

Effects of Platelet Rich Plasma in Combination with Hyaluronic Acid in the Treatment of Primary Knee Osteoarthritis

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Abstract

Background: Platelet Rich Plasma (PRP) is increasingly applied in clinical practice to treat knee degenerative pathology. Both PRP and hyaluronic acid (HA) have been extensively used to improve lubrication, modulate inflammation and modify the catabolic micro-environment of the joint. **Objective:** This study was aimed to evaluate the potential synergistic effects of PRP in combination with hyaluronic acid in primary knee osteoarthritis. **Methodology:** This randomized control trial was carried out on adult patients with primary knee osteoarthritis who attended the Pain Clinic of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, during the period of September 2015 to August 2017. The patients were randomly assigned to one of the two groups designated as group P (control group) who were only treated with PRP and group PH (experimental group) who were treated with the combination of PRP and hyaluronic acid. After providing the allocated treatment, all patients were undergone follow-up examination at 1st week, 1st month and 3rd month for pain improvement by VAS scale and for functional improvement by International Knee Documentation Committee (IKDC) score. **Results:** A total number of 34 patients were recruited for this study. Visual analogue score 1st month (5.85 ± 0.83) and 3rd month (3.01 ± 0.12) follow up showed statistically significant difference among two group ($p=0.001$). Inter group comparison showed that, mean VAS score of group PH (3.01 ± 0.12) decreased more than Group P (4.01 ± 1.01). In case of functional improvement, group PH also showed statistically better improvement during 1st month (45.76 ± 3.25) and 3rd month (62.06 ± 5.37) follow up than Group P. **Conclusion:** In conclusion articular platelet rich plasma in combination with hyaluronic acid provide better pain relief and improvement of functional status than PRP therapy alone in primary knee osteoarthritis. [Journal of National Institute of Neurosciences Bangladesh, 2019;5(2): 137-142]

Keywords: Platelet rich plasma; hyaluronic acid; knee osteoarthritis; pain

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Introduction

Osteoarthritis is a disorder involving joints characterized by cell stress and extracellular matrix degradation initiated by micro and macro-injury that activates maladaptive repair responses including pro-inflammatory

pathways of innate immunity¹. This condition impairs functional capacity and decrease quality of life (QOL) in patient's by producing pain, stiffness and limitation in range of motion of the joint².

Hyaline cartilage enables almost frictionless joint

movement and protects the underlying bone from excessive load and trauma³⁻⁴. In osteoarthritis, a combination of mechanical, cellular, and biochemical processes, resulting in abnormal repair response of cartilage that ultimately leads to cartilage injury⁵⁻⁷. Once cartilage is injured, it gradually degenerates, and leads to osteoarthritis.

Various conservative treatment modalities are recommended by various clinical guidelines for treatment of knee osteoarthritis. The non-pharmacological modalities are patient education and self-management, exercises, weight reduction, transcutaneous electrical nerve stimulation therapy. Pharmacologic therapies are paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and slow-acting drugs (glucosamine and chondroitin sulfate). If orally administered drugs are ineffective, intra-articular (IA) injection (corticosteroids, visco supplements, blood-derived products) is the last non-operative modality that can be preferred⁸.

Although some of these treatment have short and mid-term effect on improving patients function and decreasing pain but none of these options has shown to delay the progression of the disease or reverse joint damage⁹. Beside these, various side effect has limited the use of NSAID and corticosteroid injection^{10,11}. Considering these factors, current research is investigating new methods to stimulate repair or replace damaged cartilage to provide long term benefit. Platelet Rich Plasma (PRP) is a simple, low- cost and minimally invasive method containing a natural concentrate of autologous growth factors from the blood to provide the biological environment of the growing cells with a combination of all factors that are needed to initiate the healing process¹².

Platelets have a high concentration of growth factors and cytokines within their alpha and dense granules. Alpha granules of the platelet contains several vital growth factors like platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) among others. Beside these the dense granules of the platelet contain neuromodulators and inflammatory mediators such as histamine and serotonin. All the aforementioned growth factors and cytokines may impact soft tissue healing and bone regeneration¹³. Both PRP and hyaluronic acid (HA) have been extensively used for OA treatment to improve lubrication, modulate inflammation and modify the catabolic micro-environment not only for reducing clinical symptoms,

but also to interfere with OA progression.

Hyaluronic acid facilitates the molecular pool released from PRP to reach the target cells by creating a pericellular bioactive scaffold around the cells. This pericellular matrix facilitate molecular diffusion and also adequate presentation of cytokines to their trans-membrane receptors located in the cytoplasmic membrane of the target competent cell. Another advantage of HA and PRP combination is facilitation of cells division and migration as this is a common hallmark of matrices that are rich in HA⁹.

Sundman et al¹⁴ showed in his basic clinical study that, separately hyaluronic acid and platelet rich plasma are beneficial for joint cells although they function through different mechanisms andb hypothesized that their combination may be synergistic. A synergistic anabolic actions of hyaluronic acid and platelet rich plasma combination has been also demonstrated in a 3D arthritic neo-cartilage and anterior cruciate ligament transection (ACLT-OA) model of animal⁹.

