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RESEARCH ARTICLE

Single Shot of Knee Intraarticular Injection of Platelets Rich Plasma versus Hyaluronic Acid Injections for Symptomatic Knee Osteoarthritis. An Observational Prospective Study

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Abstract
The aim of this study was to evaluate the effectiveness and safety of intra-articular PRP and HA in KOA patients. Methods: The current work was prospective randomized observational. Participants were divided into two groups. Group 1; 1 intra-articular PRP injection (15 mL) in 72 patients and Group 2; A single intra-articular injection of HA (80 mg/4 mL) was administered to 72 patients. All patients were evaluated before infiltration and 1, 3, 6, and 12 months after injection. Results: No significant difference was detected in the demographic distribution (gender and age) and Grade RT, Grade RL, Grade II OA and Grade III OA classifications of patients who received intra-articular PRP or HA injection for knee OA ($p>0.05$). Compared with the HA group WOMAC mean of 48.8 and $p<0.05$, there was no significant change in the PRP groups with the WOMAC mean of 68.9. At month 3, each group had significantly reduced overall WOMAC score compared to baselines in both groups. The mean WOMAC was 48.2 in the HA and 47.9 in the PRP group ($P<0.001$). At 6 months, the average WOMAC score of the PRP group was 39.4, while this rate was 56.3 in the HA group ($P<0.001$). The PRP group showed a steady improvement, while those treated with HA showed a rapid deterioration. At 12 months, the HA group's WOMAC scores (74.1) returned to baseline levels. The mean WOMAC of the PRP group was (58.9) ($P<0.001$). Conclusion: The overall PRP improvement outweighs HA injections

Keywords
Hyaluronic Acid, Intra-Articular, Platelet Rich Plasma

INTRODUCTION

A very common degenerative joint disorders is knee osteoarthritis (KOA) which slow articular cartilage damage, the synovial inflammation of the membranes, and alterations in the bones beneath the cartilage characterize (**Malemud, 2015**). Osteoarthritis of the knee affects 10–18% of people, and if left untreated, it can cause considerable physical impairment (**McDonough and Jette, 2010**). According to one study, the probability of lower limb impairment which KOA causes is at least 40% in older individuals (Johnson and Hunter, 2014), and KOA is a top 10 disability cause (**Neogi, 2013**). Since the mid-twentieth century, knee OA has increased (**Wallace et all., 2017**).

Patients usually receive several treatments in an attempt to halt the advancement of the disease; yet, there is no medications have to slow or stop of KOA. The focus of current therapies is to a great extent on the remission of the symptom to reduce the pain and increase function recovery (**Fonsi et all., 2020**). Both nonpharmacological and pharmacological methods are being used as a nonsurgical option (**Ferreira et all,. 2018**). Diet

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and exercise are the two nonpharmacological therapies that are commonly advised, although they are not always implemented. Nonsteroidal anti-inflammatory drugs (NSAIDs), duloxetine, topical NSAID acetaminophen, opioids, can relieve symptoms (**McAlindon et all., 2014**) Currently less Invasive interventions get bigger attention, like steroid, hyaluronic acid (HA), injections of platelet-rich plasma (PRP) and injections of stem cells.

