



E-ISSN: 2395-1958
P-ISSN: 2706-6630
IJOS 2024; 10(4): 94-98
© 2024 IJOS
www.orthopaper.com
Received: 16-06-2024
Accepted: 22-07-2024

All Author's name and their affiliation are below references section

Effects of addition of hyaluronic acid on platelet rich plasma in treatment of chronic osteoarthritis of knee joints

Moyeen Ahmed Ferdous, Mohammed Ramzanul Karim Khan, Md. Ibrahim Miah, Md. Alinoor, Md. Motiur Rahaman, Sharif Md. Musa, AKM Latiful Bari, Jamal Uddin Ahmed, Mohammad Faroque Eastiak, Ahsan Majid and Mahamud Mannan

DOI: <https://doi.org/10.22271/ortho.2024.v10.i4b.3629>

Abstract

Background: Osteoarthritis (OA) is one of most common musculoskeletal disease, is a chronic degenerative joint disease characterized by progressive destruction of articular cartilage, narrowing of joint space and crepitus over the joint and results in thinning and eventual wearing of articular cartilage thus resulting in painful, limited joint movement which impairs daily functional activity. The use of autologous platelet rich plasma (aPRP) either alone or in combination with hyaluronic acid (HA) for treatment of knee osteoarthritis will continue to get attention due to its anti-inflammatory and growth factors. The aim of this study was to compare the effects of addition of hyaluronic acid on platelet rich plasma in treatment of chronic osteoarthritis.

Methods: This was a prospective, randomized; single-blind study was carried out at Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh from January to June 2023. 60 patients with stage 2 and 3 moderate osteoarthritis based on the following upright front, back, and lateral radiographs of all patients were evaluated. Staging was based on the Kellgren-Lawrence classification. Patients with bilateral knee OA, diabetes mellitus, metabolic syndrome, coagulopathy, and Kellgren-Lawrence class 4, and 4 patients (2 lost to follow-up from each group) were excluded from the study. Pain intensity and functional disability were assessed, with numerical pain rating (NPR) scale and pain disability questionnaire (PDQ), at 1, 3 and 6 months follow up.

Results: Majority of the patients (90.0%) were in the age range of 41-60 years. Mean age of the study population was 54 ± 5.12 and 57.35 ± 6.67 , male to female ratio was 1:5 and 1:4 for group A and B respectively. At 6 months follow up, significant reductions in pain intensity (NRS) in the two groups were observed 7.15 ± 1.0 vs 1.33 ± 0.5 and 7.10 ± 1.2 vs 2.65 ± 1 respectively for groups A and B. The lower pain score observed among group A at 6 months follow up was statistically significant, $p < 0.05$. There was an improvement in functional activity (assessed by activity rating scale) among both groups. Pre intervention, 26.6% and 73.4% of patients in group A had moderate and severe limitations to movement respectively in comparison with 66.6% who reported no limitation and 16.7% with mild limitation to movement at the end of 6 months follow up. Similarly, 40% and 60% of patients in group B had moderate and severe limitations to movement respectively before treatment. At the end of 6 months follow up, 60% and 36.7% of patients in group B had no limitation and mild limitation to movement respectively. Patients in group A had lower PDQ scores, indicating better functional and psychological improvement. Patients in group A had lower PDQ scores, indicating better functional and psychological improvement.

Conclusion: This study found that the addition of hyaluronic acid to autologous platelet-rich plasma resulted in significant pain relief and improved psychological and functional performance compared with platelet-rich plasma alone in patients with chronic knee osteoarthritis.

Keywords: Osteoarthritis, knee joint, platelet rich plasma, hyaluronic acid

Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal disorders. It is a chronic degenerative joint disease characterized by progressive destruction of articular cartilage, narrowing of the joint space, and crepitus on the joint, leading to thinning and eventual wear of

Corresponding Author:
Moyeen Ahmed Ferdous
Asst. Professor, Department of
Orthopedic Surgery, BSMMU,
Dhaka, Bangladesh

