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RESEARCH PAPER

Intra-articular Injection of Hyaluronic Acid (HA) and Platelet-rich Plasma (PRP) in the Treatment of Mild and Moderate Osteoarthritis of Knee

Farzana Khan Shoma[1], Ziaur Rahman Chowdhury[1], Farzana Hossain[2], Abul Khair Mohammad Salek[1], Moshiur Rahman Khasru[1], Md. Nuruzzaman Khandaker[1]

Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; Freelance Researcher, MPH.

Abstract

Background: Osteoarthritis (OA) is the most prevalent chronic joint disorder worldwide and is associated with significant pain and disability. Introduction of platelet-rich plasma (PRP) injection has been viewed as an advance in the management of OA knee.

Objective: To compare the effectiveness of PRP and Hyaluronic Acid (HA) in the treatment of mild and moderate OA knee

Methods: The present randomized clinical trial had been conducted in the Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from 2018 to 2019. A total of 154 patients with mild and moderate OA knee were randomly allocated into two groups: group A (received PRP injection) and group B (received HA injection) where 133 patients completed the follow-up schedule. Outcomes were measured by OA specific translated and validated Bengali instrument- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire and visual analogue scale (VAS 0-10). They were followed-up for 6 months.

Results: There was no significant statistical difference at the baseline between the groups regarding age, sex, grading of OA knee, side involvement, mean duration of the disease, VAS scores and WOMAC scores. After one month, VAS score significantly decreased in PRP group compared to HA group (p<0.001). However, there was no statistical difference regarding total WOMAC scores between two groups (p=0.063). In third and sixth month, VAS score significantly decreased in PRP group compared to HA group (p<0.001). Though the stiffness and physical activity scores of WOMAC did not reduce significantly, the pain score reduced significantly in PRP group compared to HA group. In both groups, significant reduction of VAS and WOMAC total scores was observed after six months follow-up compared to baseline values (p<0.001).

Conclusion: Intra-articular platelet-rich plasma improves pain and function of the knee in patients with osteoarthritis. Though intra-articular hyaluronic acid also improves pain and function in the foot, PRP is more effective than hyaluronic acid. Multi-centered clinical trial with long term follow-up should be conducted to see the effects of PRP and HA.

Keywords: Platelet-rich plasma, Hyaluronic acid, Osteoarthritis of knee, Visual analogue scale

Introduction

Osteoarthritis (OA) is the most common form of joint disease and among the top 10 causes of disability worldwide.[1] This degenerative joint disease is characterised by erosion of the articular cartilage, hypertrophy of bone at the margins (osteophytes), subchondral sclerosis, and a range of biochemical and morphologic alterations of the synovial membrane and joint capsule.[2] With aging of the population and increasing obesity,

OA arises as a major public health problem and an important financial burden for the global economy.[3] It is more common in women than men.[4] OA of the knee, the principal large joint to be affected, results in disabling knee symptoms in an estimated 10% of people older than 55 years, a quarter of whom are severely disabled.[5]

The primary objectives in OA treatment focus on pain reduction, joint mobility improvement, and functional

***Correspondence:** Dr. Farzana Khan Shoma, Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*

e-mail: farzanadmck53@gmail.com;

ORCID: 0000-0002-5355-490X

impairment limitation. Furthermore, secondary goals are centred on the reduction of disease progression and improvement of muscular strength, in order to preserve patients' independence and quality of life.[6]

Current treatments aim at alleviating these symptoms by several different methods: Non-pharmacological treatments like education, exercise, lifestyle changes), Pharmacological treatments like paracetamol, NSAIDs, topical treatments and invasive interventions like intra-articular injections, lavage, arthroplasty.[7] However, most of the treatments have limited tolerability and their efficacy is limited to relieving pain.[8]

Viscosupplementation (such as HA), prolotherapy (such as dextrose), platelet-rich plasma (PRP) therapy, and stem cell therapy have been considered for the treatment of knee OA to increase tissue healing and to slow down the progression of degeneration.[9]

High-molecular-weight HA is a natural disaccharide polymer that can mimic the synovial fluid. In addition to supporting joint lubrication, HA can inhibit the inflammatory process and stimulate cartilage regeneration.[10-13]

Hyaluronic acid is important in maintaining articular cartilage integrity, being one of the major glycosaminoglycans in the extracellular matrix. By binding proteoglycans, it provides and maintains intra-articular lubrication, optimizing the viscoelastic properties of synovial fluid.[14] Synovial fluid with normal HA concentration acts as a viscous lubricant during slow joint movements and as an elastic shock absorber during rapid joint movements.[15] HA functions through anti-inflammatory, anabolic, analgesic, and chondroprotective mechanisms.[16]