Intra-articular injections, as a less invasive cure for KOA, has been found to be safe and efficacious (**Cook & Smith, 2018**). While traditional conservative methods such as NSAID treatment primarily target symptoms including pain and inflammation, alternative procedures including HA or PRP intraarticular application for the stimulation of the endogenous producing HA, promoting cellular metabolism and regenerating tissue and stopping cartilage tissue catabolism (**Filardo et all., 2012**) have been shown to improve cellular metabolism and tissue regeneration. Chondrocytes, synoviocytes, and fibroblasts production of HA, a high-molecular-weight glucosamine is significant to the knee joint viscoelasticity and lubrication (**Chen et all., 2019**). The concentrations of HA in osteoarthritic knees have been found to be lower. Increasing data suggests that HA enhances joint functions, alleviate pains, and reduce analgesic doses (**Zhang et all., 2018**). HA is involved in the dissipation and lubricating of traumatic energy (**Tascıoglu and Öner, 2003**). IA-HA reduces OA pain-related nerve impulses. The use of exogenous HA raises endogenous proteoglycan and hyaluronic acid synthesis (**Moreland, (2003**). On chondrocytes, HA is connected to CD44 and inhibits the IL-1action, which decreases MMP-1, 2, 3, 9, and 13 (**Julovi activitieset all., 2004**). The hyaluronan mediated motility (RHAMM) receptor binds to HA, which may be beneficial for chondroprotection (**Karna et all., 2008**). The generation of nitric oxide in the synovium is also suppressed & IA-HA has been shown to slow aggrecan degradation (**Peng et all., 2010**). IA-HA therapy reduces TNF-a, IL-1, IL-6, IL-17, MMP-13, and Nf-kB by inhibiting numerous inflammatory pathways via Toll-Like Receptors (**Yatabe et all., 2019**). IA-HA has effects on the sub-chondral bone and its aberrant metabolism (**Campo et all.,2011**). In OA knee joints, IA-HA concentration and molecular weight are lower than normal (**Hiraoka et all., 2011**). Molecular weight, concentration, HA sources (HA which is derived from biological fermentation vs. that derived from avian), dose (how many injections and intervals), estimated impact length of time, cross linkages, and additional formulations are all factors to consider while using it (**Dahl et all., 1985**).

Growth factors, particularly platelet-rich plasma (PRP) injection, have piqued people's attention in the last ten years due to their ability to heal tissue lesions and preserve normal tissue structure (**Migliore et all. 2016**). Autologous blood centrifugation produces a high platelet concentration of PRP (**Milants et all., 2018**). After platelets degranulate, releasing many growth aspects and cytokines helps in hastening producing cartilage matrix, reducing synovial membrane inflammation, and improving cartilage repair (**Mishra et all., 2012**). PRP is frequently utilized in musculoskeletal disorders including rotator cuff tears, patellar tendinopathy, lateral epicondylitis, and osteoarthritis due to its regeneration and anti-inflammation (**Anitua et all., 2007**). Yet, whether (PRP vs. HA) is the most effective for knee OA is still controversial. In an PRP meta-analysis versus HA for KOA (**Di Sante et all., 2006**).

Performed PRP intra-articular injections to viably treat KOA, yet according to some studies, PRP was not better than HA in effectiveness. However, (**Di et all., 2018**) some research works failed to prove that PRP is better than HA clinical improvement. Clinical Guidelines of the American Academy of Orthopaedic Surgeons stated that HA injection does not cure KOA, whrereas PRP injection is “not advised for or against” (**Filardo et all., 2015**). The OA Research Society International (OARSI) (**McAlindon., 2014**) proves HA injections to treat KOA but not PRP injections. According to Campbell (**Campbell et all., 2015**) PRP injections could trigger local adverse responses than HA in comprehensive examinations of an overlapping meta-analysis. There were many past meta-analyses (**Dai et al., 2017; Xu et al., 2017; Shen et al., 2017**) which state that PRP injection cause no more adverse effects than HA injections. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the well known in assessing evaluating pain, stiffness, and physical functions in arthritis studies or the visual analogue scale (VAS) for the quantification of the pain severity (**Filardo et all., 2012; Cerza et all.,2012**). In these studies, PRP positively

impacts regenerating biological cartilage in spite of the results of inhomogeneous (**Guermazi et all., 2004**). The current work assessed effectiveness and safety of intra-articular PRP and HA in those who suffer from KOA.

MATERIALS AND METHODS

Participant

This study was approved by the Research Ethics Committee of the State Al-Iraqia Med School with reference number No (1311-1-10-2021), and all procedures and protocol complied with the Helsinki World Medical Association Declaration on the ethical conduct of research involving human subjects. Participant provided informed consent, with the volunteer form covering research details, risks, benefits, confidentiality, and participant rights. The research strictly adhered to the ethical principles of the Declaration of Helsinki, prioritizing participant's rights and well-being in design, procedures, and confidentiality measures.

The current work is prospective randomized observational. Patients with knee discomfort who could be suitable were pre-screened. the ethical committee of Al-Iraqia Med School approved the study. All methods were performed based on the ethical committee of Al-Iraqia Med School guidelines and regulations.

