

COMPARISON OF THE EFFECTIVENESS OF PLATELET-RICH PLASMA (PRP), HYALURONIC ACID AND THE COMBINATION OF BOTH IN THE TREATMENT OF MILD AND MODERATE OSTEOARTHRITIS OF THE KNEE

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Abstract

Osteoarthritis (OA) is by far the most common form of arthritis characterized by focal loss of articular cartilage, subchondral osteosclerosis, osteophyte formation at the joint margin, and remodeling of joint contour with enlargement of affected joints. This randomized, clinical trial aimed to compare the effectiveness of Platelet Rich Plasma (PRP) and Hyaluronic Acid (HA) as individual treatments and PRP in combination with HA in the treatment of mild to moderate knee Osteoarthritis (OA). The study was conducted among 89 patients with mild to moderate knee osteoarthritis in the Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Patients were randomly allocated to one of the three interventions: HA (n=30), PRP (n=30), or HA+PRP (n=29). Patients in HA group received 3 intra-articular knee injections with 1 week interval while patients in PRP group and PRP+HA group received 2 intra-articular knee injections with 2 week interval. Functional outcome of the treatment were evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Visual Analogue Scale (VAS) questionnaire at baseline and after 1,3,6 and 9 months of treatment. Majority of the patients in all groups were female where mean age of the patients were about 50 years. Pain scores in VAS scale significantly reduced in PRP group when compared to HA group and also in PRP+HA when compared to HA group which persist till nine months ($p<0.05$). No significant statistical difference was found in VAS scores between PRP and PRP+ HA group. WOMAC pain scores also significantly reduced in PRP group when compared to HA group and also in PRP+HA when compared to HA group ($p<0.05$). WOMAC stiffness significantly reduced in PRP+ HA group when compared to HA group at three month ($p<0.001$) and at six month ($p=0.011$). At nine month, physical activity scores significantly reduced in PRP group compared to HA group ($p=0.002$) and in PRP+HA when compared to HA group ($p<0.001$). No significant reduction was observed in WOMAC scores when the outcome of PRP+HA was compared with PRP alone. PRP provides better functional outcome than HA. The combination of PRP and HA also provides better outcome than HA alone but does not provide better outcome than PRP alone.

Key words: Platelet-Rich Plasma (PRP), Hyaluronic Acid, Osteoarthritis of the knee.

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Introduction

Osteoarthritis (OA) is by far the most common form of arthritis characterized by focal loss of articular cartilage, subchondral osteosclerosis, osteophyte formation at the joint margin, and remodeling of joint contour with enlargement of affected joints.¹ It is strongly associated with age. Over 80% of people over 55 years of age have OA at least one joint. Knee OA is one of the most important because of high prevalence of pain and disability that they cause in older adults and the massive health care resource input that results from this.²

The targets of OA treatment are pain reduction, function and mobility improvement, prevention or correction of the deformity, and slowing the progression of the disease. There are numerous conservative treatments for knee OA with benefits and disadvantages.³ For example, Non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid are common treatments of arthritis. Despite their low cost and easy access, these treatments have systemic adverse effects and may cause joint cartilage destruction and flare up of the osteoarthritic process.⁴

Hyaluronic Acid (HA) is a naturally occurring glycosaminoglycan and a component of Synovial Fluid and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize Hyaluronic Acid and secrete into the joint. Hyaluronic Acid enhances viscosity and elastic nature of Synovial Fluid.⁵ The efficacy of intra-articular HA injection for the treatment of OA knees remains a matter of conflict. A Cochrane review⁶ and recent systematic review and meta-analysis⁷ concluded that HA had beneficial effects on pain, functional improvement. However, several meta-analyses contrarily reported that intra-articular HA injections were not clinically effective and might even be associated with a greater risk of adverse effects.^{8,9,10}

PRP is an autologous concentration of human platelets which contains growth factors, cytokines, and many other mediators.^{11, 12} It has antinociceptive and anti-inflammatory activities to reduce pain and modulate the OA process.¹³ PRP with its potent mixture of growth

factors and cytokines has also been shown to increase the production of HA from native synoviocytes.¹⁴ Thus, it is hypothesized that their combination may be synergistic. According to literature, combining PRP and HA may benefit from their dissimilar biological mechanisms and helping with the signaling molecules as inflammatory molecules, catabolic enzymes, cytokines and growth factors. Also, it was demonstrated that the association of HA+PRP showed synergic effects in the potentials regenerative and anti-inflammatory in comparison to HA or PRP alone. This association can alter the inflammatory cytokines in the degeneration process of the chondrocytes through specific mediators (CD44, TGF- β R2) and also promote the regeneration of cartilage and inhibit inflammation in OA.^{15,16}

However, there is not much research examining such synergistic effects in human. Hence the present study aimed to compare the effectiveness of Platelet Rich Plasma (PRP) and Hyaluronic Acid (HA) as individual treatments and PRP in combination with HA in the treatment of mild to moderate knee Osteoarthritis (OA).