The purpose of the present study is to assess the potential synergistic effects of platelet rich plasma in combination with hyaluronic acid in primary knee osteoarthritis and to evaluate the effectiveness PRP as mono therapy and compare their effectiveness on chronic knee pain.

Methodology

This randomized control trial was conducted from September 2015 to August 2017 at Pain Clinic, Bangabandhu Sheikh Mujib Medical University, Bangladesh. It was a parallel designed, single blinded and single center study. After institutional ethical Board approval patients aged between 40 to 60 years, with symptomatic knee osteoarthritis for at least 4 months, not responding to conservative treatment with radiological evidences of K-L grade I and II were enrolled into the study. Patients refusal along with blood diseases, hepatitis B or C, HIV-positive status, infection and septicemia, local infection, severe cardiovascular diseases and immunosuppression, advanced and tri-compartmental osteoarthritis, rheumatoid or polyarticular arthritis, significant joint swelling or clinical signs of acute inflammation, anatomical deformity (Varus-valgus mal-alignment above 5°, patella-femoral maltracking or untreated instability), and total or subtotal meniscectomy (more than 2/3 excised), pretreatment blood platelets value 25% below the reference value, treatment with corticosteroids less than 3 months or medication less than 7 days that could interfere with platelet aggregation and patients on therapy with

anticoagulants–antiaggregants were excluded from the study. The patients were randomly assigned to one of the two groups where group P (control group) treated with only PRP therapy and group PH (experimental group) treated with combination of PRP and hyaluronic acid (correction made as per advice). They were advised to take prophylactic oral antibiotic tab. Cefixime 200 mg before starting of 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 pre-treated with 2 ml of anticoagulant Citrate Dextrose Solution Formula (ACDA), 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 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 by 22 gauge needle. For Group P patient, freshly prepared 3 ml autologous PRP were given intra-articularly and for group PH patient, immediately after introducing needle 3 ml freshly prepared autologous PRP was given first, then 2 ml of prefilled sodium hyaluronate was introduced through the same needle. After injection, all patients were instructed for early continuous passive movement to facilitate its diffusion and to apply ice at the injected site for 20 minutes at every 2-3 hours interval for 24 hour and to avoid NSAIDs and vigorous activities for at least 48 hour. All patients were undergone follow-up examination at 1st week, 1st month and 3rd month after the procedure by personal visit at Pain Clinic. Visual analog scale was used to assess the severity of pain and International Knee Documentation Committee (IKDC) score was used to assess the functional improvement. All patients were advised to follow Activities of Daily Living Instructions (ADLs) for knee osteoarthritis. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). A descriptive analysis was performed for all data. The mean values were calculated for continuous variables. The qualitative observations were presented as frequencies and percentages. Unpaired t-test was used to compare continuous variables between control and experimental group. Chi-square test was used to compare categorical data like clinical signs and symptoms. A “p” value <0.05 was considered as significant.

Results

Two groups matched statistically comprising age, weight, sex, OA grade, BMI having no difference between them (Table 1).

Table 1: Characteristics of studied subject in two groups

Character(s)	Group P	Group PH	P value
Age (in years)			
Mean±SD	48.53±4.93	48.82±2.56	0.830ns
Sex			
Male	12 (70.6)	12 (70.6)	1.000ns
Female	5 (29.4)	5 (29.4)	
Radiological OA Grade			
Grade I	6 (35.3)	6 (35.3)	1.000ns
Grade II	11 (64.7)	11 (64.7)	
Dominant knee involvement			
Right side	5 (29.4)	5 (29.4)	1.000ns
Left side	12 (70.6)	12 (70.6)	
Weight (In kg)	58.12±9.39	56.41±5.1	0.066ns
Range (min,mix)	52,72	49,61	
BMI (kg/m ²)	23.06±2.36	22.72±1.02	0.589ns

*values are expressed as mean±SD. Within parenthesis are percentages over column total. ns= Not significant; p value reached from unpaired t –test and chi square test.

Table II shows VAS score at pretreatment and different follow up period. Mean VAS score at pretreatment were not statistically significant among two groups. Early follow up at 1st week VAS score was not significantly different but at later follow up during 1st month and 3rd month VAS score decreased more in group PH than group P, which was statistically significant.

Table 2: VAS score at different follow up period of two studied groups

VAS Score	Group P	Group PH	P value
At pretreatment	7.21±0.83	7.65±0.51	0.718ns
At 1st week	6.59±1.28	5.85±0.83	0.054ns
At 1st month	4.94±0.83	3.35±0.83	0.001s
At 3rd month	4.01±0.10	3.01±0.12	0.001s

Values are expressed as Mean±SD, s= significant, ns= non-significant, p value reached from student t-test.

Figure 1 shows functional outcome measured by International knee documentation committee (IKDC) score at pretreatment and different follow up period to assess the functional outcome in line diagram.

Mean IKDC score at pretreatment were not statistically significant among two groups. But at 1st week, 1st month and 3rd month follow up period, mean IKDC

score was increased more in group PH than group P. At 1st week, 1st month and 3rd month outcome were statistically significant (<0.05).

