Original Article

Autologous Plasma Rich Platelet versus Low Molecular Weight Hyaluronic Acid in knee osteoarthritis: A Non-Placebo Randomized Controlled Trial

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Abstract

Background: This study aimed to compare the effect of autologous plasma rich platelet (PRP) versus Low molecular weight Hyaluronic acid (HA) on pain, function, and stiffness in knee osteoarthritis during six months follow-up.

Methods: Through a non-placebo blocked randomized controlled trial with parallel design on 77 patients with knee osteoarthritis; 50 in the intervention group, treated by PRP; 27 in the control group, treated by HA. They received three injections and assessed before, after two and six months. Pain, stiffness and function were assessed using WOMAC and VAS. Descriptive statistics, chi-square, and ANOVA were used when appropriate.

Results: Pain reduced in both groups compared to their respective baseline (P<0.001); the reduction rates were similar in both groups (P>0.05). WOMAC and VAS scores were different between before injection and both two and six months follow-ups in both groups (P<0.001); although the increase of VAS score between two and six months follow-ups was more considerable in PRP but not statistically significant (P=0.08). Considering Kellgren-Lawrence classification of knee osteoarthritis, WOMAC scores were different in patients with grade 2 and 3 in both groups (P<0.001); but VAS scores were different with grade 3 only in the PRP group (P=0.009).

Conclusion: There was no difference between PRP and HA in reducing symptoms of knee osteoarthritis compared to their baseline but the sustainability of the effect may be more with HA.

Keywords: Controlled Clinical Trial; Hyaluronic Acid; Osteoarthritis; Knee; Platelet-Rich Plasma

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Introduction

Knee osteoarthritis is the most common joint disease. Its prevalence increases with aging and causes suffering, a decrease in quality of life and patients' performance (1). The burden of knee and hip osteoarthritis has been increased from 1990 to 2015 by near 50%; now, it is responsible for 0.52%

of the total burden of diseases among totally 291 defined conditions (2, 3). Most of the routine treatment recommendations focus on analgesics for relieving pain. They improve knee function and decrease disability but have no influence on disease processes; it leads to long-term complications, especially in the elderly, and high health expenditure. Low molecular weight Hyaluronic acid and plasma rich platelet are two approaches to affecting disease process in different ways (4). They were used in different studies and their effectiveness in relieving symptoms of osteoarthritis has been evaluated (5-8). Although patients' quality of life could be affected by PRP (9, 10) and its effectiveness was assessed in different studies, but there is controversy in the effectiveness and also in its priority as a choice of treatment (11, 12); on the other hand, there are few systematic reviews on their effectiveness and almost all of them reviewed less than 10 paper (5, 13).

This study designed to compare the effect of autologous plasma rich platelet (PRP) versus Low molecular weight Hyaluronic acid (HA) on knee osteoarthritis during six months follow-up.

Methods

This study was a non-placebo blocked randomized controlled trial with parallel design on patients with knee osteoarthritis who came to a referral teaching hospital of Loghman. This hospital is the main rheumatologic center of Shahid Beheshti University of Medical Sciences which is covering more than five million people in Tehran, the Capital of Iran (14, 15).

The diagnostic criteria for osteoarthritis in this study were chosen based on recommendations of the American College of Rheumatology. They were a history of chronic pain or swelling for at least 4 months and the presence of degenerative changes in knee joint radiographs. The history of taking non-steroidal anti-inflammatory drugs during the last five days (before administration of PRP) should be negative. The exclusion criteria were systemic disorders like diabetes, rheumatoid arthritis; varus or valgus of more than 5 degrees in the knee; a history of hematologic disorders including malignancies and coagulopathies; a history of severe chronic heart diseases; active infections; immune deficiency; hemoglobin level less than 11 g/dl; platelet count less than 150,000/ mm^3; incomplete questionnaires; incomplete treatment course; no interest to participate in the study; multi-arthritis, pseudo-gout, and hyperuricemia; intra-articular injection of hyaluronic acid in last 6 months; intra-articular injection of steroids in last 3 months.

Totally 77 patients were eligible to enter the study. They were randomly assigned to two intervention groups. We used blocked randomization for allocating the patients to the groups. The allocation ratio of intervention groups was about two in this study. We used 26 blocks of three in which we considered two chances for the PRP group and one chance for the HA group in each. The process of allocation to the groups has been done by a secretary that was not involved in the intervention process.

