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A comparative study between intraarticular infiltration of platelet rich plasma and hyaluronic acid in osteoarthritis knee

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ABSTRACT

Background: Osteoarthritis (OA) is the most common progressive musculoskeletal condition that can affect joints, but it mainly affects the hips and knees as predominant weight-bearing joints and is characterized by structural modifications to primarily articular cartilage and subchondral bone, Hoffa's fat pad, synovia, ligaments and muscles, leading to the concept of OA as a whole joint disease. Hence the present study was undertaken to evaluate the outcomes of platelet rich plasma (PRP) and hyaluronic acid (HA) intra-articular injections in patients with OA in terms of pain by numerical pain score and VAS and to evaluate the outcomes of PRP and HA intra-articular injections in patients with OA in terms of functional outcome by WOMAC scores.
Methods: The study was a prospective hospital-based study in Kempegowda Institute of Medical Sciences between 2020 to 2022. The study was conducted on 100 patients, more than the age of 50 years of either gender with grade I-III OA of the knee fulfilling the inclusion and exclusion criteria. Patients were followed up at 6, 12 and 24 weeks for data collection and data was analyzed after follow-up visits were completed for all patients.
Results: On intragroup analysis, there was significant reduction in the mean WOMAC score in both the study groups across time-points ($p<0.05$). On intragroup analysis, there was significant reduction in the mean VAS score in both the study groups across time-points ($p<0.05$). On intergroup analysis at any time point of follow-up, the mean WOMAC score was noted to be statistically comparable between the study groups ($p>0.05$).
Conclusions: In patients with symptomatic knee OA, intra-articular HA and PRP provide short term improvement in pain and function. Both the therapy agents for OA were associated with equivalent safety, with no complications.

Keywords: WOMAC, OA, PRP, HA

INTRODUCTION

Osteoarthritis (OA) is a degenerative condition of the joints which is currently one of the most important causes of disability in the adult population globally.[1] Worldwide, OA is the eighth most common cause of being physically impaired, with the knee being the commonest affected joint.[2] In India, OA is the second commonest rheumatological disorder, with a prevalence rate mentioned in published scientific evidence to be anywhere between 22% and 39%.[3] According to reports published by the planning commission on disease burden (2011), OA contributed for half of all chronic disorders in the aged population (>65 years).[4]

OA is gradually progressing disease, which can cause clinical features ranging from mild to disabling. OA is a common cause of knee pain mainly in the elderly population. It is characterized by loss of articular cartilage, joint deterioration, subchondral sclerosis, and formation of osteophytes.[5] The current management protocol for knee OA consists of conservative management with the help of exercise, physiotherapy, pharmacological agents as well as, in a few cases, surgical treatment with the help of knee arthroplasty.[6] While several of the commonly used

conservative management option have been recognized to be efficient and successful, there is still inadequate evidence obtainable. Among the pharmacological alternatives for knee OA, oral non-steroidal anti-inflammatory drugs (NSAIDs) act quickly and are suggested for the treatment of OA, though repeated and severe adverse effects of NSAIDs have been identified.[7] Notwithstanding the growing burden of this disabling condition, there is no recognized disease-modifying treatment available till date.[8]

The normal adult knee includes nearly 3.0 mL of synovial fluid (SF), with a concentration of HA between 2.5 to 4.0 mg/ml.[9] In an osteoarthritic knee, the concentration as well as the molecular weight of HA are reduced by 33% to 50%, leading to lower shock absorption, lubrication as well as joint protection.[10] HA, administered as intra-articular injections may supplement the regenerative effects of endogenous HA on the articular cartilage, reinstate the viscoelasticity of synovial fluid, stimulate the production of endogenous HA as well as other components of the extracellular matrix by synoviocytes, thereby preventing the breakdown of proteoglycans as well as extracellular matrix collagen fibers. HA also promotes chondrocyte metabolism and thereby leads to prevention of its apoptosis; it also inhibits chondral breakdown and inflammation in the joint.[11] These effects are credited to not only the HA's capability to decrease OA-related clinical features, but also to its meddling in the advancement of inflammatory responses as well as degeneration of joint.[12]