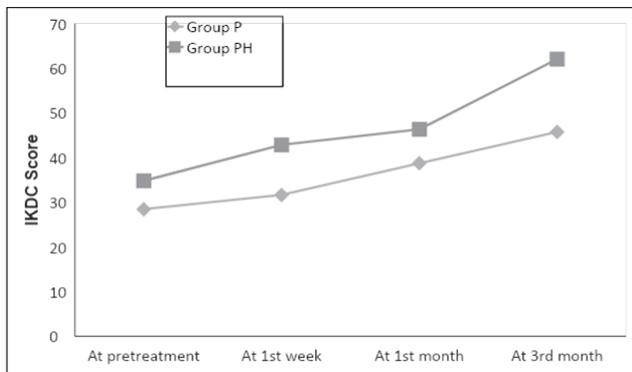


Figure 1: Line diagram shows mean IKDC score at different follow up period.

Discussion

Osteoarthritis being the most prevalent form of arthritis has become a major public health problem and causing pain and disability in one third of all affected patients¹⁵. This randomized clinical trial was carried out with the aims to assess the effectiveness of intra-articular platelet rich plasma (PRP) therapy alone versus combined PRP and hyaluronic acid (HA) therapy in relieving pain due to primary knee osteoarthritis, been evaluated by visual analog scale (VAS) for improvement of pain and functional outcome by international knee documentation committee (IKDC) score¹⁶. This study also compare the outcome between two treatment groups.

All the demographic variables like age, sex, weight, BMI, OA K-L grading were almost alike between two groups and statistically non-significant. In this current study it was observed that mean VAS score at pretreatment were not statistically significant among two groups ($p=0.718$). Early follow up at 1st week VAS score was not significantly different but at later follow up during 1st month and 3rd month VAS score decreased more in group PH than group P, which was statistically significant.

In this current study functional outcomes were evaluated using the International Knee Documentation Committee (IKDC) scores. Mean IKDC score at 1st week, 1st month and 3rd month were statistically significant ($p<0.05$) among two group. This study results showed that mean IKDC score was significantly ($p<0.05$) increased in group PH than group P. Group PH had significantly more improvement ($p=0.001$) at all follow-up period.

Sanchez et al¹⁷ showed that PRP is better in pain, physical activity and overall WOMAC scores improvement upto 5 weeks compared to hyaluronic acid. Spakova et al¹⁸ showed statistically significant better results in the PRP group compared to HA at 3 and 6 month follow up periods in both WOMAC and numeric rating scale (NRS) scores. In another study Kon et al¹⁹ comparing PRP to hyaluronic acid concluded that autologous PRP injections provide more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function upto 6 month. In a placebo controlled randomized clinical trial, Patel et al²⁰ treated 78 patients (156 knees) with bi-lateral osteoarthritis. Patients were divided randomly into 3 groups as Group A treated by a single PRP injection, group B by 2 PRP injections 3 weeks apart, and group C by 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 of placebo. Spaková et al¹⁸ and Lubowitz et al²¹ studies have suggested that the application of hyaluronic acid and PRP may have potentially positive effects on cartilage repair and slow down the progression of OA. Manunta et al²² assess the efficacy of associating the micro-fracture 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 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.

However, there are many pre-clinical study that explains the success behind combination of hyaluronic acid and PRP therapy observed in this study. Studies show that HA provides appropriate matrix and supportive scaffold material for cartilage repair and enhances the mechanical properties of the cartilage²³⁻²⁵. 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 cultures, but not in PRP treated cells, suggesting that both treatments influence inflammation through different mechanisms. The expression of catabolic enzymes like metalloproteinases was reduced in synoviocytes and chondrocytes treated with PRP but not in cells treated with HA. Thus, separately, HA and

PRP are beneficial for joint cells although they function through different mechanisms. Thus they concluded that their combination may be synergistic¹⁴. Anitua et al²⁶ 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. Their study shows 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 33.5% in motility was observed in the case of HA and PRP treatment compared with HA. Therefore, this in vitro study definitely proves that PRP improves the biological properties of HA. The same has also been supported by Marmotti et al²⁷ in his vitro study.

A synergistic anabolic actions of HA and PRP combination has been also demonstrated in a 3D arthritic neo-cartilage and anterior cruciate ligament transection (ACLT-OA) model of animal. Indeed, the combination of HA and PRP can synergistically promote cartilage regeneration and inhibit inflammation in the joint²⁸.

Our study showed that this method of treatment is very safe as no complications such as infection or fever occurred among study subjects. Only minor adverse events were detected such as mild pain at injected area and skin bruises. Patel et al²⁰ reported mild complications such as nausea and dizziness, which were of short duration but these complications were not reported in these patients.

Altogether, platelet rich plasma (PRP) has significant positive effect on patients with primary knee osteoarthritis and PRP in combination with hyaluronic acid provide better pain improvement and functional outcome than PRP alone.

Conclusion

The present study shows that intra articular platelet rich plasma in combination with hyaluronic acid provide better pain relief and improvement of functional status than PRP therapy alone in primary knee osteoarthritis. So combination treatment could be recognized as a future regenerative osteoarthritis therapy.

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