The PRP group consisted of 50 patients, treated by Plasma Rich Platelet (PRP). One of them exit the study and did not answer follow-ups. Three intra-articular injections of PRP were done by two weeks interval. We choose the worst knee for injection and the other knee was remained untreated. PRP was prepared using the Iranian Blood transfusion organization's (IBTO) kits. They have pockets of 35 mL with 6 mL of anticoagulant CPDA1. This kit was sterile and the process has been done under the supervision of an expert from IBTO. Before we start the study, the Kits were standardized by using for ten patients, after informed consent. In order to concentrate platelets, 35 ml of the patient's venous blood sample was gone under centrifugation in two steps; the first at 1200 rpm for 15 minutes to separate erythrocytes and white blood cells and the second

one at 4000 rpm for 5 minutes at room temperature. In this way, the concentration of platelets after 30 minutes of rest increased by 4-5 folds compared to whole blood values. Finally, 5 mL of PRP extracted and four mL injected into the knee in the same room. A sample of the patient's venous blood and a sample of PRP were sent to the laboratory for platelet count before every injection. We added 0.2 mL calcium gluconate to four mL of PRP to activate the platelets. We used this standardized protocol for all the patients. The concentrated platelets could be used for 5 days at room temperature on the platelet rotator, but it was recommended to use it as soon as possible.

The HA group consisted of 27 patients, treated by Low Molecular weight Hyaluronic Acid (trademark of Hyalgan). We injected one vial of Hyalgan in the knee every week for three consecutive weeks.

All the patients were followed for six months after the final injection. Primary outcomes were severity of pain, stiffness, and knee function. Secondary outcomes were severe pain and effusion following injection. Data gathering tools were Visual Analog Scale for Pain (VAS Pain) and Western Ontario and McMaster Universities (WOMAC questionnaire for the assessment of pain, stiffness and function) which is validated for the Iranian population by Naderian et al. (16). Data were collected in three periods of time: at the beginning of the intervention process, two months after the final injection, and six months after the final injection. Data gathering and all injections were done by a fellow of rheumatology to avoid variation in technique and related bias.

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, directed in accordance with the Declaration of Helsinki and also, registered to Iranian Registry of Clinical Trials by ID No: IRCT2015041121697N1. All the patients were given enough information for decision making for participation in the study. Written signed consent was taken from all patients who accepted to participate in the study. They were free to enter the study and also they were allowed to exit the study every time they wanted. They were informed about the complications of intra-articular injection; they were asked to report the complications as soon as possible when they appeared. There was a cell phone number to report any conflict or complication at any time after injections and during six months follow-up; a fellow of rheumatology was responsible to manage their problem by phone or invite them to be visited. They were invited for follow-up if they missed the appointment.

We used descriptive statistics, chi-square, and one-way analysis of variance to analyze the data. All data analysis performed using SPSS software 16 (SPSS Inc., Chicago, IL, USA).

Results

Basic characteristics of the participants are shown in table 1; they were similar in both groups of intervention: there was no statistically significant difference in sex distribution between the two intervention groups (P=0.95). In the PRP group mean age was 55.3 (SD=10.6) with a range of 34-75 years. In the HA group, the mean age was 56.9 (SD=9.7) with a range of 32-79 years (P=0.5). In the PRP group, the mean for body mass index (BMI) was 28.4 (SD=3.3) with a range of 21.5-34.5. In the HA group, the mean for BMI was 29.3 (SD=3.3) with a range of 24-34.5 (P=0.3).

In the PRP group only one out of 50 patients, who went under intervention, missed the follow-ups and exit the study. 25 out of 49 in the PRP group (51%) had a little self-limited pain after injection for a few days; 10 patients (20.5%) had little swelling and pain for a week which was relieved by acetaminophen and local cold compression; one case had swelling and severe effusion for 21 days after the first injection that relieved by drugs and did not repeat after the next injections.

Table 1. Sex distribution among intervention groups

	Male (%)	Female (%)	Total (%)
PRP group	7 (14.3)	42 (85.7)	49 (100)
Hyaluronic acid group	4 (14.8)	23 (85.2)	27 (100)
Total	11 (14.5)	65 (85.5)	76 (100)

P=0.95

Table 2. VAS score before, two, and six months after injection in intervention groups

	Mean (SD) of VAS score			
	before injection	2 months after injection	6 months after injection	*P*
PRP	7.3 (2.4)	5.6 (2.6)	5.9 (3.1)	0.005
Hyaluronic Acid	7.1 (2.1)	5.3 (2.7)	5.4 (1.9)	0.006
P	0.7	0.6	0.5	

VAS: visual analog scale

In table 2, between-groups analysis of ANOVA shows that both interventions have reduced the pain compared to their baseline in the follow-ups, but the pain reduction rates were similar in two groups of intervention and there was no statistical difference between PRP and HA groups. Within-group analysis has been done by comparing means among three measurements of the PRP group using a posthoc test. It showed that before injection VAS score was statistically different from two months follow-up (*P*=0.008) and six months follow-up (*P*=0.03); but there was no difference between two and six months follow-ups (*P*=1). On the other hand, comparing means among three measurements of HA group also revealed the same within-group result; before injection VAS score was statistically different from two months follow-up (*P*=0.01) and six months follow-up (*P*=0.02); but there was no difference between two and six months follow-ups (*P*=1).

