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Original Article

Effect of single or multiple injection of platelet-rich plasma in comparison with hyaluronic acid on knee osteoarthritis

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ABSTRACT

Aim: To compare the effect of administration of 2 different doses of platelet rich plasma (PRP) and a single dose of hyaluronic acid (HA) preparation on pain and daily life activities of knee osteoarthritis (KOA) patients.

Method: In this nonrandomized comparative study, three groups of patients who received either a single dose of intraarticular (IA) PRP (PRP1 group), three doses of IA PRP (PRP3 group), or single dose IA HA (HA group) were included. Assessments were before treatment, and in the 3rd week and 6th week after treatment (after the final injection). The pain-visual analog scale (VAS), Euro-Qol (EQ)-5D-3L, EQVAS, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were used.

Results: In the 3rd week, there were statistically significant differences between the PRP1-HA groups in all parameters except EQ5; between PRP3-HA groups in all parameters except EQ5 and WOMAC stiffness; and between PRP3-PRP1 groups in all parameters except EQVAS, WOMAC pain and WOMAC stiffness. In the 6th week, there were statistically significant differences between the PRP1-HA groups in all parameters except WOMAC stiffness; between PRP3-HA groups in all parameters; and between PRP3-PRP1 groups in all parameters except WOMAC pain.

Conclusion: Intraarticular PRP injections (single or three doses) were found to be more beneficial in the short term in terms of pain and functional improvement than HA injection and administration of three consecutive doses of PRP may be more effective compared to single-dose PRP administration in KOA patients.

Keywords: Knee osteoarthritis, platelet rich plasma, hyaluronic acid, intraarticular injection.

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Introduction

Osteoarthritis (OA) is the most commonly observed rheumatologic disease in the world resulting from primary progressive cartilage destruction [1]. Variations occurring as a result of OA are the main reason for situations leading to disability and are mostly observed in the knee joints [1-3]. Knee osteoarthritis (KOA) is a progressive joint disease frequently involving intra and periarticular structures characterized by joint cartilage lesions, synovitis, subchondral sclerosis and osteophytes. As a result of these, problems like pain, sensitivity, joint stiffness, swelling in the joint, movement limitation, joint deformity, muscle strength loss, reduced functional capacity and disrupted quality of life may be observed [1-3].

The targets of KOA treatment are to reduce pain, resolve joint stiffness, preserve and improve joint movement, preserve and increase muscle power, prevent trauma or protect against movements that may cause trauma and increase quality of life. Frequently used treatment methods for symptomatic KOA patients before surgery include systemic-effect anti-inflammatory medications, physiotherapy, topical anti-inflammatory gels and intraarticular injections. In spite of medical advances, there is no proven medication or surgical intervention to prevent or delay the development of KOA [3-6].

Intraarticular and periarticular injections have begun to be chosen for KOA treatment in recent years with the aim of improving symptoms and regulating daily life activities. Many studies have reported that hyaluronic acid (HA) has visco-induction properties and may increase the intraarticular viscosity and positively contribute to pain and mobilization. As a result, intraarticular HA injection is commonly used for KOA treatment [7]. Platelet rich plasma (PRP) is obtained by centrifuging full blood and is the plasma component containing higher concentrations of platelets than full blood [8]. As it contains many growth factors, the use of PRP injections for treatment of a variety of musculo-skeletal system diseases has come to the agenda. Growth factors, considered to affect the healing process, are locally injected into the lesion site with increasing effect on tendon and cartilage tissue regeneration and are stated to have potential use for treatment [9]. The minimal invasive treatment choice of intraarticular PRP injection is commonly used for treatment of clinically associated diseases like KOA. Some publications have proposed that PRP is a more reliable and effective treatment compared to other intraarticular joint injections [10, 11]. Additionally, though intraarticular HA and PRP administration are shown to resolve pain and improve joint functions in patients, there are contradictory publications about the efficacy for KOA patients [12].

