

COMPARING CLINICAL AND BIOLOGICAL EFFECTS OF INTRA-ARTICULAR INJECTION OF PLATELET-RICH PLASMA AND HYALURONIC ACID AMONG PATIENTS WITH MILD TO MODERATE KNEE OSTEOARTHRITIS**Dr. Burhan Zafar*, Dr. Jazirah Rehmat, Dr. Javeria Ali, Wardah Rehmat and Waqas Khan**

Sheikh Zayed Medical College and Hospital, Rahim-Yar-Khan, Punjab, Pakistan.

***Corresponding Author: Dr. Burhan Zafar**

Sheikh Zayed Medical College and Hospital, Rahim-Yar-Khan, Punjab, Pakistan.

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ABSTRACT

Background: Knee osteoarthritis is considered among the common articular diseases. The modern therapeutic methods including the use of platelet-rich plasma (PRP) are responsible for stimulating the healing process of cartilages and improve the damage. Moreover, increase in the incidence of osteoarthritis has forced to conduct this study by assessing long-term impact of intra-articular injection of PRP and Hamon quality of life of the patients suffering from osteoarthritis. **Purpose:** The main aim of this study is to compare the clinical and biological impact of PRP and HA among patients with mild to moderate knee osteoarthritis. **Methods:** The study is based on randomized control trial by recruiting 54 patients suffering from knee osteoarthritis. The patients were divided into 2 groups with 26 patients in each group. Group I (PRP injections) PRP intraarticular injections; whereas, group II was administered HA injections. The patients were evaluated before receiving treatment and 6 months after receiving the desired treatment. The results were analyzed through descriptive statistics. **Results:** The results have shown reduction in pain among both the groups after 6 months of receiving treatment. PRP injections proved to be more effective among the patients with lower grades of osteoarthritis. The VAS scored improved by 50% from its initial value for the group of patients who were administered PRP injections after 3 months of receiving treatment. However, these results were obtained among the patients administered HA injections after a period of 6 months. However, both the treatment modalities improved the knee pain without any statistically significant difference between them. **Conclusion:** As compared to HA injection, PRP injection was more effective in improving pain after final filtration among the lower grades of osteoarthritis patients.

KEYWORDS: Intra-articular Injection, Platelet-Rich Plasma, Hyaluronic Acid, Knee Osteoarthritis.**INTRODUCTION**

Knee osteoarthritis (OA) is known as a chronic progressive condition, which affect the individuals older than 45 years (Lawrence et al., 2008). It is likely to cause loss of work performance due to lower back pain. A sharp increase in knee arthroplasty has been observed with increase in life expectancy, which results in certain economic burdens for controlling pain and rehabilitating patients. The search for less aggressive alternatives for joint replacement has increased due to increase in the average life expectancy (Montañez-Heredia et al., 2016). The main aim of these treatments is to decrease pain, prevent/correct deformity, increase mobility, and slow down the progression of disease. Although, there are many treatments for knee OA, but all have certain benefits and disadvantages.

Some of the treatments like intra-articular corticosteroid and steroidal anti-inflammatory drugs (NSAIDS) possess adverse systemic effects resulting in destruction of joint cartilage, which might flare up the process of

osteoarthritis (Kon, 2012). In the recent years, the therapeutic options effective in the process of tissue healing are considered to prevent the progression of osteoarthritis because of increased cost of managing knee OA (Gobbi t al., 2012). The growth factors play an important role in the healing and remodeling of the tissue cartilage. They are also effective in the differentiation of mesenchymal stem cells, chemotaxis, and synthetic activities of cartilaginous and osseous cells.

Platelet-rich plasma (PRP) is known as an autologous biological treatment, which contain certain growth factors that release from endogenous fibrin scaffold and platelets (Sánchez et al., 2008). PRP is responsible for stimulating the cascade of natural healing process and tissue regeneration via 'supra-physiologic release of the factors derived from the platelets into the site of treatment, directly. Depending upon the contents of leukocyte and fibrin, PRP has been classified into 4 categories; leukocyte- and platelet-rich plasma (L-PRP), pure platelet-rich plasma (P-PRP), leukocyte- and

platelet-rich fibrin (L-PRF), and pure platelet-rich fibrin (P-PRF) (Ehrenfest *et al.*, 2009). There is significant increase in the application of biological treatments including PRP in the musculoskeletal disorders. The intra-articular injections are the most common therapeutic approach for administering PRP injection because it can easily be performed in an outpatient setting (Montañez-Heredia *et al.*, 2016).