Table 3. WOMAC score before, two, and six months after injection in intervention groups

	Mean (SD) of WOMAC score		
	PRP	Hyaluronic Acid	*P*
Before injection			
Pain	11.9 (4.5)	11.2 (3.6)	0.7
Stiffness	4.6 (2.1)	4.4 (1.4)	0.6
Function	36.0 (13.6)	30.8 (10.7)	0.5
Total	52.5 (18.9)	46.4 (13.8)	0.15
Two months after injection			
Pain	6.8 (4.5)	6.5 (4.9)	0.8
Stiffness	3.1 (2.2)	2.4 (1.7)	0.2
Function	21.4 (14.5)	15.9 (11.7)	0.2
Total	31.3 (20.2)	24.8 (17)	0.2
Six months after injection			
Pain	6.6 (4.7)	6.2 (4.5)	0.7
Stiffness	2.9 (1.8)	2.7 (1.6)	0.7
Function	20.3 (12.9)	16.2 (10.7)	0.2
Total	29.8 (18.0)	25.1 (15.3)	0.3

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 4. VAS score before, two, and six months after injection in intervention groups based on the grade of knee osteoarthritis

	Mean (SD) of VAS score			
	before injection	2 months after injection	6 months after injection	P
PRP group				
Grade 1	6.0 (2.6)	5.8 (1.8)	5.0 (3.5)	0.8
Grade 2	6.5 (2.2)	5.2 (2.8)	5.3 (3.1)	0.2
Grade 3	8.5 (2.2)	5.8 (2.5)	6.8 (2.9)	0.008
Hyaluronic Acid				
Grade 1	7.3 (2.5)	5.7 (0.6)	4.0 (3.6)	0.4
Grade 2	6.7 (2.1)	4.5 (3.1)	5.3 (1.8)	0.1
Grade 3	7.3 (2.2)	5.9 (2.5)	5.8 (1.6)	0.1

VAS: visual analog scale

Table 5. WOMAC score before, two, and six months after injection in intervention groups based on the grade of knee osteoarthritis

	Mean (SD) of WOMAC score			
	before injection	2 months after injection	6 months after injection	*P*
PRP group				
Grade 1	36.8 (24.6)	22.0 (11.4)	23.0 (21.1)	0.4
Grade 2	48.2 (19.1)	28.5 (21.0)	25.3 (16.3)	<0.001
Grade 3	62.3 (11.5)	37.4 (19.0)	37.2 (17.6)	<0.001
Hyaluronic Acid				
Grade 1	43.7 (13.3)	23.0 (8.5)	26.0 (13.5)	0.2
Grade 2	44.1 (13.0)	22.7 (19.6)	19.8 (9.9)	0.001
Grade 3	49.0 (15.1)	27.0 (16.9)	29.3 (18.6)	0.004

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

In table 3 between-group ANOVA analysis shows that the WOMAC scores in pain, stiffness, and function were not statistically different between PRP and HA groups in different follow-ups. Within-group analysis in each group revealed the total WOMAC score was different between before, after two and six months of injection; in the PRP group (f=17.8, d=2 and $P<0.001$) comparing means revealed that before injection WOMAC was different from both two months follow-up ($P=0.001$) and six months follow-up ($P<0.001$); but there was no difference between two and six months follow-ups ($P=0.08$). On the other hand, in the HA group (f=17.5, d=2 and $P<0.001$) comparing means also had the same result and revealed that before injection WOMAC was different from both two months follow-up ($P<0.001$) and six months follow-up ($P<0.001$); but there was no difference between two and six months follow-ups ($P=1$).

In table 4 within-group ANOVA analysis shows that VAS score in the PRP group was different between phases of follow-up only in patients with grade 3 based on the Kellgren-Lawrence classification of osteoarthritis. The difference in this subgroup was related to before injection and two months follow-up ($P=0.009$); after six months although the pain was reduced, it was not statistically significant ($P=0.15$). In the HA group, this score had no difference among groups.

In table 5 within-group analysis shows that WOMAC score was different between phases of follow-up in patients with grade 2 and 3 in both intervention groups; posthoc test showed that the intervention reduced the score in the follow-ups. The difference in this subgroup was related to before injection and two months follow-ups ($P=0.002$ for grade 2 and $P<0.001$ for grade 3 for PRP group; and $P=0.007$ for grade 2 and $P=0.008$ for grade 3 in HA group); and before injection and six months follow-ups ($P<0.001$ for both grade 2 and 3 for PRP group; and $P=0.002$ for grade 2 and $P=0.02$ for grade 3 in HA group); there was no

significant difference between two and six months follow-ups (P =0.8 for grade 2 and P=0.99 for grade 3 for PRP group and P=0.9 for both grade 2 and 3 in HA group). On the other hand, analyses showed no difference between the same grades of knee osteoarthritis between the two intervention groups (P>0.05 for all).