PRP and HA injections have increasing areas and frequency of use with every day and are chosen for musculoskeletal system pathologies with different indications. In spite of this frequent use, there is no treatment algorithm prepared based on evidence related to definite indications and administration frequency. Additionally, there are many different brands on the market, and PRP kits with different features and contents and HA preparations which causes further confusion. In our study we compared the effect of administration of 2 different doses of PRP and a single dose of HA preparation on pain and daily life activities of KOA patients.

Materials and Methods

Study design

This nonrandomized comparative study was carried out in the Bolu İzzet Baysal Physical

Medicine and Rehabilitation Training and Research Hospital, after Ethical Committee approval (Usak University Medical School Ethics Committee, decision number 31-5-13, dated 2018/04/25). The study protocol abided by the principles of the Helsinki Declaration. Participants in the research first read and then signed the consent form.

Participants

The study included patients attending the Physiotherapy and Rehabilitation Clinic from January 2019-January 2020 with diagnosis of KOA who received knee intraarticular PRP or HA treatment and agreed to complete the survey forms.

Inclusion criteria for the study were age over 30 years, gonarthrosis diagnosis according to American College of Rheumatology (ACR) criteria [3], and cases identified as stage 1-2-3 according to radiological Kellgren-Lawrence classification [12].

Exclusion criteria for the study were presence of inflammatory rheumatologic disease, coagulation disorder, and immunosuppressive disease, diseases causing disruption to hemogram parameters, serious cardiovascular disease, previous operation in the knee region, varus and valgus deformity of the knee region, malignancy, infection, anticoagulant medication use, and use of anti-inflammatory medication in the last 1 week.

A total of 278 patients were assessed for the study. The study included 210 patients abiding by the study criteria and providing consent with the patient information form (Figure 1). The study grouped patients according to the treatment they received; 70 patients with a single dose of intraarticular (IA) PRP (PRP1 group), 70 patients with three doses of IA PRP (PRP3 group) and 70 patients with single dose IA HA (HA group). It was not possible to blind the patients due to the design of the study and nature of the treatment. The outcome assessment process was blinded. Patient assessment and statistical analysis of outcomes were performed by a clinician and biostatistics expert blind to the treatments and groups of patients.

Interventions

In our study, all injections performed by a single clinician in the injection clinic under sterile conditions. IA injection used a single-use 10 mL 21 G green-tip injector with the lateral approach in the suprapatellar region. In our clinic, PRP was administered either as single dose or three doses with one-week interval; this approach was previously investigated in Görmeli et al.'s study [11].

The PRP1 group had one single IA PRP dose administered. The PRP amount was 3 mL. Before injection, and in the 3rd and 6th weeks after injection patients were assessed in terms of pain and functional status.

The PRP3 group had three doses of IA PRP administered at one-week intervals. The amount of PRP administered in each session was 3 mL. Before injection, and in the 3rd and 6th weeks after injection patients were assessed in terms of pain and functional status.

The HA group had a single dose of IA HA injection administered. Before injection, and in the 3rd and 6th weeks after injection patients were assessed in terms of pain and functional status.

All patients with PRP administration used a Dr PRP®□ Kit with FDA approval and CE certification offered to the market by Cureacell Ltd. Co. The kit is offered to the market after gamma ray sterilization according to ISO 13485 standards. For preparation of the Dr.PRP kit®□, 3–4 ml of PRP with a concentration of 8–10 times the average normal value and 2 cc of anti-coagulant were placed in a 20 cc syringe, then 18 cc of blood from patient was drawn.

The drawn blood was injected into the Dr. PRP® kit through the upper injection port until the blood level reaches the 20-cc scale marked on the kit. After the first centrifugation at 3000 rpm for 3-4 mins, the plasma layer and the red blood cell (RBC) layer were separated and then the separation position of the plasma and the RBC layer were identified and the height of the separated boundary to the indicated point was adjusted by pushing up or pulling down the adjusting knob located at the lower part of the Kit. In order to block the plasma and the RBC layer completely, the adjusting knob and the valve were fastened (clockwise). Finally, the adjusting knob was fastened again. The fastened PRP Kit was put into the centrifuge with counterbalance for the second centrifugation to enrich the concentrated platelets at 3250 rpm for 4-6 mins The PRP Kit was placed in upright position and the upper silicone lid on the Kit was opened. The PPP (platelet poor plasma) layer was slowly removed from the upper part using a 10-cc syringe with a needle, leaving 3 cc in the lower part (PRP). The PRP preparation procedure was performed by a trained nurse in our clinic.