Patients who completed informed consents and met the criteria to be included into two groups in a 1:1 ratio.

A commercial computer-generated randomized list which is a blind randomization assisted program was used to assign patients into groups. Patients in group 1(platelet-rich plasma (PRP)) received one autologous PRP injection intra-articularly. Patients in group 2 (hyaluronic acid) got one hyaluronic acid injection intra-articularly. The primary result was to change from the pain baseline, which WOMA for an Arab population determines (**Kayo et all., 2009**) at one year. From February 2018 to May 2020, 144 patients (88 females and 56 males) with symptomatic, radiologically with approved knee OA (Kellgren-Lawrence grades II–III) were included in this research. Over age 50, swelling, a persistent discomfort history, and/or some motion in the knee joint were all criteria for inclusion. X-ray pictures in anteroposterior and lateral projections were used to validate clinical and radiologic evidence of knee OA (Kellgren-Lawrence grades II–III). Post-traumatic knee osteoarthritis, oncological, endocrine (gout, diabetes), autoimmune (rheumatoid arthritis) and acute/chronic infectious diseases, blood clotting disorders (thrombocytopenia, coagulopathy) and previous interventions on the knee joint were all excluded .

Group1; 72 patients were injected with 1 PRP intra-articular injections. The blood drawn was 15 mL. For infiltration, noncommercial double syringe PRP Kit was used with 1 mL anticoagulant (sodium citrate). We centrifuged Citrated blood at 3000 rpm for 10 min. Pure PRP solution 3-5 mL was produced from the plasmatic fraction for the injection of Intra-articular PRP. Group 2; 72 people received single intra-articular injections of cross-linked HA (80 mg/4 mL).

The injections were performed by the physicians who had involved in this study. For both groups alcohol or an iodine-based antiseptic disinfected the skin prior to the injection. Both groups employed the superolateral infiltration technique, confirmed as the safest and most effective to ensure intra-articular drug penetration. A popliteal cushion was used to locate the patient was in a supine posture with the slight bending of the knee. The patella's medial, lateral, and superior margins were always marked. A superolateral approach was used after local anesthesia with lidocaine chlorohydrate, where we inserted the needle at an approximate 45 angle toward the medial joint knee line until accessing the "soft spot" in the middle of the femur-patella, adjacent the line junction through the lateral patellar edges and the line through the superior patella pole. The patients were observed for 10 to 15 minutes after the infiltration to verify if there were any adverse responses.

All physicians followed these instruction guidelines while they doing the injections for both group. Physical activity was not restricted as part of the post-injection regimen for both groups and all patients in both groups were advised and monitored not to use any analgesic drugs during the study and no special physiotherapy programs were advised. All of the patients were assessed prior to the infiltration as well as 1, 3, and 6 and a year after injection. In terms of safety, all patients in both groups were followed for any adverse events during and after the injections, and these were all reported. Western Ontario and McMaster

(WOMAC) osteoarthritis index questionnaire helped in assessing pain, articular stiffness, and functional restrictions. The same physicians were in charge of this stage.

Statistical analysis

The study used the statistical Package for the Social Sciences Version 22.0 (SPSS) for the data entry to calculate P value, means and standard deviations. Continuous variables were reported as mean ± standard deviation. The Mann-Whitney U test was used as appropriate for univariate analysis and the Bonferroni test for multiple comparisons.

RESULTS

A total of 144 consecutive patients, treated for knee OA between 2018 and 2020, were included into this study. Of them, 72 patients (50%) received PRP injections while 72 (50%) received HA injections. Baseline characteristics are outlined in Table 1, showing. It was determined that there was no significant difference in the mean ages of the PRP and HA groups ((61.80±10.2), (62.54±10.4), respectively (p>0.05). Grade values of PRP and HA groups were respectively (Grade RT (1.56 ± 0.49), Grade RL (1.54 ± 0.50) and HA; Grade RT (1.29 ± 0.45) and Grade RL (1,26 ± 0,44). It was determined that there was no significant difference (p>0.05). The total of Grade II OA in the PRP and HA group was 64, and the total in the Grade III OA group was 80.

