Original Article

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Exploring the Superior Efficacy of Hyaluronic Acid and Platelet-Rich Plasma Co-Administration Over Hyaluronic Acid Alone in Pain Reduction and Functional Status Improvement of Knee Osteoarthritis Patients

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ABSTRACT

Objective: To determine whether concurrent injection of hyaluronic acid (HA) with platelet-rich plasma (PRP) would enhance therapeutic effectiveness compared to HA alone in the management of knee osteoarthritis (OA) over a 12-month follow-up.

Methodology: A prospective, comparative study was conducted in department of orthopedic Nawaz Sharif Medical College / Aziz Bhatti Shahed Hospital Gujrat from Jan 2023 to Dec 2023 on 100 patients with knee OA (Kellgren-Lawrence grades I-III). The patients were divided into two groups: Group 1, consisting of 50 patients, received intra-articular HA injections, while Group 2, comprising the remaining 50 patients, received a combination of HA and PRP. Pain and functional outcomes were assessed using the Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at baseline, and at 2, 6, and 12-months post-injection.

Results: Assessments at baseline, 2 months, 6 months, and 12 months post-injection revealed significant improvement in both groups compared to baseline. However, patients in Group 2 (HA+PRP) showed significantly greater improvement than those in Group 1 (HA alone), with WOMAC scores at 2-, 6-, and 12-months yielding p-values of 0.001*, 0.001*, and 0.000*, respectively.

Conclusions: The study concluded that the combination of PRP and HA is more effective than HA alone in reducing pain and improving joint function in patients with knee OA. The findings suggest that PRP+HA offers superior benefits for managing knee osteoarthritis compared to HA alone.

Keywords: Platelet Rich Plasma, knee osteoarthritis, hyaluronic acid, WOMAC, VAS.

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Introduction

Joint space reduction and degradation of the knee cartilage are the hallmarks of knee osteoarthritis. Osteoarthritis (OA) most commonly affects the knee. About 6%,of the adults suffer from this disease and among those over 70, it can reach up to 40%.[1, 2] It has been determined that the foremost cause of knee discomfort along with the slow damage of joint function is knee arthritis. Pain, tenderness, stiffness, inflammation, and a decrease in range of motion inside and around the injured joint are among the main symptoms of osteoarthritis (OA).[2, 3]

The major management strategy for Knee OA, as mentioned by the Osteoarthritis Research Society International (OARSI), emphasizes the necessity of conservative therapy in addressing the illness.[4, 5]The American College of Rheumatology (ACR) has introduced a classification that includes both pharmacologic and non-pharmacologic treatments under conservative treatment options.[5, 6]

Many therapeutic approaches, including nonpharmacological, pharmacological, and surgical treatments, have been proposed for the treatment of Knee OA.[1] Nonpharmacologic therapies include food restriction, exercise, and weight loss. These are difficult to manage and may depend significantly on patient's cooperation. On the other hand, prolonged use of pharmacologic treatments, such as non-steroidal anti-inflammatory medications and basic analgesics, is connected to poor effects. Oral glucosamine, chondroitin, acetaminophen, celecoxib, and glucosamine are the mainstays of pharmacological therapy for Knee OA associated with adverse outcomes.[5, 7, 8] Consequently, in order to stop the progression of OA and lowering the need for surgical procedure, which would minimize disability and costs, it is imperative to investigate alternative therapeutic methods that are appropriate for long-term usage.[9, 10]

For the treatment of Knee OA, clinicians are now using intra-articular injections of hyaluronic acid (HA) and platelet-rich plasma (PRP), either alone or in combination.[7,11] Guidelines supported platelet-rich plasma (PRP) as an alternate injection for Knee OA, as the concept of regenerative therapy.[12]

The elasticity and viscosity of synovial fluid is caused by hyaluronic acid (HA). HA also acts as a shock absorber and it is a naturally occurring polysaccharide in the fluid. Composed of lengthy repeating disaccharides of glucuronic acid and N-acetylglucosamine, it is a big glycosaminoglycan. Because viscous supplementation with intraarticular HA which protect articular cartilage, is generally considered a successful therapy for Knee Osteoarthritis, improving pain and function.[5, 11, 13, 14]