the articular cartilage, resulting in painful restricted joint movements that interfere with daily life and impair functional activity^[1, 2]. Degeneration of articular cartilage is mainly due to altered chondrocyte activity, which also affects other joint tissues, such as alterations in the meniscus, sclerosis and edema of the underlying subchondral bone, and intermittent inflammation of the synovium^[1, 2, 3, 4]. The use of autologous platelet-rich plasma (APRP) in the treatment of osteoarthritis (OA) is increasing, but the long-term efficacy of PRP remains controversial^[2]. Globally, hip and knee osteoarthritis are the leading causes of disability, with 3.8% of the population affected by KOA^[5]. With an aging population and rising rates of obesity, the prevalence of KOA is expected to increase, resulting in a significant increase in the demand for total knee arthroplasty. As a result, KOA poses a significant burden to healthcare systems and societies worldwide^[6-8]. Based on current clinical and scientific knowledge, it is believed that a high concentration of autologous growth factors in PRP shortens the required healing time^[9]. Therefore, the use of platelet-rich plasma in the treatment of knee OA will continue to attract attention, as the growth factors released by APRP improve quality of life by reducing pain and increasing functional activity^[9, 10]. Hyaluronic acid (HA) is often used to treat knee osteoarthritis^[3]. The beneficial effects of HA are thought to be due to its function as a viscosupplement and its anti-inflammatory effect. Several reports have been published comparing the clinical outcomes of HA and PRP in osteoarthritis^[4, 9, 10]. PRP is obtained from an autologous blood sample and consists of concentrated platelets and growth factors^[11]. These growth factors play a variety of roles, including promoting local angiogenesis, regulating inflammation, inhibiting chondrocyte apoptosis, remodeling bone and blood vessels, synthesizing collagen, inhibiting catabolic enzymes and cytokines, recruiting stem cells and fibroblasts locally to the injury site, and stimulating adjacent healthy cells to produce more growth factors^[12]. However, the clinical outcomes of co-injection of HA and PRP have not been well studied, especially in Africa and sub-Saharan regions, where the economic burden of the disease and the cost of surgery are high^[4]. Published an *in vitro* study on the synergistic effect of the combination of HA and PRP on cartilage regeneration in OA. In this report, the combination of HA and PRP reduced the levels of proinflammatory cytokines and increased the proliferation and chondrogenic differentiation of articular chondrocytes. The authors concluded that the observed synergistic effect was the result of different molecular mechanisms. Intra-articular injection of hyaluronic acid (HA) has been widely accepted for the treatment of pain associated with OA. The goal of HA mucosupplementation is to reduce pain and improve synovial fluid viscoelasticity. Autologous platelet-rich plasma (APRP) has been used to treat OA to possibly induce cartilage regeneration. The combination of HA and APRP could provide many advantages for tissue repair. Indeed, it compliment HA viscosupplementation with APRP regenerative properties^[9, 13]. The aim of this study is to determine the effectiveness of single injection of autologous platelet rich plasma as monotherapy for treatment of mild-moderate knee joint osteoarthritis compared with combination of autologous Platelet rich plasma and Hyaluronic acid.

Materials and Methods

This was a prospective, randomized; single-blind study was carried out at Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh from January to June 2023. 60 patients with stage 2 and 3 moderate osteoarthritis based on the following upright front, back, and lateral radiographs of all

patients were evaluated. Staging was based on the Kellgren-Lawrence classification. Patients with bilateral knee OA, diabetes mellitus, metabolic syndrome, coagulopathy, and Kellgren-Lawrence class 4, and 4 patients (2 lost to follow-up from each group) were excluded from the study. Pain intensity and functional disability were assessed, with numerical pain rating (NPR) scale and pain disability questionnaire (PDQ), at 1, 3 and 6 months follow up.

Patients were randomized using sealed envelopes into group A, which received intra-articular PRP and HA, and group B, which received intra-articular PRP injections only. There were 30 patients (30 knees) in the PRP and HA groups and 30 patients (30 knees) in the PRP group. Prior to the procedure, all patients underwent clinical examinations including routine complete blood counts to determine the adequacy of platelet counts, and informed consent was obtained. Demographic variables, baseline numerical scores, pain interference scales, and activity-related scales were used to assess and record motion limitations. Platelet-rich plasma was prepared from 15 ml of autologous venous blood drawn from the upper extremity. Blood was placed in a 15-ml centrifuge tube containing 1.5 ml of 3.2% sodium citrate and centrifuged at 3,600rpm for 5 min at room temperature. After centrifugation, 4 ml of PRP was collected between the lower layer of red blood cells and the upper layer of plasma just above the buffy coat. The knee joint was prepped with povidone-iodine and sterile drapes, and 2 ml of 1% pure lidocaine was used to infiltrate the intended surgical site and achieve anesthesia at the injection site.