HA injections are, however, expensive and synthetically manufactured and have shown inconsistent effects on inflammation.[13] Despite the lack of clear recommendations for PRP, encouraging outcomes reported by preliminary clinical evidence and the unfavorable qualities of HA have led many clinicians to adopt PRP as an effective form of treatment for degenerative knee OA.[14] PRP involves modulation of the intra-articular environment by introducing autologous blood products in the joint, which can lead to reduced inflammatory distress and promote chondrogenesis. The strategy of administering PRP stems from biochemical research on anabolic growth factors, such as transforming growth factor b (TGF-b), insulin-like growth factor 1 (IGF-1), bone morphogenetic proteins (BMPs), and platelet-derived growth factor (PDGF), and their role in inhibiting inflammation and pain as well as enhancing the biosynthesis of cartilage and the bone matrix.[15,16] In contrast, catabolic factors such as tumor necrosis factor α (TNF-α) and interleukin (IL)-1, IL-1b, and IL-6 are pro-inflammatory and have nociceptive properties, which are postulated to be inhibited by PRP.[17]

Literature search has revealed that there is published evidence to back the effectiveness of intra-articular injection of HA as well as PRP in OA patients. However, the comparative studies, especially in the Indian setting evaluating HA and PRP in OA cases are lacking. Hence, to add to the current evidence for HA as well as PRP in OA in an Indian setting, we decided to evaluate and compare the effects of intra-articular HA injection with PRP injection in symptomatic knee osteoarthritis. This study will help in solving an important research question and help in creating valuable Indian evidence in relation to the topic.

Objectives

Objectives of the study were to evaluate the outcomes of PRP and HA intra-articular injections in patients with OA in terms of pain by numerical pain score and visual analogue scale (VAS) and to evaluate the outcomes of PRP and HA intra-articular injections in patients with OA in terms of Functional outcome by Western Ontario and McMaster universities arthritis index (WOMAC) scores (WOMAC pain, function, stiffness, and total scores).

METHODS

Study design

Study design was of prospective study.

Study duration

Study conducted for 18 months (April 2021 to October 2022).

Study area

Department of orthopedics at Kempegowda Institute of Medical Sciences and Research Centre, Bangalore.

Study participants

Adults more than the age of 50 years of either gender with confirmed grade I-III OA of the knee attending the department of orthopedics at Kempegowda Institute Of Medical Sciences And Research Centre, Bangalore.

Inclusion criteria

Patients of age 50 years and above, patients of either gender, patients with radiographic assessment revealing confirmed grade I-III OA of knee, patients having minimum three months' duration of symptoms, patients undergone conservative treatment for a minimum period of three months. Patients should experience pain restricting his or her daily activity. Patient should not have a local steroid injection in last 2 months and patients who are ready to sign the informed consent and ready to come for regular follow-up were included in the study.

Exclusion criteria

Patients suffering from inflammatory arthritis, patients affected by infective arthritis or rheumatoid arthritis, patients suffering from grade IV OA knee, patients diagnosed with seronegative spondyloarthritis, patients

administered intra-articular corticosteroid in studied knee within prior 3 months, patients suffering from known hypersensitivity to HA or PRP, patients suffering from venous or lymphatic stasis in the limb to be injected and patients having skin disease or infections in the area of injection site were excluded.

Estimation of sample size

The Sample size estimation was done using the following formula:

$d=\mu 2-\mu 1/\sigma$

$Z\alpha/2-1.96$ [For an alpha level of 5%, $\alpha=0.05$].

$Z1-\beta-0.84$ [For power of the study at 80%, $1-\beta=0.80$].

d -is effect size or Cohen's d [d=0.60, a difference of 60% in the postoperative outcomes (WOMAC scores) among the study group to yield a statistically significant result].

r= ratio of patients in group 2/group 1=1.

n=45 per group and considering a 10% loss-to-follow-up proportion, the sample size per group will come to around 50.

The total sample size for the present study will be 100 (50 patients per group).