Platelet-Rich Plasma (PRP) is a concentration of platelets and plasma proteins generated from a patient's own blood that is used to treat a range of diseases, including osteoarthritis, by providing high doses of platelet-associated growth factors and biologically active substances. The bulk of platelet-rich plasma (PRP), an autologous blood product, is composed of concentrated platelets and growth factors. Growth factors perform multiple functions such as inducing healthy neighboring cells to produce additional growth factors, drawing local stem cells and fibroblasts to damaged regions, blocking cytokines and catabolic enzymes, reducing inflammation, and encouraging local angiogenesis. Furthermore, it has been shown that PRP increases endogenous HA synthesis. Based on current studies, PRP may be used to address irregularities in the cartilage, reduce symptoms of osteoarthritis, and improve joint function while maintaining a reasonable level of safety and positive outcomes.[1, 2, 11, 14, 15]

PRP+HA therapy has been used more often as a Knee OA therapy in the last few years. A number of studies have proposed that PRP+HA therapy might have a synergistic effect, reducing pain, improving joint function, and delaying the advancement of Knee OA. PRP and HA may work in collaboration to improve joint healing through several processes, which makes their combination beneficial without changing the essential qualities of each substance.[5] This approach is based on the fact combining these two therapies may prove to be more advantageous than utilizing them alone.[1, 2, 3] This study's main goal was to ascertain if injecting HA concurrently with PRP would increase therapy effectiveness in comparison to PRP alone in the management of problematic Knee OA with a long-term follow up of 12 months.

Methodology

A prospective, comparative study was conducted in department of orthopedic Nawaz Sharif Medical College / Aziz Bhatti Shahed Hospital Gujrat from Jan 2023 To Dec 2023 on 100 patients with knee OA (Kellgren-Lawrence grades I-III). Hyaluronic acid (HA) alone was injected in knee joints of 50 patients (group 1) while other fifty patients were treated with Platelet Rich Plasma plus Hyaluronic acid (PRP+HA) intra-articular knee injection (group 2). The internal review board and hospital's ethics committee had approved prospective comparative study of this clinical experimentation. Consent Performa was taken from all patients.

Patients with history of knee pain or swelling not improving with medications and physiotherapy for at least 4 months were advised plain Radiographs of Knee joint. The plain radiographs were done to determine the OA grade on the basis of Kellgren-Lawrence grading scale. The patients who showed presence of degenerative changes in the joint radiographs were included in study

group. Kellgren-Lawrence grade 1,2 and 3 were included in study whereas Kellgren-Lawrence grade 0 and 4 patients were excluded from the study. The Exclusion criteria also considered systemic illness such as rheumatoid arthritis, diabetes mellitus and severe cardiovascular diseases, bleeding disorders (coagulopathies), infections, patients receiving immunosuppressive drugs or anticoagulants. Those patients that have hemoglobin (g/dl) values of less than 10 and platelet less than 100,000/mm3 were also excluded from study. Based on these criteria they were randomly divided into a PRP/ HA group or a HA group.

Mixture is prepared by adding 4 ml of autologous venous blood in a closed tube that contains 2ml of natural, non-cross linked, thixotropic cell-separation gel and the sodium citrate anticoagulant solution at a concentration of 20 mg/ml (40 mg total). One step closed system centrifugation of this mixture at 3100 rpm for 5 minutes is used to separate erythrocytes and produce 6 ml of PRP-HA mixture. Under complete aseptic measures infiltration was performed using the 4 ml of PRP-HA mixture using a 22-gauge needle inserted through lateral approach. At the end of the procedure, active and passive movement of the knee was done a few times to evenly distribute mixture over articular surface. This process was repeated 3 times with 3 weeks interval.

Prior to treatment and at follow-up visits after two, six, and twelve months, patients were evaluated using the WOMAC and VAS score. After the treatment with IA injections, patients were given instructions on limiting the excessive walking and to avoid use of pain killers or any other anti-inflammatory medication. Rather, patients were encouraged to use cold therapy for pain, patients were initially allowed mild activities and a gradual resumption of normal daily routine activities subsequently as tolerated by patients. Adverse events and patient satisfaction in terms of pain management and improvement in function were noted.

SPSS 24 was used for statistical analysis of the collected data. Mean and SD with 95% confidence interval was used to compare two groups using WOMAC and VAS scores. Appropriate tests of significance were used according to the type of data and a P value less than 0.05 were considered statistically significant.