The procedure was performed through an anterolateral portal using a 25G needle. Five minutes after the injection, the patient's activity-related pain was assessed, and a reduction of 50-75% of pre-procedure activity-related pain was considered to diagnose a successful intra-articular injection. The patient was observed for 1 hour and discharged home accompanied by a responsible adult and advised to rest for 1 day and ice the affected area. After the first day, patients were allowed to resume tolerable daily activities. Doluxetine 30 mg was recommended as an analgesic. Patients in both groups were assessed using the Pain Disability Questionnaire before the procedure and at 1-month and 6-month follow-up. In addition, a numerical assessment was performed before surgery and after 1-month and 6-month follow-up.

Clinical data showed that intra-articular injection of PRP was more effective in restoring joint function, relieving symptoms, and reducing joint and body pain compared with HA treatment. Combined treatment with PRP and HA significantly improved joint pain, reduced humoral and cellular immune responses, and promoted angiogenesis, resulting in improved histological parameters, compared with PRP or HA injection alone. These results suggest that PRP and HA play an important therapeutic role in the progression of knee osteoarthritis and highlight the potential of PRP and HA in the treatment of knee osteoarthritis in the future.

Statistical analysis

Data are expressed as the mean \pm standard deviation. Statistical analysis was performed using a students t-test for unpaired data. Comparisons of data between multiple groups were performed using one-way analysis of variance followed by a Dunnett's t test. Treatment effect was presented as median reduction in knee osteoarthritis over the treatment period. Robust nonparametric Responder rates and treatment-emergent adverse events were analyzed using a χ^2 test. $p < 0.05$ was considered to indicate a statistically significant difference.

Results**Table 1:** Demographic variables

Variables	Groups	
	Group A	Group B
Age years	54.35±15.12	57.35±6.67
Sex M/F	5/25	6/24
Weight Kg	76.62±12.62	65.96±11.61
Height M2	1.56±0.3	1.55±0.4
Duration months	21.23±9.79	19.85±10.24

Table 1: showed the mean age of the study population was 54± 5.12 and 57.35±6.67, male to female ratio was 1:5 and 1:4 for group A and B respectively.

Group A patients had longer duration of onset of joint pain 21.23±9.79 compared to group B 19.85±10.24.

Table 2: Numerical rating scores and pain disability scores

Variables	Pre -intervention	Post -Intervention	
		1month	6 months
Group A			
Numerical Rating score	7.15±10.78	3.73±7.11	2.08±0.89
Pain disability score			
Psychological	29.23±8.32	20.16±3.34	17.62±2.90
Functional	68.84±13.94	48.80±5.20	37.38±8.08
Group B			
Numerical Rating score	7.12±0.65	4.50±1.03	2.8±0.74
Pain disability score			
Psychological	31.84±10.78	26.12±3.21	21.80±7.0
Functional	68.78±9.54	54.21±8.47	44.88±10.2

Table 2 showed reduction in numerical rating pain from 7.15±10.78 to 3.73±7.11 at one month and further reduction to 2.08±0.89 at 6 months follow up.

Functional and psychological score on pain disability scale were significantly decreased at 6 months follow up.

Table 3: Joint involved and radiological grading (Kellgren-Lawrence classification)

Variables	Groups	
	Group A (n=30)	Group B (n=30)
Joint involved		
Right	20 (66.6%)	24(80.0%)
Left	10 (33.4%)	6 (20.0%)
Grade		
Grade II	22 (73.3%)	17 (56.6%)
Grade III	8 (26.7%)	13(43.4%)

Table 3 showed right knee joint was affected in about 66.6% and 80.0% of the patients in group A and B respectively. However, majority 73.3% of the patients in group A have radiological grade II affection compared to 56.6% among group B patients.

Table-4 & 5 showed pre intervention, 26.6% and 73.4% of patients in group A had moderate and severe limitations to movement respectively in comparison with 66.6% who reported no limitation

and 16.7% with mild limitation to movement at the end of 6 months follow up. Similarly, 40% and 60% of patients in group B had moderate and severe limitations to movement respectively before treatment. At the end of 6 months follow up, 60% and 36.7% of patients in group B had no limitation and mild limitation to movement respectively. Patients in group A had lower PDQ scores, indicating better functional and psychological improvement.