Methods

Research design: The study was a randomized, clinical trial, conducted among 89 patients with mild to moderate knee osteoarthritis in the Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Patients with primary osteoarthritis of the target knee fulfilling the ACR clinical criteria were selected for the study. Patients having history/ evidence of acute swollen joint (septic arthritis), recent trauma, fracture, unstable knee joint, Tubercular arthritis, Crystalline arthritis, Inflammatory disease (e.g. rheumatoid arthritis, psoriatic arthritis), peripheral neuropathy/Neurological deficit of lower extremities were excluded from the study. Patient who had received intra-articular corticosteroid injection or PRP injection over the previous 6 months or viscosupplementation to the target knee and underwent joint replacement or arthroplasty on the target knee or any surgical procedure

scheduled in the next six months were also excluded from the study. Patients were randomly allocated by lottery to one of the three interventions: HA (n=30), PRP (n=30), or HA+PRP (n=29).

Blood sample collection and PRP preparation: Selected patients were sent to transfusion medicine department. There about 30 ml blood was collected to prepare platelet rich plasma. Blood was collected in sterile procedure (venepuncture technique almost identical to having a standard blood collection for pathology testing) and allowed it to spin in a centrifuge machine for 15 minutes about 3200 rpm. Then blood was separated into its various constituents; red blood cells on the bottom, plasma on the top, and platelets in the middle. On the top of the red blood cell layer, there was buffy coat. Then buffy coat was extracted which was the Platelet rich plasma. This platelet rich plasma was used in our study. The entire process took less than 30 minutes.

Details of Treatment: With aseptic technique, injection was administered through a direct parapatellar approach. Preadministration of anesthetic skin spray or subcutaneous local anesthetics was permitted.

Patients in HA group received 3 intra-articular knee injections (4 ml) with 1 week interval.

Patients in PRP group received 2 intra-articular knee injections (10 ml) with 2 week interval.

Patients in PRP+HA group received 2 intra-articular knee injections (6 ml PRP and 4 ml HA) with 2 week interval.

The patient was then observed for 15-20 min and then discharged.

Post-injection protocol: The use of NSAID was prohibited. Because there might be discomfort experienced by the patient at the site of the injection for up to 48 hours, patients were encouraged to ice the injection site, elevate the limb and modify activities. Patients were discharged to home with instruction to limit their activities for 48 hours.

Respondents of both groups were assessed to see the effects of treatment at 4th week, 12th week, 24th week and 36th week.

Paracetamol was allowed for break-thru pain < 2000mg/day.

Quadriceps strengthening exercise was advised in the form of extension of knees 10 repetition 2 times daily.

Instruction for activity of daily living (ADLs) was prescribed for all patients.

Outcome Measures: Outcome were measured by OA specific translated and validated Bengali instrument- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire: WOMAC is a 24-item self-report questionnaire, that include Pain score (5 domain), Stiffness score (2 domain), Physical function score (17 domain). All scores were converted into a scale of 0 to 100 for better representation.

Pain score was collected on visual analogue scale (VAS 0-10).

Data processing and analysis: The statistical analysis was conducted using SPSS (statistical package for social science) version 25 statistical software. Descriptive analyses are provided for demographic and clinical characteristics. Independent sample t test was applied to compare the continuous data. Here, $p < 0.05$ was considered significant. Here, all p-values were two sided.

Ethical implication: Ethical clearance was taken from Institutional Review Board (IRB) of BSMMU. Informed written consent was taken from every patient before enrollment.

Results

Demographic and clinical characteristics: Majority of the patients in all groups were female where mean age of the patients were about 50 years. Majority of patients have grade III of OA by Kellgren-Lawrence in the left knee (table 1).

VAS scores: At baseline there was no significant difference between the groups regarding pain on VAS scale. Significant statistical difference was observed in VAS scores from one month in PRP vs HA group and HA vs PRP+ HA group which persist till nine months ($p < 0.05$). No significant difference was found in VAS scores in PRP vs PRP+ HA group (table 2).