Hyaluronic acid (HA) comprises of repeated units of acetyl glucosamine and D-acid glucuronic, which is synthesized by fibroblasts, chondrocytes, and synoviocytes. It has high molecular weight and is present within the synovial fluid. It functions as a lubricant for the synovial fluid (Raeissadat *et al.*, 2015). The dilution of synovial fluid, molecular fragmentation and abnormal production of synoviocytes results in decrease of the molecular weight and concentration of HA. HA plays an important role in providing mechanical support; however, the mechanism of intra-articular injection of HA to improve the symptoms of osteoarthritis is not clear (Raeissadat *et al.*, 2015).

The proteins released from platelet's alpha granules tend to increase the release of angiogenic growth factors, which significantly contribute towards tissue regeneration. Good and satisfying results within the soft tissue injuries have been achieved through local infiltration of PRP. The use of PRP in articular pathology has not been proved by controlled studies; however, it plays an important role to stabilize angiogenesis in arthritic knees (Montañez-Heredia *et al.*, 2016). Intra-articular injections of PRP and hyaluronic acids are given before performing surgical treatment, when pain persists even after administering analgesics and anti-inflammatory drugs (Ringdahl & Pandit, 2011). A previous study has shown that PRP tends to be more effective as compared to HA in controlling pain associated with osteoarthritis (Ringdahl & Pandit, 2011).

The use of PRP injections for easing osteoarthritis pain as compared to HA has demonstrated mixed clinical and biological outcomes within the randomized control trials (Raeissadat *et al.*, 2015). Studies depicting the amount and duration of efficiency of PRP and its comparison with HA lacks severely, despite of its wide clinical applications. There are only few studies that have compares PRP and HA as a treatment for knee osteoarthritis. Moreover, HA is being used more frequently as compared to PRP, despite of its conflicting impact. Therefore, the present study aims to compare the clinical and biological impact of PRP and HA among patients with mild to moderate knee osteoarthritis.

Research Questions

1. Is there any difference between the clinical and biological effects of PRP and HA among the patients suffering from knee osteoarthritis?

2. Which treatment is much effective in minimizing the feeling of pain among the patients suffering from knee osteoarthritis?

Hypothesis

H0: There is significant difference between clinical and biological effects of PRP and HA among the knee osteoarthritis patients.

H1: There is no significant difference between clinical and biological effects of PRP and HA among the knee osteoarthritis patients.

MATERIAL AND METHODS

Study Design

The present study is an interventional study that has been registered as EUDRACT: 2013-001303-36 in European Clinical Trials Database

Study Participants

Initially, the study has recruited 54 patients suffering from knee pain from January 2018 to March 2018. The study was approved and declared to meet the ethical standards by the ethics committee a renowned hospital. The patients were given full detail about the study and its significance in a written form before conducting the study. Informed consent was obtained from all the patients before recruiting them in the study.

Exclusion and Inclusion Criteria

The patients aged between 45 – 85 years of age, arthritis level I, II or III, and pain intensity more than 5 (according to Visual Analogue Scale) were recruited in the study. The patients who were positive for syphilis, HIV, or Hepatitis were excluded. Moreover, any patient with appearance of pathology and required necessary anticoagulation was also excluded. On the other hand, patients with platelet count more than 150.000/mm³ was included in the study. All the recruited patients were strictly told not to take any kind of anti-coagulants and anti-aggregants 5 days before the blood extraction.

Study Setting

After completion of the recruitment phase, the patients were assigned a table of random numbers. The patients were divided into 2 groups; group I and group II with 27 patients in each group. Group I has been injected with PRP; while group II has been injected with HA.