Data collection

The study was initiated after getting permission from the institutional ethics committee. The study was conducted on 100 patients who were adults more than the age of 50 years of either gender with confirmed grade I-III OA of the knee, at the tertiary health care study center, fulfilling all the inclusion and exclusion criteria of the study. Only the patients who fulfilled all the screening criteria were included. The patients were enrolled in the study only after written informed consent was signed by them. After enrolment of the patients in the study, detailed history and physical examination findings were recorded. Clinical features of the patients were also assessed properly and noted.

Pre-preparation

All patients underwent a 10-ml blood draw for the PRP preparation and a 3-ml peripheral blood draw for a complete blood count with a leukocyte differential. This was performed on patients who received HA to maintain patient blinding and to characterize the peripheral WBCs and platelet counts. A complete blood count was performed on PRP before injections to evaluate the fold increase in platelet concentrations and to confirm the rarity of red and white blood cells.

Intra-articular injection and administration of HA and PRP

Intra-articular injections were performed under sterile conditions; the aseptic technique was followed to avoid joint infection. The procedure was usually performed in an outpatient setting, with the patient lying supine with the knee in full extension. Joint injections were delivered into the joint space. Multiple approaches have been described for knee injection, with studies reporting that the superolateral injection site is the most consistently reliable site for reaching the synovial joint space of the knee. Subcutaneous local anesthetic was also administered. The injection technique involved insertion of an 18-gauge needle at an angle of 45 degrees directed toward the center of the knee joint. Patients were advised to avoid strenuous or prolonged weight-bearing activities for approximately 48 hours after treatment. Patients were followed up at 6 weeks, 12 weeks and 24 weeks for data collection and VAS and WOMAC was analyzed after complete follow-up visits were completed for all patients.

Statistical analysis

The data was collected and compiled in MS Excel. Descriptive statistics has been used to present the data. To analyse the data SPSS (Version 26.0) was used. Significance level was fixed as 5% ($\alpha=0.05$). Qualitative variables are expressed as frequency and percentages and quantitative variables are expressed as mean and standard deviation. To compare the proportion between groups, chi-square test was used. To compare the mean values between groups, student t test and ANOVA was used.

RESULTS

A total of 100 patients were enrolled in study, 50 in HA group and 50 in PRP group. Majority of the patients in both the study groups were between 51-60 years. The mean age and the gender distribution were noted to be statistically comparable between study groups (p>0.05). Majority of patients in both the study groups were females.

Table 1: Demographic details

Demographic details		Group (n=50) (%)		P value
		HA group	PRP group	
Age group (years)	51-60	27 (54)	29 (58)	0.32
	61-70	16 (32)	16 (32)	
	71-80	6 (12)	4 (8)	
	>80	1 (2)	1 (2)	
	Mean± SD	61.08± 8.22	60± 7.66	
Gender	Males	22 (44)	13 (26)	0.09
	Females	28 (56)	37 (74)	

Mean height, mean weight and mean BMI were noted to be statistically comparable between study groups (p>0.05).

Table 2: Anthropometric parameters.

Anthropometric measurements	Groups (n=50)		P value
	HA	PRP	
Height (cm)	163.86± 9.91	163.44± 9.36	0.62^
Weight (kg)	73.48± 12.4	73.98± 7.07	0.71^
BMI (kg/m^2)	27.17± 3.08	27.73± 2.18	0.48^

Table 3: OA grading distribution in study groups.

OA grading	Groups (n=50) (%)		P value
	HA	PRP	
Grade 1	12 (24)	14 (28)	0.363
Grade 2	31 (62)	28 (56)	
Grade 3	7 (14)	8 (16)	

Majority of the patients in both study groups were noted to be suffering from grade 2 OA, followed by grade 1 and 3.

Table 4: Mean WOMAC score at various time-points in study groups.

WOMAC score	Groups (n=50)		P value (inter-group)
	HA	PRP	
Baseline	33.8±2.07	33.96±2.32	0.55
6 weeks	31.62±2.09	31.6±2.43	0.68
12 weeks	30.28±1.9	29.4±2.1	0.43
24 weeks	27.98±2.28	26.6±2.22	0.39
P value (intra-group)	0.01*	0.01*	

On intragroup analysis, there was significant reduction in the mean WOMAC score in both the study groups across time-points ($p<0.05$). On intergroup analysis at any particular time point of follow-up, the mean WOMAC score was noted to be statistically comparable ($p>0.05$).

