

ORIGINAL ARTICLE

Outcome Comparison between Platelet Rich Plasm in Combination with Hyaluronic Acid Versus Steroid Alone in the Treatment of Primary Knee Osteoarthritis

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Abstract

Background: Platelet-rich plasma (PRP) and hyaluronic acid (HA) are two promising intra-articular therapies for osteoarthritis (OA). These agents have demonstrated effectiveness in the healing and regeneration of OA joints. However, a few studies have assessed their combined effect in the treatment of OA in humans. The present study aimed to fill that gap.

Methods: This open-label randomized clinical trial was conducted among a total of 51 patients with OA of the knee who did not respond to conservative treatment. Equal number of patients were randomly assigned to one of three intervention groups using the block randomization method. Group S (control group) received intra-articular steroids only, Group P (control group) received only PRP, and Group PH (experimental group) was treated with a combination of PRP and HA. All the participants underwent follow-up examinations at the 1st week, 1st month and 3rd month after the procedure. Outcomes were assessed using the visual analogue scale (VAS). All procedure were in accordance with the Declaration of Helsinki. Statistical analysis was carried out using SPSS version 20.

Results: The patient characteristics of the three groups at baseline were statistically similar. Patients had an average age of 46.12 ± 7.16 , 48.53 ± 4.93 and 48.82 ± 2.56 years for groups S, P and PH, respectively ($p > 0.05$). The proportion of males was high in all three groups, and the majority had radiologically grade II disease. The perception of pain assessed by the VAS score showed improvement in all three groups up to 1 month. However, for group S, pain increased after the 1st month. The improvement was considerably higher among the PH patients. Functional outcome assessed by the international knee documentation committee (IKDC) score increased in all three groups over time; the improvement was significantly higher in the PH group than in the other groups although.

Conclusion: The combination of PRP and HA is highly effective against knee osteoarthritis over at least a period of 3 months. Further long-term studies could be carried out to ascertain the duration of effectiveness among OA patients.

Keywords: Platelet-rich plasma, hyaluronic acid, intra-articular steroid, knee osteoarthritis, pain

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Introduction

Osteoarthritis (OA) is the most common form of arthritis, affecting millions of people worldwide. As of 2017, the global prevalence of OA was estimated to be 3.8%¹ by Global Burden of Disease studies. In Bangladesh, an estimated 7.3% of people suffer from osteoarthritis of the knee². OA is a chronic disease characterized by degeneration of articular and other joint tissue cartilage, sclerosis and edema. It impairs the functional capacity and quality of life (QOL) of patients by producing pain, stiffness and limitation in the range of motion of affected joints³. A combination of mechanical, biochemical and cellular alterations occurs in OA, resulting in an abnormal repair response of cartilage⁴. As a result, once injury occurs, it leads to further destruction of the covering cartilage because of its avascularity and limited healing potential. Various pharmacological and non-pharmacological treatments are advised for OA patients⁵. However, if orally administered drugs are ineffective, intraarticular (IA) injection (corticosteroids, viscosupplements, and blood-derived products) is the last nonoperative modality that can be preferred⁶. Although some of these treatments have short and mid-term effects on improving patient function and decreasing pain, none of these options had been shown to delay the progression of the disease or reverse joint damage⁷. In addition, potentially damaging side effects associated with long-term use of these drugs have limited their use^{8,9}. Considering these factors, current research is investigating new methods to stimulate repair or replace damaged cartilage to provide long-term benefit. Intraarticular injection of platelet-rich plasma (PRP) is a simple, low-cost and minimally invasive method that provides the biological environment of growing cells and the physiological combination of all factors that are needed to initiate the healing process. Thus, it creates a positive feedback cycle that sustains itself throughout stages of repair¹⁰. PRP is an appealing treatment option for the stimulation and acceleration of regeneration in joints. Platelets have a high concentration of growth factors and cytokines within their alpha and dense granules. All these molecules may impact soft tissue healing and bone regeneration¹¹. Hyaluronic acid (HA) facilitates the molecular pool released from PRP to reach the target cells by creating a pericellular bioactive scaffold around the cells. The signaling molecules then reach synovial

cells before being degraded and change their secretory pattern to improve joint health. The HA and PRP combination also facilitates cell division and migration, thereby enhancing the healing process⁷. Both PRP and HA have been extensively used for OA treatment. Studies have demonstrated that these agents reduce inflammation through different mechanisms¹². Hence, the combined use of PRP and HA has the potential for synergistic effects in OA. Synergistic anabolic actions of the HA and PRP combination were demonstrated in a 3D arthritic neocartilage and anterior cruciate ligament transection (ACLT-OA) animal model⁷. The purpose of the present study was to assess the synergistic effect of PRP and HA in primary knee osteoarthritis and compare it with monotherapy of PRP and intra-articular steroids.