Discussion

In this randomized controlled trial, we showed that prescription of both, PRP and HA reduce similarly pain, stiffness, and improve function in knee osteoarthritis compare to baseline. These interventions were more effective in grades 2 and 3 based on the Kellgren-Lawrence classification of osteoarthritis.

We found that pain severity was reduced significantly after two months of intervention and this effect was remained unchanged up to six months follow-up. Our findings support Kon et al. and Filardo et al.'s findings; they found that VAS score and other indicators decreased during two, six, and 12 months follow-ups; they found no difference between two months of follow-up and six and 12-month follow-up too (17-19). In a systematic review of six articles, Khoshbin et al. reported that the WOMAC score for PRP was decreased more than Hyaluronic acid but the VAS score remained the same between them(20). In another systematic review, Kanchanatawan et al. on nine articles found that PRP was effective but not more than HA (13). This finding shows that the pick effect of treatment happens during the first two months and there is no more increase and decrease in pain during the next 4 months of follow-ups; based on these findings it is recommended that the cost-effectiveness of the third injection will be assessed in future studies.

We found that PRP and HA had the same sustainability in both groups of intervention during six months of follow-up. In another study, Kon et al. found that response to the treatment, sustainability of the effect, and patient satisfaction in PRP and Hyaluronic acid groups were the same two months after injection but they were better in the PRP group after six months follow-up (20). Filardo et al. also found that three weekly injections of PRP and Hyaluronic acid both were effective in relieving pain but there were no differences between them after 2, 6, and 12 months follow-ups (18, 21). Wang-Saegusa et al. found that PRP injection could lead to pain relief and improvement in function and quality of life after six months of follow-up (9, 10). Raiessadat et al. in a one-year follow-up found that WOMAC score and bodily pain in PRP and HA both were effective; although PRP was more effective (22). Say et al also found that PRP was more effective and less expensive than HA in 3 and 6 months follow-ups (23). Other studies also found that PRP could be more effective compare to HA (12, 22, 24). These variations could be the result of different inclusion criteria, treatment protocols, sample size, criteria for outcome assessment, and even random error. It is recommended that more studies with a larger sample size will be designed and strong systematic reviews summarize the results in the future.

We found that PRP and HA were more effective in grades 2 and 3 of osteoarthritis in 2 and 6 months follow-ups. Gormeli et al. and Kon et al. found that PRP is more effective in the early stages of osteoarthritis after six months and response to HA was not good in the late stages of osteoarthritis. (18, 20). Spakova et al. also found PRP was more effective in the initial stages of osteoarthritis (25). It seems that choosing the right patients based on osteoarthritis grades could increase the efficacy of intervention but for the right time of injection we need more studies. Raeissadat et al. also found more achievement in grade 2 but it was not statistically significant. This difference may be due to different protocols: They injected two times by monthly interval but we injected biweekly interval for three times (22).

Basic characteristics like age, sex, body mass index, the grade of osteoarthritis, pain severity, and WOMAC score (in pain, stiffness and function) were not statistically different between the two groups of intervention, so they had no confounding effect in this study. It also supports the internal validity of the results. Patel et al also found that age, sex, weight, and body mass index did not influence response to treatment (26). In this study most of the patients were women and it was like Sanchez et al. (27) and Patel et al. (26)

We used the well-known diagnostic criteria of the American College of Rheumatology in this study. The inclusion criteria were limited as much as possible as the selected participants were representative of the osteoarthritic population. The participants were allocated to the intervention groups by blocked random assignment. This method prevented biases and supported the external validity of the study.

One of the limitations of this study was that the outcomes measures in this study were subjective. We used only one fellow of rheumatology for outcome assessment to prevent probable bias. The other limitation was the long term follow-up period and the probability of loss to follow-ups. We considered a cell-phone number for the patients to be connected to their physician all the time during the study. Active follow-up of the participants when they missed the appointment also prevented the loss of follow-ups.

Although improvements in symptoms may be somewhat the same in our study, additional evidence for the cost-effectiveness, longer-term outcome, and/or structural outcome (X-ray or MRI) would be needed to be assessed in future researches.

In our study, PRP and HA had the same effect in reducing pain in knee osteoarthritis. The sustainability of treatment was slightly more with Hyaluronic Acid. The same studies with a higher sample size should be done. If the effect will be the same, a cost analysis will be helpful in choosing the best intervention.

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