Table 4: Activity related scale

Variables	Pre-intervention	Post- intervention	
		1 month	6 months
Group A (n=30)			
No limitation of movement	-	-	5 (16.6%)
Mild limitation of movement	-	10 (33.3%)	20 (66.6%)
Moderate limitation of movement	8 (26.6%)	20 (66.7%)	5 (16.6%)
Severe limitation of movement	22 (73.4%)	-	-
Group B (n=30)			
No limitation of movement	-	-	-
Mild limitation of movement	-	2 (6.6%)	1(3.3%)
Moderate limitation of movement	12 (40.0%)	27 (90.0%)	18 (60.0%)
Severe limitation of movement	18 (60.0%)	1 (3.4%)	11 (36.7%)

Table 5: Pair T-test table pre and 6 months post intervention CI: Confidence interval, PDS: Pain disability score, NRS: Numerical rating score

Group A: Pre and Post Intervention PDS				
Variables	95% CI		T-test value	p-value
	Lower	Upper		
NRS	5.05	6.11	39.52	< 0.001
Functional	26.05	36.86	11.99	< 0.001
Psychological	8.56	15.36	7.25	< 0.001
Group B: Pre and Post Intervention PDS				
NRS	4.15	4.77	29.91	< 0.001
Functional	17.20	28.87	8.13	< 0.001
Psychological	6.75	13.01	6.50	< 0.001

Discussion

In orthopaedics, PRP and hyaluronic acid injections are often used together to treat joint pain and inflammation, especially in patients with osteoarthritis. Our study showed preponderance of osteoarthritis among female gender, with right knee joint most affected. Whereas hyaluronic acid injections only provide temporary joint lubrication and symptom relief, PRP injections harness the body's natural regenerative properties to actually promote long-term tissue repair and healing. This study revealed significant reduction of base line pain score among patients that received addition of hyaluronic acid (HA) in autologous platelet rich plasma (aPRP) compared to patients with intra articular injection of autologous platelet rich Plasma alone $p < 0.001$ this indicated better clinical improvement in patients that received intra-articular injection of hyaluronic acid and platelet rich plasma than platelet rich plasma only. PRP is often used as a conservative treatment option for mild to moderate knee osteoarthritis. Several recent systematic reviews and meta-analyses have compared PRP with corticosteroid and HA injections. Significant pain relief was observed 6 months after injection, which is due to the fact that the stimulating effect appears mainly after several months. These results suggest that the stimulating effect of HA on growth factor release occurs slowly [9, 10]. The results of this study are similar to those of K. Lio et al. [9]. Who conducted the study. The authors reported that aPRP can stimulate the healing process of various tissues by providing various growth factors and cytokines released from platelets. The authors concluded that the addition of HA to aPRP increases the concentration of growth factors released, resulting in reduced pain compared to platelet-rich plasma alone. Similarly, other studies have reported that both HA and aPRP may improve the cartilage healing process and slow the progression of osteoarthritis (OA). Thus, it may be possible to achieve better clinical improvement than with either agent alone. These findings suggested that combining aPRP with HA in the treatment of OA may have a potential additive effect and a greater improvement in clinical symptoms. However, there are few studies in the literature that have explored the combination of HA and aPRP [2, 10, 14]. An activity-related scale was used to assess the patients' joint mobility. At the end of 6 months follow up, 60% and 36.7% of patients in group B had no limitation and mild limitation to movement respectively. Patients who received hyaluronic acid and platelet-rich plasma showed significant improvement at 6-month follow-up compared to those who received only platelet-rich plasma. Several studies have shown that HA provides a suitable matrix and supportive scaffold material for cartilage repair and improves the mechanical properties of cartilage [15]. It is therefore believed that their combination may have a synergistic effect. According to existing data, the combination

of aPRP and HA can benefit from their different biological mechanisms and aid in anti-inflammatory properties, catabolic enzymes, cytokines and growth factors [13]. Moreover, the combination of HA and aPRP was shown to exhibit synergistic effects in regenerative and anti-inflammatory capacity compared to aPRP alone [2, 16]. This combination can alter inflammatory cytokines in the process of chondrocyte degeneration through specific mediators (CD44, TGF- β RII), as well as promote cartilage regeneration and inhibit inflammation in osteoarthritis (OA). All these changes occur within 1-3 months after application. This explains why the significant improvement in activity-related movements observed in our study was delayed until 6 months later [4]. Although the functional and psychological pain disability scores on the pain disability scale decreased in both study groups, the decrease in scores was higher in patients who received intra-articular injections of hyaluronic acid and platelet-rich plasma, indicating an improved quality of life for these patients. This may be due to the benefits of their synergistic and different biological mechanisms [9, 10, 13]. Our results showed that intra-articular injection of aPRP resulted in pain reduction and functional and psychological improvement, but the majority of patients did not show clinical improvement at 6 months compared with patients who received aPRP in combination with HA. The Kellgren-Lawrence classification is the radiological classification of knee OA used in our study, which is graded from 1 to 4, with higher scores indicating greater disease severity. In our study, most patients who received hyaluronic acid in addition to platelet-rich plasma were radiological grade II, compared with 57.7% of patients who received only platelet-rich plasma. However, the former group was not as severe as Zhu Y et al. [17], reported similar results, with the combination of HA and aPRP providing significant pain relief and reduced functional limitations up to 1 year after treatment compared with HA alone.