Platelet-rich plasma could be defined as autologous blood with platelets concentration of 94% while normal platelets concentration is only 6%.[17] PRP injections intend to trigger the inflammatory response, which promotes the healing process by renovating injured tissue structure and simultaneously preventing further tissue degeneration.[18] Infiltration with autologous blood, buffered platelet rich plasma or autologous growth factors seems promising, but requires further investigation.[19]

PRP has shown promise in the treatment of various musculoskeletal conditions including chronic lateral epicondylitis, osteoarthritis, plantar fasciitis, muscle strain, ligament sprain, cartilage damage, fractures, tendon injury and has been approved by the International Olympic Committee in the treatment of soft tissue injuries and tendon disorders.[20] The key components of PRP are the platelets which store and release a wide range of bioactive factors including growth factors that can modify the biological environment at injury sites, thus enhancing tissue healing. PRP is not known to have any adverse effects unlike the commonly used nonsteroid anti-inflammatory drugs (NSAIDS) that are known to affect the gastrointestinal, cardiovascular and renal systems.[21]

There is scarcity of published data about the effectiveness in the management of knee OA with PRP and HA in Bangladesh. Hence this study had been conducted with the objective of comparing the effectiveness of Platelet-rich plasma (PRP) and Hyaluronic Acid (HA) in the treatment of mild and moderate osteoarthritis of the knee.

Materials and Methods

The study was a randomized clinical trial conducted in the Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka from 2018 to 2019. With an alpha error of 0.05, 90% power, a standard deviation of 16.36 and a minimal clinically significant difference of 9.02,[11] the minimum sample size was 69 for each group. Considering a possible drop out of 10%, a total of 154 patients were required.

Inclusion criteria: Adult patients of both sex, diagnosed according to the criteria developed by the American College of Rheumatology Radiologic and Clinical Criteria for Osteoarthritis (ACR) were included in the study.

Exclusion criteria: Patients having history/ evidence of acute swollen joint (septic arthritis), recent trauma, fracture, unstable knee joint, malignancy, tubercular arthritis, Inflammatory disease (e.g. rheumatoid arthritis, psoriatic arthritis, SpA) etc. and patients on therapy with anticoagulant, severe anemia, receiving aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) within a week ago, bleeding disorder were excluded from the study.

Randomization

To keep the study blinded, all patients underwent blood harvesting to obtain autologous PRP, which was then used only in the PRP group. Before the injection,

the syringe was appropriately covered to prevent patients from discovering the substance they were receiving. Group selection was done randomly by the way of lottery. Patients were divided into two groups: group A and group B. In each group, 77 patients were allocated. In group A, patients were allocated with single dose intra-articular injection PRP (10 ml) and in group B, patients were allocated with single dose intra-articular HA (Sylocet) (4 ml) injection.

Before injection patient was prohibited to take NSAID at least 7 days. The injection was administered through a direct parapatellar approach using 10 cc disposable syringe. If effusion was present in the knee would be aspirated and send to laboratory for synovial fluid analysis. Aspiration was performed by using a separate sterile syringe before injection. 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.

Paracetamol was allowed for break-thru pain < 2000mg/day. Quadriceps strengthening exercise was advised in the form of extension of knees10 repetition 2 times daily. Instruction for activity of daily living (ADLs) was prescribed for all patients. Respondents of both groups were assessed to see the effects of treatment at 4^{th} week, 12^{th} week, and 24^{th} week.

Outcome measures: Outcome were measured by OA specific translated and validated Bengali instrument-Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. The WOMAC evaluates 3 dimensions: pain, stiffness, and physical function with 5, 2, and 17 questions, respectively. The Likert version of the WOMAC is rated on an ordinal scale of 0 to 4, with lower scores indicating lower levels of symptoms or physical disability. Each subscale is summated to a maximum score of 20, 8, and 68, respectively.[22]

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

A VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they felt represents their perception of their current state. The VAS score was determined by measuring in millimeters from the left hand end of the line to the point that the patient marked.

Data processing and analysis: Data were collected by the investigator who was involved in administering the injection. The statistical analysis was conducted using SPSS (statistical package for social science) version 25 statistical software. Associations of categorical data were assessed using Chi-square test and continuous data were assessed using Independent Sample t-test and paired t test. Here, $p<0.05$ was considered significant. Here, all *p*-values were two sided.