Table 1. Demographic distribution of patients who underwent intra-articular injections of PRP or HA for knee OA.

Variables	PRP Group	HA Group	Z-Value	P-Value*
	n = 72 (%50)	*n = 72 (%50)*		
Females	45	42		
Mean age (years)	61,80±*10,2*	*62,54±10,4*		*>0.05*
Male	27	30		
Mean age (years)a	64,18±*9,1*	*59,63±9,3*		*>0.05*
OA Grade	PRP (1,55 ± *0,50)*		-,257	.797
OA Grade	HA (1,55 ± *0,49)*		-,655	.512
OA Grade RT	1,56 ± *0,49*	1,54 ± *0,50*	-1,582	.114
OA Grade RL	1,29 ± *0,45*	1,26 ± *0,44*	-,910	.363
Grade II OA	31	33		
Grade III OA	41	39		

PRP: platelet-rich plasma; HA: hyaluronic acid; OA: osteoarthritis; RT:Right; RL: Left; *Bold values are statistically significant.

While the scores in the PRP and HA WOMAC groups were close to one at the beginning (72.84 ± 8.83; 76.31 ± 10.14), significant differences were detected after the first month (p<0.001*). At 3 months, the overall WOMAC scores of both groups decreased significantly compared to baseline values (PRP (47.94 ± 15.00), HA (48.22 ± 14.80, respectively). The groups' difference was statistically significant (P< .001*) at this time point.

At 6 months, a reversal of the pattern was noted, with continued improvement in patients treated with PRP and slight deterioration in those treated with HA, as shown in Tables 2 and 3. WOMAC mean PRP (39.44 ± 14.00), HA (56.34 ± 10.10, respectively). A statistically significant difference was detected between the PRP and HA groups (P < .001*)

Table 2. Mean Western Ontario and McMaster (WOMAC) scores of the PRP and HA groups at baseline and follow-up periods within the group

Variables	WOMAC *PRP Group*	*P-Value**	WOMAC *HA Group*	*P-Value**
Baseline	72,84 ± *8,83*		76,31 ± *10,14*	
WOMAC 1 months	69,90 ± *9,49*		48,84 ± *16,71*	
WOMAC 3 months	47,94 ± *15,00*	*<0.001**	48,22 ± *14,80*	*<0.001**
WOMAC 6 months	39,44 ± *14,00*		56,34 ± *10,10*	
WOMAC 12 months	58,94 ± *13,29*		74,11 ± *9,95*	

*PRP: platelet-rich plasma; HA: hyaluronic acid; WOMAC: Western Ontario and McMaster *Bold values are statistically significant.*

As seen in Figure 3, Tables 2 and 3, while a steady improvement was observed in the PRP group, a rapid deterioration was seen in the HA treatment group at 12 months PRP (58.94 ± 13.29), HA (74.11 ± 9,95), respectively). WOMAC scores of most participants in the HA group decreased to baseline values. Both groups show statistically significant differences (P < .001). In terms of safety, 12 adverse events were observed during the study; these were all in the immediate postinjection period; 7 of these were 5 in the HA and PRP groups, respectively. Adverse effects were mostly minor and equal across groups. Infiltration-related discomfort was the cause of adverse events in the HA group and f PRP group, all of which were self-limiting within a few hours of injection without the need for further intervention.

Table 3. Mean Western Ontario and McMaster (WOMAC) scores between PRP and HA groups at baseline and follow-up periods

Variables	**WOMAC *PRP/ HA Group***	***Z-Value***	***P-Value****
Baseline	72,84 ± *8,83*	*-2,432*	
WOMAC 1 months	69,90 ± *9,49*	-7,169	
WOMAC 3 months	47,94 ± *15,00*	-,194	*<0.001**
WOMAC 6 months	39,44 ± *14,00*	-6,896	
WOMAC 12 months	58,94 ± *13,29*	-6,721	

*PRP: platelet-rich plasma; HA: hyaluronic acid; WOMAC: Western Ontario and McMaster *Bold values are statistically significant.*