Table 5: VAS score at various time-points in study groups.

VAS score	Groups (n=50)		P value (inter-group)
	HA	PRP	
Baseline	5.92±0.85	6.08±0.8	0.25^
6 weeks	5±0.81	5.08±0.7	0.58^
12 weeks	4.44±0.86	4.28±0.76	0.4^
24 weeks	3.42±1.01	3.28±0.73	0.28^
P value (intra-group)	0.01*	0.01*	

On intragroup analysis, there was significant reduction in the mean VAS score in both the study groups across time-points ($p<0.05$). On intergroup analysis at any particular time point of follow-up, the mean VAS score was noted to be statistically comparable ($p>0.05$).

DISCUSSION

Knee OA is a very common chronic degenerative disease, and its characterized by varying degrees of cartilage degeneration, cartilage exfoliation, and subchondral bone hyperplasia.[18] In addition, the degeneration of cartilage is mainly manifested with pain, stiffness, swelling, restriction of joint motion.[19] Moreover, this disease has a significantly impact on patient's quality of life and loss of function, and it has become the most common public health issue in the elderly.[20] According to the OA Society International, non-surgical treatment rather than surgery as the first recommendation therapeutics for knee OA. Non-surgical treatment includes oral anti-inflammatory drugs, exercise, physical therapy, and intraarticular injections, depending on the severity and compliance of articular cartilage.[21] The relevant literatures report that it can relieve pain symptoms and improve joint function in patients with knee OA, which emphasizes the importance of conservative therapeutics in the treatment of knee OA.[22,23] Although the above non-surgical therapies are beneficial to a certain degree of arthritis, there are no non-surgical or surgical interventions proven to alter the process of degenerative joint.[24] In recent years, platelet-rich plasma (PRP) or HA are the most extensive applications for intra-articular injection in alleviating pain and improving function.[25] HA, a high-molecular weight glucosamine, is generated by chondrocytes, synoviocytes, and fibroblasts and responsible for the viscoelasticity and lubrication of the knee joint. It is shown that HA concentrations in osteoarthritic knees have been reduced. Increasing evidence have demonstrated that HA is able to improve joint function, relieve pain, and reduce the dosage of analgesics.[26] Intra-articular HA had been recommended in the management of patients with knee OA by the American college of rheumatology (ACR).[27] PRP is described as an autologous blood product, including multiple growth factors and concentration of platelets. It had been used to treat different degeneration diseases, which included the bone, cartilage, and soft tissues injury. PRP contains various growth factors and other bioactive molecules, which may regulate the aberrant inflammatory processes, regenerate tissue structures, and thus promote tissue healing.[28] Literature search revealed that though there is some evidence from foreign countries which have compared HA and PRP in managing knee OA, such studies are scarce in Indian population. Present study tried to fulfil this need gap, at an Indian tertiary care teaching hospital.

The study population was composed of adults more than the age of 50 years of either gender with confirmed grade I-III OA of the knee, at a tertiary health care study centre. To maintain uniformity across the study groups, patients having minimum three months' duration of symptoms and undergone conservative treatment for a minimum period of three months were included. The patients included in

study experienced pain restricting his or her daily activity. Standardized outcome measures like pain VAS score and WOMAC score were used to assess the impact of PRP and HA. Both the key parameters were evaluated on the day of intra-articular injection, followed by evaluation at 6 weeks, 12 weeks, and 24 weeks' post-injection.

Demographic and baseline details in study groups

A total of 100 patients were enrolled in study, 50 in HA group and 50 in PRP group. The mean age and the gender distribution were noted to be statistically comparable between study groups ($p>0.05$). Majority of patients in both the study groups were females. 56% of cases in HA group and 74% in the PRP group were females respectively. Majority of the patients in both the study groups were between 51-60 years (54% in HA group and 58% in PRP group). Majority of the patients in both study groups were noted to be suffering from grade 2 OA (62% in HA group and 56% in PRP group), followed by grade 1 and grade 3. The mean age was similar in present study versus other similar studies. All studies had female predilection as noted in our present study. Most of the other similar studies which mentioned OA grading showed grade II being most common representation, as noted in our study.