Ethical implication: The protocol of the study was approved by the Ministry of Science and Technology Government of People's Republic of Bangladesh Secretariat, Dhaka. The G.O. no. was 39.00.0000.09.02.90.18-19. Informed written consent was taken from every patient after adequate explanation of the purpose and procedure of the study. Privacy, anonymity and confidentiality of data were maintained strictly. They were assured of protection of their safety. Each patient enjoyed every right to participate or refuse or even withdraw from the study at any point of time.

Results

A total 150 patients were included in the study. They were followed up for 6 months. Among the patients, 65 patients in group A and 68 patients in group B completed the study. Hence, this section presented the results of 133 patients. The mean ages of the patients were 51.3 (±6.5) (range: 37.0-67.0) and 52.7 (±5.4) (range: 40.0-65.0) years in group A and group B respectively. Out of 133 patients, 38 (58.5%) patients in group A and 39 (57.4%) patients in group B were female. The mean duration of disease of the patients were 14.5 (±6.6) and 16.6 (±6.4) months in group A and group B respectively. The mean VAS score of the patients were 7.6 (±0.6) and 7.4 (±0.5) in group A and group B respectively. The mean WOMAC total score of the patients were 1966.6 (±78.7) and 1974.1 (±91.2) in group A and group B respectively. There was no significant statistical difference at the baseline between the groups regarding age, grading of OA knee, side involvement, mean duration of disease, Visual Analogue Scale (VAS) scores and WOMAC scores.

After one month, the VAS score was 5.3 ±0.4 in group A while in group B it was 5.6 ±0.5. Student t test

showed that VAS score was significantly lower in PRP group compared to HA group as $p<0.001$. The WOMAC total score was 1830.8 ±77.3 in group A and in group B it was 1855.1 ±72.8. There was no statistical difference regarding total WOMAC scores between two groups as the *p* value was 0.063 (obtained by Student-t test) (table I).

After three months, the VAS score was 4.2 ±0.4 in group A while in group B it was 4.7 ±0.5. Student t test showed that VAS score was significantly lower in PRP group compared to HA group ($p<0.001$). The pain WOMAC and stiffness WOMAC were significantly lower in group A compared to group B ($p<0.001$ and $p=0.010$). However, there was no statistical difference regarding WOMAC physical activity scores between two groups as the p value was 0.275. The WOMAC total score was 1687.5 ±76.8 in group A and in group B it was 1711.9 ±63.9. There was significant statistical difference regarding total WOMAC scores between two groups as the *p* value was 0.048 (obtained by Student-t test) (table II).

At six month, the VAS score was 3.3 ±0.4 in group A while in group B it was 3.6 ±0.5. VAS score was significantly lower in PRP group compared to HA group ($p<0.001$). The pain WOMAC was significantly lower in group A compared to group B $p<0.001$). However, there was no statistical difference regarding WOMAC stiffness and physical activity scores between two groups as the p value was 0.651 and 0.058. The WOMAC total score was 1541.1 ±70.6 in group A and in group B it was 1571.2 ±66.5. There was significant statistical difference regarding total WOMAC scores between two groups as the p value was 0.012 (obtained by Student-t test) (table III).

The VAS score significantly decreased in group A from 7.6 ±0.6 to 3.3 ±0.4 after six months follow up (p <0.001, obtained by paired t test). The WOMAC total scores significantly decreased in group A from 1966.6 ±78.7 to 1541.1 ±70.6 after six months follow up (p <0.001, obtained by paired t test). In group B, the VAS score significantly decreased in group A from 7.41 ±0.5 to 3.6 ±0.5 after six months follow up (p <0.001, obtained by paired t test). The WOMAC total scores also significantly decreased in group A from 1974.1 ±91.2 to 1571.2 ±66.5 after six months follow up (p <0.001, obtained by paired t test) (table IV).