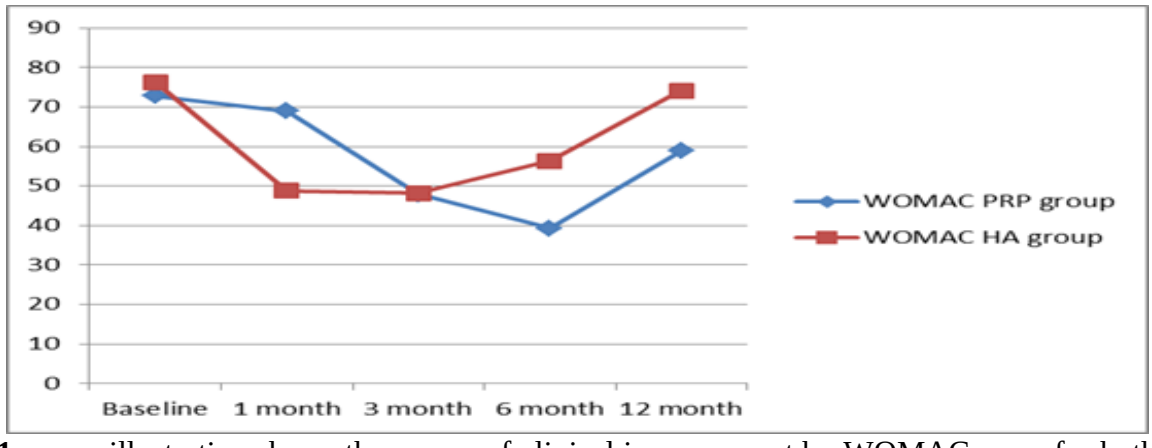

Figure 1. curve illustration shows the course of clinical improvement by WOMAC score for both PRP & HA group at baseline and through period's interval of follow up

DISCUSSION

The design of this study as randomized comparative study with one years of follow-up and applied on such a high number of patients make this study as one of the most available evidence on PRP application for knee osteoarthritis. The findings of this randomized study show that the single platelets rich plasma intra-articular injections were more effective than 1 single injection of HA in the reduction of knee pain and stiffness impring physical functions in those with knee OA for long term follow up but in short term length of times HA injections was significantly better.

The biochemical changes generated by HA therapy increases the synovial fluid's protecting, lubricating, and shock-absorbing properties. Furthermore, this treatment technique has no inflammatory side effects, which is a significant benefit (**Vaquerizo et all., 2013**), in fact, HA has been shown to have an active anti-inflammatory or chondroprotective action. I A-HA therapy reduces TNF-a, IL-1, IL-6, IL-17, MMP-13, and Nf-kB by inhibiting numerous inflammatory pathways via Toll-Like Receptors (**Di et all.,2018; Filardo et all.,2015**). The sub-chondral bone and its aberrant metabolism are also affected by IA-HA (**Hiraoka et all., 2011**). In OA knee joints, IA-HA concentration and molecular weight are lower than normal (**Dahle t all., 1985**). Molecular weight, concentrations, HA sources (HA which is derived from biological fermentation vs. that derived from avian), dose (how many injections and intervals),

estimated impact length of time, cross linkages, and additional formulations are all factors to consider while using it (**Migliore et all.. 2016**). and this could explain the earlier improvement in HA over PRP group, figure 1. There has been only one previous study about arthroplasty delay involving PRP by **Turajane et al**. (**2017**) including 60 patients. They compared intra-articular injections of autologous activated peripheral blood stem cells (AAPBSC) with PRP added growth factors, and HA along with arthroscopic mesenchymal stem cells versus the same combination without the added growth factors versus only intra-articular HA. They found that AAPBSC groups performed better than HA alone; however, they concluded that further research on the matter is required. Our study demonstrated a statistically significant difference in delaying knee arthroplasty favoring patients treated with autologous knee intra-articular injections of PRP versus high-molecular-weight HA. There have been some reports indicating.