Clinical Evaluations

150 mL of venous blood was drawn from all the patients through a sixteen-gauge needle. The blood was collected in a bag that contained 21 mL of citrate, phosphate, and dextrose. 150 mL of blood was equally poured into for Falcon test tubes and those tubes were subjected to double centrifugation and cellular testing. Three intra articular injections have been administered to each patient with an interval of 15 days. The infiltrations used in this study were not ultrasound guided and local anesthesia was not used. Among the patients of group I,

PRP was administered at 37 degree centigrade after thawing for around 30 minutes. Group II patients were given HA in the form of sodium hyaluronate, which was obtained from bacteria cultures. The methods and injections of PRP and HA including their benefits and adverse effects were explained by a physiatrist.

The evaluation scales were applied at beginning of the study and were repeated after 6 months followed by the final infiltration. The evaluation scales used in this study are as follows;

- Visual Analogue Scale – to measure the intensity of pain among the patients.
- Knee and Osteoarthritis Outcome System – to measure pain, symptoms, functioning in sports, functioning in daily life, and recreational activities.
- European Quality of Life Scale – to provide data related to quality of living standards of all the patients.

The skin was properly prepped and draped before administering injections. The patients were asked to flex and extend their knees after administration of the injection. The second and third injections were administered in the same way after gap of 15 days. The patients were allowed to go home after giving injection but were advised to rest for 24 – 48 hours and do not

exert pressure over the injected joints. Although the patients were restricted from using any kind of analgesics, steroids, or NSAIDS; however, they were prescribed acetaminophen with codeine if pain continued. Follow up was taken from all the patients after 4 weeks, 24 weeks, and 52 weeks. The patients were assessed for measuring analgesics dose, stiffness, swelling, and pain in the joint

Statistical Analysis

The condition of knees before and after the treatment was observed and evaluated using Statistical Package of Social Sciences version 20.0.

RESULTS

The baseline characteristics including age, BMI, gender, and grade of osteoarthritis have been demonstrated in table 1. The results have shown that the mean age of patients in group I was 52.36 years and group II was 54.87 years. Among 26 patients in group I, 6 were males and 20 were females; whereas, in group II 8 patients were males and 18 were females. The BMI for group I and II was 26.20 and 27.56, respectively (Table 1). Majority of the recruited patients were suffering from low grade osteoarthritis (grade I and grade II) (Table 1).

Table 1: Baseline Characteristics of study participants.

Variable	Group I (PRP)	Group II (HA)
Age	52.36 years	54.87 years
Gender		
Male	6	8
Female	20	18
BMI	26.20	27.56
Grade of Osteoarthritis		
Grade 1	5	7
Grade 2	9	10
Grade 3	10	6
Grade 4	2	3

Clinical Outcomes

The preliminary results of both the groups have shown decrease in WOMAC mean parameter after 6 months. Moreover, this decrease was much evident among the patients of group I ($p < 0.05$). Table 2 has shown that

stiffness and physical fitness of the patients in group I had improved significantly. The results have clearly shown that administration of PRP has produced promising results by minimizing pain and stiffness of the joints, unlike the administration of HA injections.

Table 2: WOMAC Index Scores (Pain, stiffness, and physical function) obtained during the study period.

Study Groups	Pain	Stiffness	Physical Function
Group I (PRP)			
Baseline	8.57	2.8	29.08
6-months	4.23	1.39	14.02
Difference between baseline and 6-months	4.34	1.41	15.06
P - Value	0.05	0.05	0.05
Group II (HA)			
Baseline	6.80	1.78	18.99
6-months	5.19	2.25	18.24
Difference between baseline and 6-months	1.61	0.47	0.75
P- Value	0.029	0.19	0.87

DISCUSSION

PRP injections have evolved as an alternative treatment for osteoarthritis. The present study has aimed to compare the effectiveness of PRP and HA injections to treat osteoarthritis in the context of public health care system. As compared to placebo, these injections have proved to improve the pain control. In agreement with the previous studies (Sánchez *et al.*, 2012; Filardo *et al.*, 2012a; Spaková *et al.*, 2012), the present study has used HA as a control treatment. There is doubt in the suitability of using frozen samples because of reduction in the concentration of growth factor. However, a study conducted by Roffi *et al.* (2014) showed that freezing is not likely to alter the beneficial impact of PRP on chondrocytes. The concentration of growth factors in PRP injections fulfils the requirement of the platelet's concentration, which has been used for transfusion therapy.