Results

Hundred patients were included in this study. They were between 45 to 75 years (Mean± SD 59.34± 6.81). Male to female ratio was 2:3. Regarding occupation; 55 patients were Unemployed, 25 employed and 20 retired patients. Table I shows data distribution among the two groups with statistically non-significant differences between them as regard of age, sex, occupation and disease degree.

Table I: Distribution of patients according to age, sex, type of OA and occupation.

	CM-PRP-HA	HA	(P value)
Gender			
Male	24(48%)	17(34%)	0.222
Female	26(52%)	33(66%)	
Age/year			
Minimum	46	45	0.113
Max	75	73	
Mean ± SD	58.26±7.131	60.42±6.36	
Type			
Mild	25(50.0%)	23(46.0%)	0.814
Moderate	25(50.0%)	27(54.0%)	
Occupations			
Employed	15 (30%)	10(20 %)	0.355
Unemployed	24(48 %)	31(62.0%)	0.227
Retired	11(22%)	9(18.0%)	0.803

Distribution of patients according to type and symptom of OA: pain was the most frequent complain (38/100), followed by joint stiffness (22/100) and effusion (19/100) and combined symptoms (21/100). Mild OA compromised (48/100), while moderate OA was (52/100).

Basal, 2 months, 6 months and 12 months assessment after intra articular injection of HA and PRP+HA was compared in table II and III. At each follow up visit, both groups demonstrated very remarkable improvement when compared to the basal assessment and same results were observed at 12 month follow up. VAS and WOMAC scores were calculated and compared in both groups.

Table II: WOMAC Scores of Groups Mean±SD (95% CI) basal, 2months,6 months and 12 months follow ups.

Groups		Basal	Post Treatment		
			02 Months	06 Months	12 Months
Group 1	Mean±SD	64.40±7.58	56.16±7.04	56.20±6.74	59.88±7.58
(Hyaluronic Acid)	Confidence Intervals	(62.24 – 66.56)	(54.16 – 58.16)	(54.28 – 58.12)	(57.72 – 62.04)
Group 2	Mean±SD	66.16±6.75	50.72±8.24	51.16±7.87	53.88±8.19
(Hyaluronic Acid + PRP)	Confidence Intervals	(64.24 – 68.08)	(48.38 – 53.06)	(48.92 – 53.40)	(51.55 – 56.21)
F value(between groups)		1.501	12.577	11.807	14.434
p (between groups)		0.223**	0.001*	0.001*	0.000*

Table III: VAS Scores of Groups Mean±SD (95% CI) basal, 2months,6 months and 12 months follow ups.

Groups		Pre-Treatment	Post Treatment		
			2 months	6 months	12 months
Group 1 (Hyaluronic Acid)	Mean±SD	6.92±1.10	5.36±0.94	5.40±1.06	6.12±1.18
	Confidence Intervals	(6.61 – 7.23)	(5.09 – 5.63)	(5.10 – 5.70)	(5.78 – 6.46)
Group 2 (Hyaluronic Acid + PRP)	Mean±SD	6.96±0.96	4.72±0.78	4.84±0.93	5.12±1.03
	Confidence Intervals	(6.68 – 7.24)	(4.50 – 4.94)	(4.57 – 5.11)	(4.83 – 5.41)
F value (between groups)		0.037	13.635	7.783	20.665
p (between groups)		0.848**	0.000*	0.006*	0.000*

However, group that was treated with combination of PRP+HA mixture showed more significant improvement as compared to HA alone.

There was significant improvement in group 2 patients receiving intra articular injection of PRP and HA when compared with group 1 receiving HA alone ($p< 0.05$) when compared after 2 months, 6 months and 12 months.

Both the group showed improvement in VAS score which is depicted by a decrease in pain threshold after receiving intra articular injections however patients in group 2 who received treatment of Hyaluronic Acid with PRP remained quite improved when compared with group 1. Significant difference in p-value is seen when both the groups in terms of betterment (VAS score) when compared after 2 months, 6 months and 12 months follow up.