Patients with IA HA administered used the product with CE, ED and REP certification sold as ArtıAid® Plus Intra-articular Injection commercial brand by Maxıgen Biotech Inc. High-purity HA has more than 1,500 kDa molecular weight with 45 mg HA (1.5%) included in 3 mL sodium hyaluronate solution prepared with buffered physiological saline in a single use sterile injector.

During the treatment, patients were told they could use local ice compression and paracetamol (max 2 g/day) if required. Additionally, patients were given a home exercise program and recommended to return to normal daily activities 3 days after injection if tolerated.

Instruments

Assessments were before treatment, and in the 3rd week and 6th week after treatment (after the final injection). Assessments used the pain-visual analog scale (VAS), Euro-Qol (EQ)-5D-3L, EQ VAS, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

VAS is a commonly used method to determine the degree of pain. It comprises a line with 100 mm length drawn on a horizontal or vertical axis. The distance from the lowest VAS value to the point indicated by the patient is measured in mm (0-100) and a numerical value is determined for the severity of pain felt by the patient [13].

The 3-level version of EQ-5D (EQ-5D-3L) was developed by the European Quality of Life (Euroqol) Group in 1990. The EQ-5D-3L comprises 2 pages of the EQ-5D descriptive system and EQ visual analog scale (EQ-VAS). The EQ-5D is defined in terms of 5 subdimensions (mobility, self-care, general activities, pain/discomfort and anxiety/depression) within a three-level structure of “no problem, moderate degree problems and advanced degree problems”. On scoring a value of 1 shows perfect health, while health status worsens as values reduce. The EQ-VAS comprises a 100 mm line to assist in scoring the health status of a person with the best health status imaginable shown at 100 and the worst health status shown at 0 [14].

The WOMAC is a health status metric commonly used for knee and hip OA patients. It comprises three sections of pain, stiffness and physical function. It includes a total of 24 items. Points for items are given according to a Likert scale. Points from 0 to 4 are given on the Likert scale determining pain and degree of difficulty. Turkish validity and reliability studies have been performed [15].

Socio-demographic (or other) variables such as age, gender and symptom duration (months) were recorded in all patients.

Statistical methods

The baseline characteristics were compared among groups by using the Kruskal-Wallis test or the Mann-Whitney U test for continuous variables and Pearson's chi-square test for categorical variables. Outcomes were analyzed with generalized linear mixed models with gamma regression. The models included group, time, some baseline characteristics (i.e. age, sex, OA grade), baseline value of outcome and group X time interaction as fixed effects. Follow-up and difference values are presented as generalized linear mixed models estimated mean (95% confidence interval). The sequential Bonferroni correction was used in the models. All statistical analyses were performed using SPSS. The level of statistical significance was set at *0.05*.

Results

Of the total of 210 patients (70 x 3 groups) included within the scope of the study, the study was completed with 66 people in the PRP1 group, 65 people in the PRP3 group and 68 people in the HA group. In the PRP1 group, 3 people did not continue to attend check-ups and 5 people used NSAIDs; in the PRP3 group 6 people used NSAIDs, 3 people ended participation after one or two injections, 1 person developed history of trauma during follow-up and 2 people had arthroscopic surgery; and in the HA group 3 people did not continue to attend check-ups so the study was completed with a total of 176 patients. The flow diagram for the study is presented in Figure 1. The basic descriptive characteristics of patients are summarized in Table 1.