A recent study conducted by Cole *et al.* (2017) compared the clinical and biological effects of PRP and HA among the patients suffering from knee osteoarthritis. The results showed no difference between HA and PRP at any time point in the primary outcome measure. A significant decrease in 2 proinflammatory cytokines suggested that the anti-inflammatory properties of PRP may contribute to an improvement of symptoms (Cole *et al.*, 2017). The intra articular appears to be reduced after six months from treatment because of the benefits provided by intra articular injection of PRP (Dold *et al.*, 2014). It has been shown that PRP injections are more affected as HA injections. However, they are not affected and show more effectiveness for people in the treatment of knee osteoarthritis. The previous studies have been associated with pre-clinical and clinical trials having pronounced effect of PRP among osteoarthritis patient (Spaková *et al.*, 2012). The inflammatory potential of PRP, important role played in the regeneration of cartilage, and its anabolic effects are associated with anti-inflammatory potential of PRP (Xie *et al.*, 2014).

The results have also shown the effective nature of HA to reduce pain and improve viscoelasticity of synovial fluid; although, the clinical evidence has shown increased effectiveness of PRP over HA. A study has also reported combined usage of PRP and HA, which demonstrated that addition of PRP was not harmful for basic research and preclinical and clinical trials (Russo *et al.*, 2016). The results of present study have clearly shown the efficiency of PRP and HA injections among the patients with knee osteoarthritis, who was experiencing pain. The increased effectiveness of PRP over HA resulted in significant improvement in function and quality of life of the patients (Cole *et al.*, 2017).

Similar to present study, another study conducted by Chang *et al.* (2014) compared PRP and HA injection within the performance of a systemic review. The results showed that significant functional improvements were observed among the patients, who were injected PRP and

its impact is likely to last for 12 years. The patients of PRP group have more and longer improvement as compared to the patients, who received HA injections. Another study conducted by Khoshbin *et al.* (2013) also produced similar results. The symptoms of improving clinical symptoms and relieving pain are likely to decrease after 6 months of receiving the injection. Another study conducted by Rodriguez-Merchan (2013) suggested that around 3 – 5 weekly injections are needed to be administered among the osteoarthritis patients before going through any surgical treatment.

A study conducted by Filardo *et al.* (2012b) compared the PRP and HA injections in treating knee osteoarthritis among a total of 109 patients. Both the injections were administered three times with an interval of 1 week. The end results showed significant improvement among both the groups in all the parameters. Therefore, the results concluded that HA has no priority over HA among the middle-aged patients with moderate osteoarthritis. Another study conducted by Raeissadat *et al.* (2017) was based on single blinded randomized clinical trial that recruited patients with symptomatic osteoarthritis of knee. The results showed no statistical difference between PRP and HA groups regarding satisfaction and decrease in pain. Therefore, the study concluded that both the treatment modalities are effective in decreasing pain among the patients suffering from osteoarthritis pain before undergoing surgery.

CONCLUSION

The results of present study have considered PRP injections to a useful therapeutic option among patients suffering mild to moderate osteoarthritis. The increased number of promising studies has depicted PRP as a novel portion in the management of pain associated with osteoarthritis. PRP injections have proved to be effective to reduce pain and improve functionality of the patients along with an effectiveness pattern to HA, which was taken as control treatment group. PRP injections showed significant improvement in quality of life of the patients; although, there was no statistically significant difference in controlling pain among both the treatments. However, the final conclusion of the study stated that PRP injections were likely to be more effective as compared to HA among the patients suffering from mild knee osteoarthritis.

There is no evidence yet, which favors the efficiency of PRP in traumatic chondral pathology. Therefore, the future studies need to focus on comparing PRP with placebo and other surgical treatments. It is believed that the impact of PRP and HA injection decrease after the period of months; therefore, future studies need to conduct 1-year study to reveal how long do these injections produce their pain-relieving effect. Another limitation of this study includes lack of objective evaluation of the impact of both the treatments on soft tissues, cartilages, and peri-articular structure of the knee and lack of placebo control group. Almost all the study

findings are based on subjective findings, despite of its wide application in the clinical setting. Therefore, future studies need to include objective findings in their analysis (such as MRI) to report much effective results.

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