Total WOMAC score and VAS score in study groups

On intragroup analysis, there was significant reduction in the mean WOMAC as well as VAS pain score in both the study groups across time-points ($p<0.05$). This indicates that over the time-points of assessment till 6 months, both the study groups showed improvement which was significant versus the baseline. Hence, both HA and PRP administration led to improvement in knee OA, with respect to WOMAC score and pain VAS score. On intergroup analysis at any time point of follow-up, the mean WOMAC score, and pain VAS score were noted to be statistically comparable ($p>0.05$). This showed that both HA and PRP were statistically identical in their effect on knee OA in terms of both, total WOMAC score and pain VAS score.

In the similar study by Li et al significant differences in IKDC score and WOMAC score, between pre- and post-injection in PRP and HA groups ($p<0.05$) was noted; however no significant difference was found between different time points (3, 4, and 6 months) ($p>0.05$), while significant differences were found between the postoperative 6th month and the postoperative 3rd and 4th months in control group ($p<0.05$).[33]

In the study by Cerza et al at 1 month follow up, both groups showed a significant reduction in the overall WOMAC score compared with baseline in both groups ($p<0.05$).[29] The mean WOMAC score was 49.6 (range, 5-80; SD, 617.7) in the ACP group versus 55.2 (range, 25-78; SD, 612.3) in the HA group. At week 12, a reverse trend was observed, with a continuous improvement in the patients treated with PRP and a slight worsening in patients treated with HA. At week 24, the subjects treated with PRP showed a continuous improvement, whereas the subjects treated with HA showed worsening. In both groups, the score was significantly better than baseline at week 24. In this study, though knee functions improved based on WOMAC score in both study groups, the improvement was better with PRP.

In the study by Cole et al the WOMAC pain score was compared between the PRP group and the HA group at 6 weeks, 12 weeks, 24 weeks just like our study.[30] The outcome measure was not found to be significant between the PRP as well as HA groups at any time point ($p>0.05$). This finding was identical to that noted in our present study.

In the study by Duymus et al significant decreases were determined in the VAS and WOMAC scores within each group at 1-month and 3-months follow-up, as noted in our study.[25] When the VAS scores and total WOMAC scores were compared between the groups, no significant differences were observed between the HA and PRP groups ($p>0.05$). At 6-month as well as 12-month follow-up, in the PRP and HA groups, although there were slight change in the scores compared to the initial values, the clinical effect continued and there were no statistically significant differences. All these findings were again, in-sync with our present study findings.

In the study by Su et al the WOMAC score was noted to be significantly reduced in the PRP and the HA groups at follow up.[31] Both the intra-articular PRP and HA study groups, differed at the 1st, 3rd, 6th, and 12th months; however, no significant difference was observed. The VAS scores were similar in the study groups till the 6th month, while at 12-month follow up the HA group showed higher VAS score versus intra-articular PRP group. However, the intra-osseous injection of PRP was noted to be better than HA and intra-articular PRP injections for knee OA in study.

In the study by Huang et al the mean WOMAC scores were noted to be statistically comparable between HA group and PRP group till 3 months of follow-up.[32] However, at 6-month and 12-month follow-up, the mean WOMAC scores were noted to be significantly lower in PRP group versus HA group ($p<0.05$). This showed that though early follow-up revealed similar effects of HA and PRP like our study, the long-term effect may be better in PRP group. The change in pain VAS score was significant in both HA and PRP study groups, and the difference in change was similar in both study groups like our study.

The study had a few limitations. The sample size was small and hence, the generalization of study results for whole Indian population should be done with caution. Additionally, effects of HA and PRP on long term outcomes was not evaluated in present study.

CONCLUSION

In patients with symptomatic knee OA, intra-articular HA and PRP provide short-term improvement in pain as well as function. There was no statistically significant difference noted in the effects of HA and PRP, which was in-line with majority of published evidence. Both the therapy agents for OA were associated with equivalent safety, with none of the two associated with complications. Future Indian studies with a larger sample size and multi-center study design will be needed to validate our study findings.

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