Methods

Study place and participants

This randomized open label clinical trial was conducted from September 2015 to August 2017 at the Pain Clinic of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. A total of 51 patients aged between 40 and 60 years with symptomatic knee osteoarthritis for at least 4 months who did not respond to conservative treatment with radiological evidence of Kellgren-Lawrence (K-L)13 grade I and II were enrolled in the study. Patients with one or more of the following criteria were excluded: blood diseases, hepatitis B or C, HIV-positive status, infection or septicemia, severe cardiovascular diseases, immunosuppression, advanced and tricompartmental osteoarthritis, rheumatoid or polyarticular arthritis, significant joint swelling or clinical signs of acute inflammation, anatomical deformity (varus-valgus malalignment above 5°, patellofemoral maltracking or untreated instability), total or subtotal meniscectomy (>2/3 excised), pretreatment blood platelet value 25% below the reference value, treatment with corticosteroids for <3 months, medication that could interfere with platelet aggregation for <7 days, and therapy with anticoagulant–antiaggregant.

Participant randomization and treatment allocation

The patients were randomly assigned to one of the three groups: Group S (control group) = intraarticular steroid; Group P (control group) = only PRP; Group

PH (experimental group)= combination of PRP and HA. A randomization sequence was created using www.randomization.com with a 1:1:1 allocation using random block sizes of 3, 6 and 9 by an independent doctor. The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed and stapled envelopes. To prevent subversion of the allocation sequence, the name and date of birth of the participant was written on the envelope. Corresponding envelopes were opened only after the enrolled participants completed all baseline assessments, and it was time to allocate the intervention.

Study procedure

All patients were advised to take prophylactic oral antibiotic tab. cefixime 200 mg before starting the procedure and to continue twice daily for 5 days. All procedures were performed in the operating room. After extraction of 18 mL of peripheral blood using a syringe pretreated with 2 ml of anticoagulant citrate dextrose solution formula (ACDA), the sample was transferred to a sterile PRP kit (Dr. PRP USA LLC, Texas, USA). Then, the kit was placed for two-stage centrifugation according to the recommendations of the manufacturer. We used REMI PRP (Remi group, Maharashtra, India.) device to obtain platelet-rich plasma (PRP) from whole blood. After sterile dressing and draping, intra-articular injection was given to the patient in the supine position, with the knee partially flexed, using the lateral approach with a in the supine position, with the knee partially flexed, using the lateral approach with a 22-gauge needle. For Group P patients, freshly prepared 3 ml autologous PRP was given intraarticularly. For group PH patients, immediately after introducing the needle, 3 ml freshly prepared autologous PRP was first given, and then 2 ml of prefilled sodium hyaluronate was introduced through the same needle. For group S, 1 ml of triamcinolone acetonide with 2 ml 1% lignocaine was pushed in the affected joint. After injection, all patients were instructed for early continuous passive movement to facilitate diffusion and to apply ice at the injected site for 20 minutes at 2-3 hour intervals for 24 hours and advised to avoid NSAIDs and vigorous activities for at least 48 hours.

Follow-up

All participants underwent follow-up examinations

at the 1st week, 1st month and 3rd month after the procedure by personal visits at Follow-up. All participants underwent follow-up examinations at the 1st week, 1st month and 3rd month after the procedure by personal visits at pain clinic. A visual analog scale was used to assess the severity of pain, and the International Knee Documentation Committee (IKDC) score was used to assess functional improvement. All patients were advised to follow Activities of Daily Living Instructions (ADLs) for knee osteoarthritis.

Statistical analysis

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Descriptive analyses were performed, categorical variables were expressed as frequencies (percentages), and continuous variables were presented as the mean \pm standard deviation. Analysis of variance (ANOVA) was used to compare continuous variables among the intervention groups. Chi-square test was used to compare categorical data. A "p" value <0.05 was considered as significant.

Results

The patient characteristics of three groups were statistically similar (Table I).

Table I: Characteristics of patients (n=51)

Character(s) n	Group S 17	Group P 17	Group PH 17	P value
Age (in years)				0.265
Mean \pm SD	46.12 \pm 7.16	48.53 \pm 4.93	48.82 \pm 2.56	
Sex				0.461
Male	9 (52.9)	12 (70.6)	12 (70.6)	
Female	8 (47.1)	5 (29.4)	5 (29.4)	
Radiological OA Grade				0.206
Grade I	2 (11.8)	6 (35.3)	6 (35.3)	
Grade II	15 (88.2)	11 (64.7)	11 (64.7)	
Dominant knee involvement				0.261
Right side	9 (52.9)	5 (29.4)	5 (29.4)	
Left side	8 (47.1)	12 (70.6)	12 (70.6)	
Weight (in kg)	59.29 \pm 3.6	58.12 \pm 9.39	56.41 \pm 5.1	0.437
BMI (kg/m ²)	24.16 \pm 2.	23.06 \pm 2.36	22.72 \pm 1.02	0.107

Continuous values are expressed as the mean \pm SD; within parentheses are percentages over column total. ns= Not significant; p-value reached from ANOVA and chi square test.