WOMAC scores: Significant statistical difference was observed in WOMAC pain scores from one month in PRP vs HA group and HA vs PRP+ HA group which persist till nine months ($p < 0.05$). No significant difference was found in pain scores in PRP vs PRP+ HA group. At nine month, physical activity scores significantly reduced in PRP vs HA group and HA vs PRP+ HA group. No significant reduction was observed in WOMAC scores when the outcome of PRP+HA was compared with PRP alone (table 3).

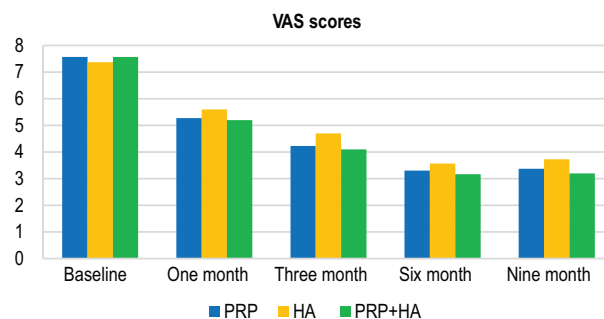


Fig.-1: VAS scores of the patients

Table-I
Demographic characteristic of the patients

Criteria	PRP group	HA group	PRP + HA group
Gender			
Male	12 (40.0)	13 (43.3)	14 (48.3)
Female	18 (60.0)	17 (56.7)	15 (51.7)
Age (mean ± SD)	49.27±6.82	52.63±5.40	51.57±4.85
Disease duration (months) (mean ± SD)	14.63±6.62	16.67±6.37	14.87±5.46
Kellgren-Laurence grade			
2	14 (46.7)	16 (52.2)	9 (31.1)
3	16 (52.2)	14 (46.7)	20 (68.9)
Side involvement			
Right	15 (50.0)	14 (46.7)	12 (41.4)
Left	15 (50.0)	16 (52.2)	17 (58.6)

Table-II
Comparison of VAS scores of the patients

VAS scores	PRP group	HA group	PRP + HA group	p values		
				PRP vs HA	PRP vs PRP+ HA	HA vs PRP+ HA
At baseline	7.57±0.57	7.37±0.61	7.57±0.50	0.196	1.000	0.174
At one month	5.27±0.45	5.60±0.49	5.20±0.76	0.009	0.681	0.019
At three month	4.23±0.43	4.70±0.47	4.10±0.30	<0.001	0.172	<0.001
At six month	3.30±0.47	3.57±0.50	3.17±0.38	0.038	0.229	0.001
At nine month	3.37±0.49	3.73±0.45	3.20±0.41	0.004	0.157	<0.001

Table-III
Comparison of WOMAC pain, WOMAC stiffness and WOMAC physical activity scores of the patients

Criteria	PRP group	HA group	PRP + HA group	p values		
				PRP vs HA	PRP vs PRP+ HA	HA vs PRP+ HA
At base line						
Pain	375.23±5.34	377.50±4.10	374.83±4.82	0.070	0.762	0.025
Stiffness	154.50±6.99	153.50±8.72	157.33±8.17	0.626	0.154	0.084
Physical activity	1435.00±78.95	1445.00±86.45	1471.33±70.44	0.642	0.065	0.201
At one month						
Pain	362.00±5.51	365.17±4.45	360.50±6.34	0.017	0.332	0.002
Stiffness	126.00±12.06	128.00±10.22	129.50±15.10	0.491	0.325	0.654
Physical activity	1340.00±74.74	1364.33±76.84	1336.67±92.78	0.219	0.879	0.213
At three month						
Pain	349.67±3.92	354.17±3.96	346.83±8.76	<0.001	0.101	<0.001
Stiffness	117.33±12.29	122.00±4.67	112.67±10.96	0.057	0.126	<0.001
Physical activity	1235.33±79.73	1257.00±67.93	1221.67±117.21	0.262	0.600	0.159
At six month						
Pain	330.17±10.29	336.00±7.12	326.50±8.72	0.013	0.142	<0.001
Stiffness	96.67±10.19	98.00±5.66	92.33±10.23	0.534	0.106	0.011
Physical activity	1110.00±71.39	1138.00±68.80	1108.33±128.04	0.127	0.951	0.270
At nine month						
Pain	331.83±10.29	339.83±7.93	328.17±6.76	<0.001	0.075	<0.001
Stiffness	98.83±10.19	97.00±3.11	93.33±9.41	0.122	0.484	0.050
Physical activity	1058.00±67.64	1117.33±76.83	1025.00±76.28	0.002	0.081	<0.001