The mean difference in pain VAS scores between the groups was identified to be statistically significant in the 3rd week. Estimated mean differences were -4.01 *(95% CI, -6.86 to -1.16; p=0.006)* between PRP1 and HA groups, -8.42 *(95% CI, -11.87 to -4.97; p<0.001)* between PRP3 and HA groups and -4.41 *(95% CI, -7.65 to -1.18; p=0.005)* between PRP3 and PRP1 groups. The mean difference between pain VAS scores between the groups was identified to be statistically significant in the 6th week. The estimated mean differences were -6.31; 95% CI, -8.66 to -3.97; *p<0.001*, between PRP1 and HA groups, -9.86; 95% CI, -12.34 to -7.39; *p<0.001* between PRP3 and HA groups and -3.55; 95% CI, -5.27 to -1.83; *p<0.001)* between PRP3 and PRP1 groups (Table 2, Figure 2).

Mean differences between the EQ5 scores in the groups was only identified to be statistically significant between the PRP3 and PRP1 groups in the 3rd week. The estimated mean differences were -0.21; 95% CI, -0.06 to 0.019; *p=0.303* between PRP1 and HA groups, 0.03; 95% CI, -0.10 to 0.078; *p=0.132* between PRP3 and HA groups and 0.06; 95% CI, 0.01 to 0.10; *p=0.016* for PRP3 and PRP1 groups. In the 6th week, the estimated mean differences were 0.14; 95% CI, 0.07 to 0.21; *p<0.001* between PRP1 and HA groups, 0.24; 95% CI, 0.16 to 0.31; *p<0.001* between PRP3 and HA groups and 0.10; 95% CI, 0.02 to 0.18; *p=0.006* for PRP3 and PRP1 groups (Table 2, Figure 2).

The mean differences between the EQ VAS scores in the groups was identified to be statistically significant between the PRP1-HA and PRP3-HA groups in the 3rd week. The estimated mean differences were 5.67; 95% CI, 2.02 to 9.32; *p=0.001* between PRP1 and HA groups, 5.86; 95% CI, 2.11 to 9.60; *p=0.001* between PRP3 and HA groups and 0.19; 95% CI, -3.15 to 3.52; *p=0.913* for PRP3 and PRP1 groups. Statistical significance was identified for the mean differences between groups for EQ