PRP improves cartilage degeneration by stimulating mesenchymal proliferation, migration, and differentiation of stem cell into articular chondrocytes based on the preclinical study. PRP enhances cartilage regeneration by inhibiting inflammatory cytokines and changing the degree of enzymatic expression, which slows the course of KOA (**Di et all., 2018**). Furthermore, multiple clinical studies and systematic reviews have shown that PRP can relieve osteoarthritic symptoms including pain, stiffness, and function loss up to a year after injection (**Filardo et all., 2015**). In **Vaquerizo et al**, (**2013**) they concluded that PRP injections shows safety and significantly superiority of HA in initial and secondary efficacy analyses both at 24 and 48 weeks (**Huang and Tsai 2021**), with more significant clinical development, reduction of patients' pain and joint stiffness and physical functions, in terms of basal levels in patients with knee OA, these results agree with our study findings especially regarding the use of single shot of HA, but although in **Vaquerizo et al.,** (**2013**) they compared multiple PRP injections to single HA injection, also Huang study conclude that a single cross linked-HA injections shows more safety and effectiveness for 26 weeks in patients having knee OA by the comparison of the multiple injections of linear-HA (**Duymus et all., 2017**), in addition to that ,the manufacturer recommendations of our HA used was single injection, and so we used to compare single injection of both to quantify the native efficacy of single PRP injection in term of safety and length of time of clinical improvement and this could be attributed to the decline in the curve of clinical improvement In PRP group toward the end of our study(figure 1) although it was still better than HA group nevertheless this might suggest the necessity to evaluate the need of multiple PRP injections in some patients for better outcomes.

Surprisingly, several research have looked at the PRP and HA therapeutic effectiveness in treating KOA. Duymus et al. (**2019**) examined the effectiveness of PRP against HA intra-articular injections. In treating mild–moderate knee OA, they discovered that PRP injection showed more effectiveness than HA injections. The use of PRP might give at least a year of pain-free everyday activities. Examined the differences between PRP and HA in treating KOA and found that a leukocyte-poor PRP intra-articular injections higher function healing for at least 12 months in those with mild-to-moderate knee osteoarthritis.

It should be stated that other confounding variables, such as weight, physical activity, other concurrent medications, and so on, were not taken into account for the patient selection criteria, potentially resulting in bias that might alter the study's outcome. In numerous clinical investigations, however, PRP injection failed to outperform HA injection in terms of effectiveness. Filardo et al. (**2015**) discovered that individuals who had PRP injection had no better clinical outcomes than those who received HA injection and this was actually similar to what we noticed in first 6 months follow up length of time(figure 1). Regarding safety, the adverse effects which noticed during the study were mostly minor and evenly distributed among the groups (P 13.810). The discomfort associated with the infiltration was the cause of adverse events in the HA group and f PRP group and all were self-limiting by a matter of several hours post the injection without the need for further intervention and so both types of injections could be regarded safe therapies if done correctly as long as there are no negative effects that worsen the patient's health. Finally, we observed that less than 25% of PRP group still had significant clinical improvement in contrast to less than 5 % in HA group and almost most of them were grade II OA changes.

Conclusion

This study showed that PRP intra-articular knee injections compared to HA reduced the likelihood of knee arthroplasty in grade II to grade III knee OA patients. A significant improvement in pain was found in the PRP group at 6 months and later compared to the HA group. Similarly, a statistically significant improvement was detected in the WOMAC general score at the 6th month and at the last follow-up. An overall trend towards improvement in WOMAC was observed at 12 months. Our results suggest that PRP may be an effective treatment for patients with grade II to grade III knee OA. In short-term functional recovery, intra-articular HA injections are more effective than PRP injections in treating KOA. Furthermore, PRP injection outperformed that of HA in the long-term pain alleviation and improved functions. Additional RCTs are needed to determine the best PRP and HA dosages and intervals.

Conflict of Interest

The authors have declared no conflicts of interest.

Ethisc Committee

This study was approved by the Research Ethics Committee of the State Al-Iraqia Med School with reference number No (1311-1-10-2021), and all procedures and protocol complied with the Helsinki World Medical Association Declaration on the ethical conduct of research involving human subjects.

Author Contributions

Study design, DMA, SAAAL; Data Collection, DMA, SAAAL, WFAQ, YDRRA; Statistical Analysis, DMA, YDRRA; Manuscript preparation, DMA, SAAAL, YDRRA; Literature review, DMA, SAAAL. All authors have read and agreed to the published version of the Manuscript.

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