 6th week (t=10.656, p<0.0005), 12th week (t=13.266; p<0.0005) and 24th week (t=19.680; p<0.0005).

Table 7: Comparison of means for PRP group between pre and post intervention for WOMAC

S. No	Factor	Mean Difference	Standard Error	t value	95% CI		p value
					lower	Upper	
1.	Prior to intervention Vs. 6th week	2.433	.228	10.656	1.966	2.900	0.001
2.	Prior to intervention Vs. 12th Week	4.900	.369	13.266	4.145	5.655	0.001
3.	Prior to intervention Vs. 24th week	8.033	.408	19.680	7.198	8.868	0.001

The comparison between the WOMAC and VA scores between the HA and PRP group is shown in table 8. It was observed that the mean difference scores between PRP and HA group is statistically significant for WOMAC score (p<0.01).

Table 8: Comparison of difference in scores over the period of intervention for WOMAC score and VA Score between HA group and PRP group

S. No	Factor	Mean Difference	Standard Error	t value	95% CI		p value
					Lower	Upper	
1.	WOMAC	1.81	0.55	3.3	0.6	3.01	0.006
2.	VAS	-0.73	0.42	-1.74	-1.6	0.2	0.113

4. Discussion

This study was carried out as a comparative study between HA and PRP. In our study, majority of the study population belonged to 35-40 years of age. In most of the other studies conducted, the mean age of the participants was over 50 years. Females were higher in HA group (53.3%) while males were higher in PRP group (60%). Prior to intervention the mean VAS scores were 5.03± 0.615 and WOMAC scores were 29.83± 0.06. In a study done by Sandeep Patel the mean VAS score was 4.6 ±0.62, which was comparable with our study, while the WOMAC score was 45.5 ± 17.3[11]. There was a significant reduction in WOMAC scores at the end of 24th week for HA group with a mean difference of 4.27 (p= 0.0001) and PRP group's difference at the end of the 24th

week being 8.03 (p = 0.001). There was a significant reduction in VAS scores at 6th week with mean difference 1.33 (p=0.0001), at 12th week with mean difference of 1.7 (p=0.0001), and at the end of 24th week for HA group with a mean difference of 1.933 (p= 0.0001). For the PRP group, the mean difference was statistically significant (p<0.001). In our study it was evident that as the duration increased the mean difference rose higher for PRP group in comparison to the HA group, which proves the long term efficacy of a single administration of PRP.

Our study showed a significant difference in WOMAC scores, when a comparison is made between both the groups, concluding that PRP is better than HA (p = 0.006). There are very few studies which have compared both the interventions in a single trial. As far as VAS score is concerned, our study did not show conclusive results. As the PRP injection was a day procedure, hospital admission was not required for patients. Patients were allowed to carry out their day to day activities post procedure.

5. Conclusion

This study has highlighted the advantages of using PRP over HA in the treatment of OA knee through a randomized prospective trial. The benefits are witnessed with a remarkable improvement in WOMAC scores, and moreover, the effect of the intervention has been documented even at the 24th week. This study has focused on the key benefits of PRP in reducing the physical, social and economic burden of OA knee.

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