Conclusion

This study found that the addition of HA to autologous aPRP resulted in significant pain relief and improved psychological and functional performance compared with platelet-rich plasma alone in patients with chronic osteoarthritis of the knee joint. Further randomized controlled trials with a larger number of patients and longer follow-up periods are needed to confirm the observed long-term beneficial effects.

Conflict of Interest

None.

Source of Fund

Nil.

References

1. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: platelet-rich plasma (PRP) versus hyaluronic acid (A one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord.* 2015;8:1-8.
2. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy.* 2011;27:1490-501.
3. Ishijima M, Nakamura T, Shimizu K, et al. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center randomized, open-label, non-inferiority trial. *Arthritis Res Ther; c2014.* p. 16.
4. Chen WH, Lo WC, Hsu WC, et al. Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy. *Biomaterials.* 2014;35:9599-607.
5. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis.* 2014;73:1323-1330.
6. Schofield D, Cunich M, Shrestha RN, Tanton R, Veerman L, Kelly S, et al. The long-term economic impacts of arthritis through lost productive life years: results from an Australian microsimulation model. *BMC Public Health.* 2018;18:654.
7. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am.* 2007; 89:780-785.
8. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *E-Clinical Medicine.* 2020;29-30:100-587.
9. Lio K, Farukawa K, Tsuda K, Hu Y, Wu Y, Cai J, et al. The procoagulant properties of hyaluronic acid-collagen (I)/chitosan complex film. *J Biomater Sci Polym Ed.* 2009;20:1111-1118.
10. Pietrzak WS, Eppley BL. Platelet rich plasma: biology and new technology. *J Craniofac Surg.* 2005;16:1043-54.
11. Cook CS, Smith PA. Clinical update: why PRP should be your first choice for injection therapy in treating osteoarthritis of the knee. *Curr Rev Musculoskelet Med.* 2018;11:583-592.
12. Cugat R, Cuscó X, Seijas R, et al. Biologic enhancement of cartilage repair: the role of platelet-rich plasma and other commercially available growth factors. *Arthroscopy.* 2015;31:777-783.
13. Russo F, D'Este M, Vadalà G, Cattani C, Papalia R, Alini M, et al. Platelet Rich Plasma and Hyaluronic Acid Blend for the Treatment of Osteoarthritis: Rheological and Biological Evaluation. *PLoS ONE.* 2016;11(6). DOI: 10.1371/journal.pone.0157048.
14. Weiser L, Bhargava M, Attia E, Torzilli PA. Effect of serum and platelet-derived growth factor on chondrocytes growth and differentiation in collagen gels. *Tissue Eng.* 1999;5:533-544.
15. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil.* 2012;91(5):411-417.
16. Andia I, Abate M. Knee osteoarthritis: hyaluronic acid, platelet-rich plasma or both in association? *Expert Opin Biol Ther.* 2014;14(5):635-649.
17. Zhu Y, Yuan M, Meng AY. Basic sciences and clinical application of platelet-rich plasma for cartilage defects and osteoarthritis: A review.

Author's Details**Moyeen Ahmed Ferdous**

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Mohammed Ramzanul Karim Khan

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Md. Ibrahim Miah

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Md. Alinoor

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Md. Motiur Rahaman

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Sharif Md. Musa

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

AKM Latiful Bari

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Jamal Uddin Ahmed

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Mohammad Faroque Eastiak

Asst. Professor, Department of General Surgery, BSMMU, Dhaka, Bangladesh

Ahsan Majid

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

Mahamud Mannan

Asst. Professor, Department of Orthopedic Surgery, BSMMU, Dhaka, Bangladesh

How to Cite This Article

Ferdous MA, Khan MRK, Miah I, Alinoor M, Rahaman MM, Musa SM, et al. Effects of addition of hyaluronic acid on platelet rich plasma in treatment of chronic osteoarthritis of knee joints. *International Journal of Orthopaedics Sciences.* 2023; 3(1): xx-xx.

Creative Commons (CC) License

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.