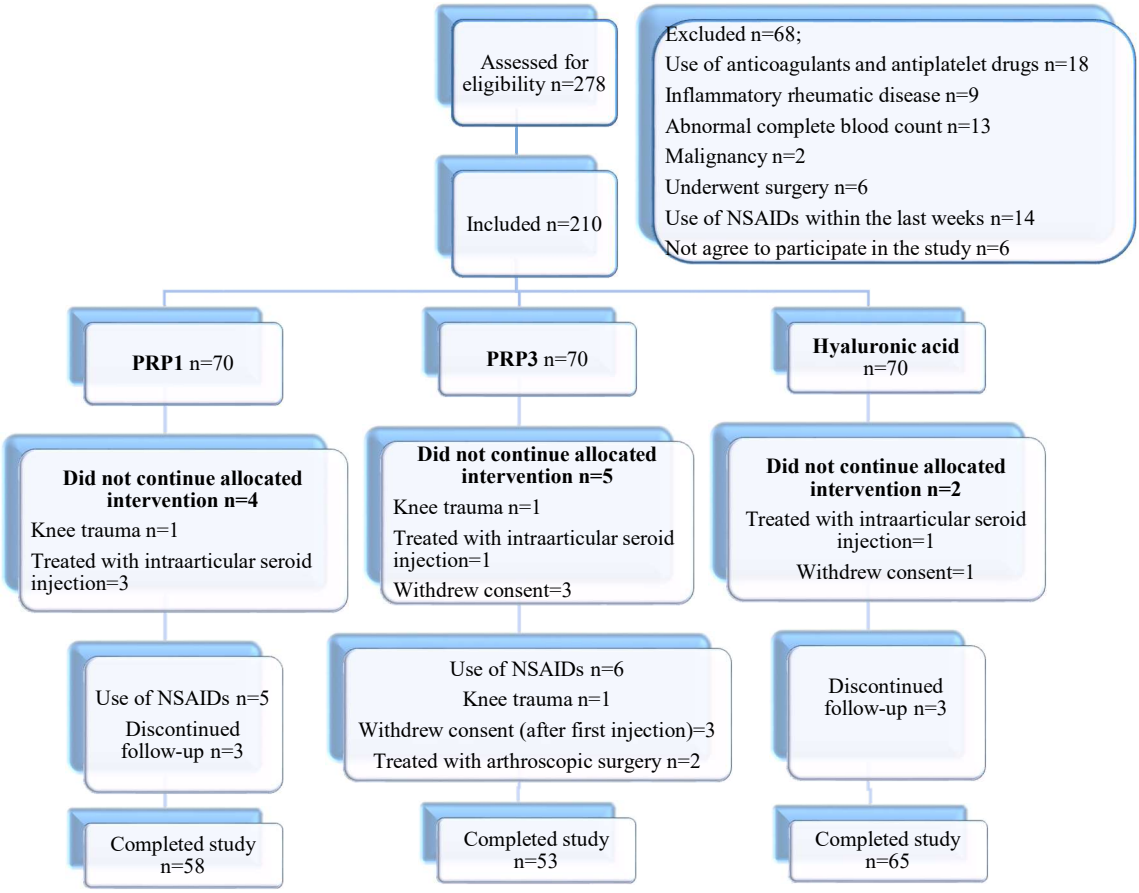


Figure 1. Flow diagram of the study population

Table 1. Baseline characteristics of patients†.

Parameters	PRP1	PRP3	Hyaluronic acid	*P value‡*	*P value§*		
					PRP1-HA	PRP3-HA	PRP3-PRP1
Age, years	46.52 ±11.22	43.49 ± 12.06	49.18 ± 12.64	*0.042*	*0.185*	*0.016*	*0.159*
Female sex	32 (55.2%)	29 (54.7%)	34 (52.3%)	*0.943*	*NA*	*NA*	*NA*
Kellgren-Lawrence **Grade 1** **Grade 2** **Grade 3**	 23 (39.7%) 28 (48.3%) 7 (12.1%)	 19 (35.8%) 22 (41.5%) 12 (22.6%)	 18 (27.7%) 27 (41.5%) 20 (30.8%)	*0.158*	*NA*	*NA*	*NA*
Body mass index (kg/m2)	26.95 ±3.64	26.68 ± 3.42	27.54 ± 3.32	*0.230*	*NA*	*NA*	*NA*
Duration (Years)	4.38 ± 1.14	4.62 ± 1.37	4.86 ± 1.78	*0.341*	*NA*	*NA*	*NA*
VAS Pain	72.50 ±9.56	80.66 ± 12.86	75.23 ± 10.13	*0.001*	*0.216*	*0.007*	*<0.001*
EQ5	0.16 ± 0.22	0.09 ± 0.22	0.09 ± 0.19	*0.068*	*NA*	*NA*	*NA*
EQ VAS	27.50 ±9.56	18.96 ± 12.38	24.77 ± 10.13	*<0.001*	*0.063*	*0.004*	*0.037*
Womac Pain	11.29 ± 2.29	13.42 ± 3.10	12.45 ± 2.23	*<0.001*	*0.002*	*0.023*	*<0.001*
Womac Stiffness	3.86 ± 1.07	4.91 ± 1.26	4.14 ± 1.00	*<0.001*	*0.105*	*0.001*	*<0.001*
Womac Function	46.86 ± 7.43	52.70 ± 9.34	49.14 ± 7.47	*<0.001*	*0.031*	*0.010*	*<0.001*
Womac Total	61.98 ± 10.33	71.15 ± 13.34	65.69 ± 9.60	*<0.001*	*0.016*	*0.004*	*<0.001*

† The data are expressed as mean ± standard deviation or number (%). PRP: Platelet-Rich Plasma, VAS: Visual Analog Scale, EQ: European Quality of life, WOMAC: Western Ontario and Mc Master Universities Osteoarthritis index, NA: Not applicable.

‡ The Kruskal-Wallis test was used for continuous variables; and Pearson's chi-square test was used for categorical variables between three groups (PRP1, PRP3, HA). § The Mann-Whitney U test was used for continuous variables between two groups.