Table-I: Comparison of VAS, WOMAC scores of the patients at one month

Criteria	Group A (n=65) Mean± SD (Range)	Group B (n=68) Mean± SD (Range)	*p* value
VAS	5.3 ±0.4 (5.0-6.0)	5.6 ±0.5 (5.0-6.0)	<0.001
Pain WOMAC	362.3 ±5.5 (350.0-370.0)	365.1 ±4.3 (360.0-375.0)	0.002
Stiffness WOMAC	126.1 ±11.6 (110.0-160.0)	128.1 ±10.3 (115.0-145.0)	0.311
Physical activity WOMAC	1342.3 ±73.5 (1200.0-1450.0)	1361.9 ±75.9 (1230.0-1455.0)	0.132
WOMAC total	1830.8 ±77.3 (1665.0-1945.0)	1855.1 ±72.8 (1745.0-1950.0)	0.063

Foot notes: bold value indicates the level of significance $p\leq0.05$
Abbreviations: SD: Standard Deviation, VAS: Visual Analogue Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table-II: Comparison of VAS, WOMAC scores of the patients at three month

Criteria	Group A (n=65) Mean± SD	Group B (n=68) Mean± SD	*p* value
VAS	4.2±0.4 (4.0-5.0)	4.7 ±0.5 (4.0-5.0)	<0.001
Pain WOMAC	349.8 ±3.8 (340.0-355.0)	354.1±4.0 (350.0-365.0)	<0.001
Stiffness WOMAC	117.6 ±11.8 (100.0-150.0)	121.8±4.5 (115.0-135.0)	0.010
Physical activity WOMAC	1240.3 ±78.9 (1100.0-1350.0)	1254.1 ±66.1 (1150.0-1355.0)	0.275
WOMAC total	1687.5 ±76.8 (1535.0-1805.0)	1711.9 ±63.9 (1605.0-1820.0)	0.048

Foot notes: bold value indicates the level of significance $p\leq0.05$
Abbreviations: SD: Standard Deviation, VAS: Visual Analogue Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table-III: Comparison of VAS, WOMAC scores of the patients at six month

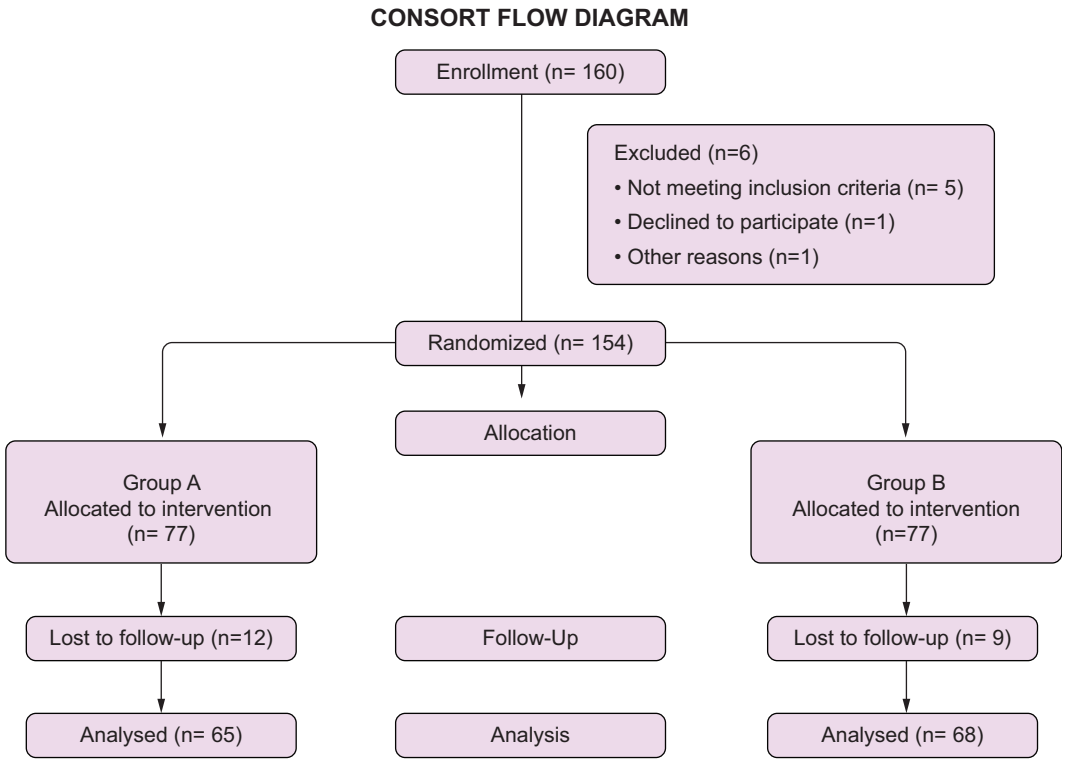
Criteria	Group A (n=65) Mean± SD	Group B (n=68) Mean± SD	*p* value
VAS	3.3 ±0.4 (3.0-4.0)	3.6 ±0.5 (3.0-4.0)	<0.001
Pain WOMAC	329.5 ±10.1 (315.0-345.0)	336.0 ±7.0 (325.0-345.0)	<0.001
Stiffness WOMAC	97.2 ±10.0 (85.0-120.0)	97.9 ±5.4 (90.0-110.0)	0.651
Physical activity WOMAC	1114.3 ±71.1 (1000.0-1050.0)	1137.3 ±67.9 (1250.0-1250.0)	0.058
WOMAC total	1541.1 ±70.6 (1400.0-1675.0)	1571.2 ±66.5 (1445.0-1690.0)	0.012