The average age of the patients was 46.17 \pm 7.16 years (SD), 48.53 \pm 4.93 years and 48.82 \pm 2.56 years for groups S, P and PH, respectively. The majority

were male, had grade II knee involvement, and had their left knee affected. The average BMI was within the normal range for all groups.

Figure 1 shows the VAS score at pretreatment and different follow-up periods across groups. The average VAS score at pretreatment was not significantly different among the three groups. During the early follow-up at the 1st week, the VAS score decreased in all groups but was not significantly different among the groups. However, at later follow-up during the 1st month and 3rd month, the VAS score decreased more in group PH than in groups P and S, which was statistically significant ($p < 0.05$). Interestingly, the mean VAS score increased in group S after the 1st month.

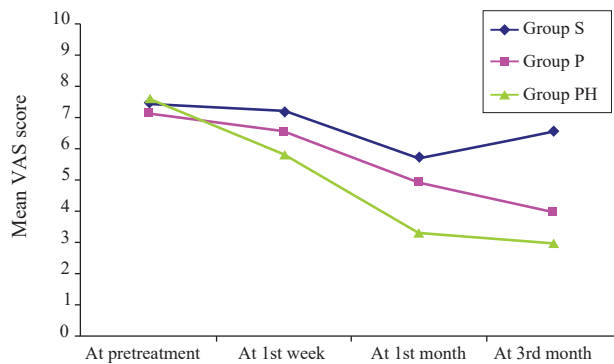


Fig. 1: Line diagram showing the mean VAS score at different follow-up periods.

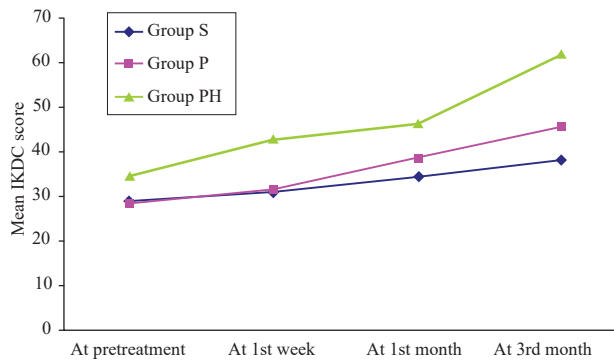


Fig. 2: Line diagram shows the mean IKDC score at different follow-up periods

Figure 2 shows the functional outcome measured by the international knee documentation committee (IKDC) score at pretreatment and at different follow-up visits. The mean IKDC score at pretreatment was statistically similar among the three groups. At the 1st week, 1st month and 3rd month

after treatment, the average IKDC score increased in all groups. However, the increase was significantly higher in group PH than in groups P and S ($p < 0.05$).

Discussion

Osteoarthritis, the most prevalent form of arthritis, has become a major public health problem and causes pain and disability in one-third of all affected patients¹⁴. This randomized clinical trial was carried out with the aim of assessing the effectiveness of PRP and hyaluronic acid (HA) therapy in relieving pain due to primary knee osteoarthritis. A comparison was made with intra-articular platelet-rich plasma (PRP) therapy alone and intra-articular steroid therapy. The outcome was evaluated by the visual analog scale (VAS) for improvement of pain and functional outcome by the international knee documentation committee (IKDC) score. All patient characteristics, including age, sex, weight, BMI, and OA K-L grading, were comparable among the three groups at enrollment, which ensured proper randomization carried out at onset. The functional outcome measured by VAS score and IKDC at pretreatment was statistically similar among the groups ($p = 0.075$). After the intervention, the average VAS score decreased progressively up to the 1st month in all three groups. Then, the decrease continued in groups PH and P. However, participants receiving steroids (group S) showed an increase in VAS score at the 3rd month. The improvement VAS scores were significantly higher in the PH group than in the other groups. The mean IKDC score showed an improvement compared to baseline pretreatment values in all through groups at the 1st week, 1st month and 3rd month after the treatment. However, IKDC scores were significantly different among the three groups ($p < 0.05$), with the score showing the highest improvement in the PH group. Sanchez et al.¹⁵ showed that PRP improved pain, physical activity and overall WOMAC scores for up to 5 weeks better than hyaluronic acid. Spakova et al.¹⁶ showed significantly better results in the PRP group than in the HA group at the 3 and 6-month follow-up periods in both WOMAC and numeric rating scale (NRS) scores. In another study, Kon et al.¹⁷ compared PRP to hyaluronic acid and concluded that autologous PRP injections provide increasingly longer efficacy than HA injections in reducing pain and symptoms and recov-