Discussion

Osteoarthritis is a degenerative joint disease that occurs primarily in older individuals, characterized by erosion of the articular cartilage, hypertrophy of bone at the margins (i.e., osteophytes), subchondral sclerosis, and a range of biochemical and morphologic alterations of the synovial membrane and joint capsule. In early stage, anabolic changes, characterized by proliferation of chondrocytes and increased matrix production, are followed by a predominantly catabolic state, characterized by decreased matrix synthesis, increased proteolytic degradation of matrix, and chondrocyte apoptosis. Many of the features of the chondrocyte in the catabolic state are related to the production of inflammatory mediators by synovium and chondrocytes that act locally to perpetuate cartilage degradation.¹⁷

Pain is the main clinical problem of OA knee. After intervention, VAS scores significantly decreased in PRP group compared to HA group

and PRP+HA group. HA when added to PRP did not provide any extra effect on pain reduction. Other studies also found superior result when treated with PRP compared to HA.^{18, 19, 20} The platelet concentrate is activated by addition of calcium chloride, which results in the formation of platelet gel and this stimulates the release of growth factors and bioactive molecules.²¹ Therefore, platelets actively PRP actively participate in healing processes by delivering a broad spectrum of growth factors (insulin-like growth factor, transforming growth factor b.I, platelet-derived growth factor, and many others) and other active molecules (e.g., arachidonic acid metabolites, cytokines, chemokines, ascorbic acid, extracellular matrix proteins, and nucleotides) to the injured site.²² These factors altogether contribute to comprehensive roles of PRP, including anti-inflammation, angiogenesis, chondrogenesis, chondrocyte proliferation, bone remodeling, coagulation, and cell differentiation and this, in turn, reduces inflammation and pain.²³

Response rate was quicker in VAS scale than WOMAC scale. When clinical outcome was measured in WOMAC scale, only pain significantly decreased in PRP group compared to HA group. Pain also significantly decreased in PRP+HA group compared to HA group. However, other subscales like stiffness and physical activity showed no difference between groups till six months. At nine month of treatment, physical activity improved significantly in PRP group compared to HA group which was also prominent in PRP+HA group compared to HA group. This supports the findings of other studies that showed PRP having superior results versus HA in the treatment of knee OA. Sánchez et al. showed that PRP is better in pain, physical activity and overall WOMAC scores in 5 weeks compared to HA.²⁴ Spaková et al. showed statistically significant better results in the PRP group compared to HA at 3 and 6 month follow up periods in WOMAC scores.²⁵ Kon et al. showed that the PRP group showed better results than the HA group at 6 months follow up in the International Knee Documentation Committee and VAS scores and concluded that autologous PRP injections showed more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function.²⁰ Raeissadat et al. had conducted a non-placebo-controlled randomized clinical trial among 160 patients affected by knee OA. In the PRP group, two intra-articular injections at 4-week interval were applied, and in the HA group, three doses of intra-articular injection at 1-week interval were applied. At the 12-month follow-up, WOMAC pain score and bodily pain significantly improved in both groups; however, better results were determined in the PRP group compared to the HA group ($p < 0.001$).¹⁸

PRP was found superior in terms of pain reduction and functional improvement in knee when compared to HA. However, the combination of PRP+HA did not prove superior to PRP though it was found superior to HA. Separately HA and PRP are beneficial for joint cells although they function through different mechanisms. Anitua et al. evaluated the potential of pure PRP to induce tendon cells and synovial fibroblasts migration and examined

whether the combination of PRP with HA improves their motility in vitro. PRP stimulated the migration of fibroblasts, as well as HA, but this effect was more prominent when HA was combined with PRP. Indeed, an increase of 335% in motility was observed in the case of HA+PRP treatment compared with HA. Therefore, this 'in vitro' study definitely proves that PRP improves the biological properties of HA.²⁶ The randomized controlled trial which evaluated the effectiveness of HA and PRP as monotherapies for mild to moderate OA and compare the results to the combination of PRP+HA, found that the combination of HA and PRP resulted to better outcomes than HA alone up to 1 year and PRP alone up to 3 months.²⁷

Conclusion

PRP provides better functional outcome than HA. The combination of PRP and HA also provides better outcome than HA alone but does not provide better outcome than PRP alone.

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Conflict of Interest: None

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