Foot notes: bold value indicates the level of significance p≤0.05
Abbreviations: SD: Standard Deviation, VAS: Visual Analogue Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table-IV: Comparison of VAS and WOMAC total score of the patients before and after treatment with PRP in group A

Criteria Group A	Before treatment Mean± SD	After treatment Mean± SD	*p* value
VAS	7.57 ±0.56	3.28 ±0.45	<0.001
WOMAC total	1966.63 ±78.69	1541.08 ±70.61	<0.001
Group B			
VAS	7.41 ±0.55	3.57 ±0.49	<0.001
WOMAC total	1974.12 ±91.22	1571.25 ±66.54	<0.001

Foot notes: bold value indicates the level of significance p≤0.05
Abbreviations: SD: Standard Deviation, VAS: Visual Analogue Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index



Discussion

The present randomized clinical trial study had been conducted to compare the effects of intra-articular PRP and HA injection in the management of mild to moderate knee OA. The mean age of the patients was more than 50 years which matched other studies. [11, 23, 24] In the study, conducted in Iran, the mean age of patients was shown 56.0 years and 61.0 years in PRP and HA group respectively while the Italian study found the mean age of patients was 55.0 years and 58.0 years in PRP and HA group respectively.[11,23]. Spakova et al. showed the mean age of patients was 52.0 and 53.0 years in PRP and HA group respectively. [24] More than half of the patients in both groups were found female. Women are about twice as likely as men to develop OA. Although women have a lower prevalence of OA than men before age 50 years, there is a marked increase in prevalence among women after 50.[2]

At the initial stage of treatment, the VAS scores of the patients was 7.6 (±0.5) in group A which significantly decreased to 3.3 (±0.4) after six months of intervention with PRP (p>0.001). The platelet concentrate is activated by addition of calcium chloride, which results in the formation of platelet gel and this stimulate the release of growth factors and bioactive molecules.[26] In group B, the VAS scores also significantly decreased from 7.4 (±0.5) to 3.6 (±0.5) after six months of intervention with HA (p<0.001). The analgesic properties of HA could be attributed to a specific activity on opioid receptors.[27]

After one month of intervention, there was highly significant statistical difference between the two groups regarding the VAS scores (p<0.001) which was consistent at the end of six months (p<0.001) which supported other study (p=0.0034 and p<0.001 respectively).[28]

After one month of treatment, significant statistical difference was observed in the pain subscale between the two groups. However, other subscales and WOMAC total scores did not show any significant statistical difference. After three months of treatment, highly significant statistical difference was observed in the pain subscale and significant statistical difference was observed in the stiffness subscale. However, physical activity subscales did not show any significant statistical difference. At the end of six month, highly significant statistical difference was observed in the pain subscale only. Though, stiffness and physical activity subscales did not show any significant statistical difference, the WOMAC total scores reduced significantly in PRP group than HA group.

This supports the findings of other studies that showed PRP having superior results versus HA in the treatment of knee OA. Sanchez et al.[29] showed that PRP is better in pain, physical activity and overall WOMAC scores in 5 weeks compared to HA (p=0.010). Spakova et al.[24] showed statistically significant better results in the PRP group compared to HA at 3 month follow up periods in WOMAC scores (p<0.01). Kon et al.[30] showed that the PRP group showed better results than the HA group at 6 months follow up (p<0.005). Raeissadat et al. reported that 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). [11]

No adverse effect was observed in any group. PRP is prepared from autologous blood, so any concerns of allergic reactions or disease transfer are eliminated. PRP does not promote hyperplasia, carcinogenesis, or tumor growth.[31]

Conclusion

Findings of the study suggest that the use of autologous PRP and HA are safe and effective methods for treatment of mild to moderate osteoarthritis of the knee. The PRP group had significantly greater reduction in VAS scores at one, three and six months and significantly greater WOMAC physical activity improvement at three and six months compared to the HA group. Multi-centered clinical trial with larger numbers of patients are needed to confirm these findings and to investigate the persistence of the beneficial effects observed.

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