Discussion

Osteoarthritis (OA) is the second leading cause of joint function loss. It is a chronic, degenerative joint disease that involves cartilage destruction brought on by an insufficient healing response in an inflammatory environment.[16] OA causes significant economic and social impacts worldwide.[17] The main pathological process involves periarticular components and degeneration of articular cartilage.[18]

One of the most promising injectable strategies for mild knee osteoarthritis that has been developed recently is the combination of HA and PRP since it combines the benefits of both of its constituents. Naturally occurring in synovial fluid, hyaluronic acid has the ability to both decrease articular inflammation and improve joint viscosity and lubrication.[19] PRP offers a variety of stimulants to the surrounding tissues and the synovial membrane.

Sun SF et al[14] demonstrated that combining PRP with HA better prevented nonbacterial inflammation of the synovium and enhanced local synovial hyperplasia and blood flow than did HA or PRP alone. This combination therapy successfully raised pain and function ratings while lowering the risk of negative side effects. The amount of inflammatory factors (IFs) and MMPs in the synovial fluid was partially decreased by PRP alone and in combination with HA.[14]

Our findings are consistent with previous research that has been published in the literature; after two months, HA injection therapy had positive outcomes for both pain reduction and knee functioning restoration. According to the visual analogue scale, patients did not report any appreciable improvement in pain six months following the HA therapy, and at twelve months, they even reported a little deterioration in knee functioning. These finding correlates with the study by Ciapini et al.[3]

In cases of grade 3 and 4 knee osteoarthritis, Saturveithan et al[13] compared the benefits of PRP + HA with those of HA alone and found that at six months following the conclusion of their therapy, patients who had PRP in addition to HA had significantly superior results in terms of knee functioning and pain alleviation. Similar results were shown by the study done by Papalia et al.[20]

Sundman et al. demonstrated that PRP can decrease the breakdown of cartilage at the gene expression level and promote the body's natural synthesis of hyaluronic acid by harvesting cartilage and synovium from patients undergone total knee replacement surgery and co-culturing them in medium containing either PRP or Ha. They demonstrated that PRP and HA therapy both decreases the cartilage loss in OA joint tissue. Additionally, they noticed that PRP therapy dramatically improves the activity of hyaluronan synthase-2, which promotes cartilage production, and considerably reduces the expression of matrix metalloproteinase-13 in synoviocytes.[22]

The most recent Knee OA recommendations did not support HA as the main treatment since it has little effect on cartilage repair. Researches have shown that the efficacy of HA diminishes with repeated administrations

and that it is considered a symptomatic treatment unrelated to the underlying etiology of Knee OA.[21]

In order to determine if these biologic agents may have a synergistic effect, a meta-analysis on the impact of PRP-HA conjugates proposed to compare the combined injections with injections of PRP or HA alone. Sun SF et al[14] administered three weekly injections of HA in addition to PRP to patients with knee OA. The outcomes were compared to those of patients treated alone with PRP after a period of time. They came to the conclusion that PRP with HA worked just as well as PRP alone. Both HA and PRP support joint healing through several mechanisms; when combined, they appeared to be beneficial for treating knee OA, as evidenced by a 12% improvement in lower limb WOMAC scores. At six months, patients in the one-injection group showed a 41.1% improvement in WOMAC scores from baseline, whereas the combined-injection group showed a 39.0% improvement.[14]These results are contrary to our study where combined HA and PRP showed more improvement than the other group.

Aw et al[11] observed improved WOMAC, and VAS ratings in patients who underwent PRP and HA dual-therapy when compared with PRP alone at 3, 6, and 12 months. Furthermore, WOMAC function ratings significantly improve after treatment with PRP and HA as opposed to PRP alone. This conclusion is supported by Lana et al.'s study, which shown that, in comparison to PRP-alone therapy, PRP and HA dual therapy improved median WOMAC Pain scores at 30 and 90 days whereas HA alone caused worse outcomes at up to 1 year and PRP alone at up to 3 months.[23]

PRP and HA dual therapy produced superior WOMAC scores at 12 months compared to PRP-alone therapy, according to Zhang et al[1] Due to limited number of studies that compared WOMAC function scores at three and six months, it was difficult to draw any meaningful conclusions.[1] The study by Branch EA et al[2] showed that HA plus PRP combination led to much reduced discomfort and functional impairment than HA alone. He conducted a two-year follow-up to validate the long-term benefits of PRP and HA.[2]

Conclusion

PRP combined with HA is superior to HA alone both in terms of efficacy and adverse effects. Study on larger scale is required with more follow up is required to establish the effectiveness of these injections.

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