ering articular function up to 6 months. In a placebo-controlled randomized clinical trial, Patel et al.¹⁸ treated 78 patients (156 knees) with bilateral osteoarthritis. Patients were divided randomly into 3 groups: Group A was treated with a single PRP injection, Group B was treated with 2 PRP injections 3 weeks apart, and Group C was treated with a single normal saline injection. Outcomes were evaluated by WOMAC and VAS score. It was verified that the groups treated with a single or double injection of PRP had an improvement in relation to placebo Spaková et al.¹⁶ and Lubowitz et al.¹⁹ studies have suggested that the combined application of hyaluronic acid and PRP may have potentially positive effects on cartilage repair and may slow down the progression of OA. Combining various strategies for OA management is not a new concept and has been tried by many researchers Manunta et al.²⁰. assessed the efficacy of associating the microfracture technique with platelet-rich plasma (PRP) injections in the treatment of chondral lesions to promote acceleration and optimization of the healing process. Microfracture is a technique in which the subchondral bone is penetrated to stimulate the formation of a new articular surface. Their results also showed a better functional outcome (based on the IKDC score) in the patients treated with the combination of PRP and microfractures, even at 12 months. Similarly, many preclinical studies explain the success behind the combination of hyaluronic acid and PRP therapy observed in our study. Studies show that HA provides an appropriate matrix and supportive scaffold material for cartilage repair and enhances the mechanical properties of the cartilage^{21,22}. Another study compared the effects of PRP or HA on inflammation, as measured by TNF- α , IL-6 and IL-8 proteins; they found that although both treatments decreased TNF- α production, IL-6 was decreased only in HA treated but not in PRP-treated cells, suggesting that both treatments influence inflammation through different mechanisms. The expression of catabolic enzymes such as metalloproteinases was reduced in synoviocytes and chondrocytes treated with PRP but not in cells treated with HA. Thus, HA and PRP are beneficial for joint cells through different mechanisms, explaining their potential synergistic effect when combined¹². Anitua et al.²³ evaluated the potential of pure PRP to induce tendon cell and synovial fibroblast migration and examined whether

the combination of PRP with HA improves motility *in vitro*. Their study showed that 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 35% in motility was observed in the case of the combination treatment compared to HA alone. These findings prove that PRP improves the biological properties of HA. The same has also been supported by Marmotti et al.²⁴ in his *in vitro* study. Synergistic anabolic actions of the HA and PRP combination have also been demonstrated in a 3D arthritic neocartilage and anterior cruciate ligament transection (ACLT-OA) animal model. Indeed, the combination of HA and PRP can synergistically promote cartilage regeneration and inhibit inflammation in the joint²⁵. Based on these concepts, Andia et al. (2014) observed that HA and PRP may be better than PRP alone. Our findings endorse their observation. This study showed that the combination of HA and PRP was very safe, as no complications, such as infection or fever, occurred among the study subjects. Only minor adverse events were detected, such as mild pain at the injected area and skin bruises. Patel et al.¹⁸. reported mild complications such as nausea and dizziness, which were of short duration, but these complications were not reported in our patients. Altogether, platelet-rich plasma (PRP) has a significant positive effect on patients with primary knee osteoarthritis, and PRP in combination with hyaluronic acid provides better pain improvement and functional outcome than PRP alone. Our study was limited in that blinding of treatment was not possible. Additionally, it was a single center study. However, this was one of the earliest reports of the combination of PRP and HA in the treatment of OA, which found a significantly better improvement in this group of patients.

Conclusion

The present study showed that the intra-articular combination of platelet-rich plasma with hyaluronic acid was highly effective for OA of the knee and can provide better pain relief and improved functional status than PRP and steroid therapy alone. Therefore, the combined use of platelets to reach plasma and hyaluronic acid should be considered for patients with resistant osteoarthritis. Further large-sample and long-term follow-up studies are recommended to assess the long-term effect of

PRP and HA therapy in osteoarthritis patients.

Declaration

Ethics approval:

The study protocol was approved by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University Hospital.

Author Contributions:

Conception and development of the idea: MSR, SAI, SS, MJH, and FA

Data collection: MSR, SAI, SS

Data analysis: MSR

Writing - Original Draft Preparation: MSR, SAI, SS, JH, and FA

Review & Editing: MSR, SAI, SS, MJH, and FA

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