Table 2. Outcomes for PRP1, PRP3 and HA groups at 3 week and 6 week †

	Platelet-Rich Plasma-1 (PRP1)	Platelet-Rich Plasma-3 (PRP3)	Hyaluronic acid (HA)	Treatment difference			Pvalue‡		
				PRP1-HA	PRP3-HA	PRP3-PRP1	PRP1-HA	PRP3-HA	PRP3-PRP1
Pain VAS									
Baseline	72.50 ± 9.56	80.66 ± 12.86	75.23 ± 10.13						
3 week	35.99 (33.98 to 38.12)	31.57 (29.74 to 33.52)	40.00 (38.00 to 42.10)	-4.01 (-6.86 to -1.16)	-8.42 (-11.87 to -4.97)	-4.41 (-7.65 to -1.18)	0.006	<0.001	0.005
6 week	11.83 (10.65 to 13.15)	8.28 (7.19 to 9.54)	18.14 (16.58 to 19.86)	-6.31 (-8.66 to -3.97)	-9.86 (-12.34 to -7.39)	-3.55 (-5.27 to -1.83)	<0.001	<0.001	<0.001
EQ5									
Baseline	0.16 ± 0.22	0.09 ± 0.22	0.09 ± 0.19						
3 week	0.44 (0.41 to 0.47)	0.49 (0.46 to 0.53)	0.46 (0.43-0.49)	-0.21 (-0.06 to 0.019)	0.03 (-0.10 to 0.078)	0.06 (0.01 to 0.10)	0.303	0.132	0.016
6 week	0.88 (0.83 to 0.94)	0.98 (0.92-1.04)	0.74 (0.70-0.79)	0.14 (0.07 to 0.21)	0.24 (0.16 to 0.31)	0.10 (0.02 to 0.18)	<0.001	<0.001	0.016
EQ VAS									
Baseline	27.50 ±9.56	18.96 ± 12.38	24.77 ± 10.13						
3 week	65.05 (62.79 to 67.40)	65.24 (62.88 to 67.68)	59.38 (57.46 to 61.36)	5.67 (2.02 to 9.32)	5.86 (2.11 to 9.60)	0.19 (-3.15 to 3.52)	0.001	0.001	0.913
6 week	89.24 (87.39 to 91.12)	95.92 (93.89 to 97.99)	81.03 (79.54 to 82.55)	8.21 (5.54 to 10.87)	14.89 (11.74 to 18.05)	6.69 (3.89 to 9.48)	<0.001	<0.001	<0.001
Womac Pain									
Baseline	11.29 ± 2.29	13.42 ± 3.10	12.45 ± 2.23						
3 week	6.23 (5.82 to 6.67)	6.12 (5.72 to 6.56)	7.60 (7.16 to 8.06)	-1.37 (-2.06 to -0.68)	-1.48 (-2.24 to -0.71)	-0.11 (-0.71 to 0.50)	<0.001	<0.001	0.729
6 week	1.99 (1.75 to 2.27)	1.66 (1.46 to 1.89)	3.73 (3.32 to 4.19)	-1.74 (-2.31 to -1.17)	-2.07 (-2.66 to -1.48)	-0.33 (-0.671 to 0.003)	<0.001	<0.001	0.052
Womac Stiffness									
Baseline	3.86 ± 1.07	4.91 ± 1.26	4.14 ± 1.00						
3 week	2.00 (1.83 to 2.17)	2.08 (1.91 to 2.27)	2.34 (2.17 to 2.52)	-0.34 (-0.63 to -0.06)	-0.25 (-0.55 to 0.04)	0.09 (-0.16 to 0.34)	0.013	0.104	0.492
6 week	1.08 (0.94 to 1.23)	0.81 (0.68 to 0.96)	1.23 (1.12 to 1.36)	-0.16 (-0.34 to 0.03)	-0.43 (-0.66 to -0.20)	-0.27 (-0.51 to -0.04)	0.099	<0.001	0.019
Womac Function									
Baseline	46.86 ± 7.43	52.70 ± 9.34	49.14 ± 7.47						
3 week	27.47 (26.10 to 28.91)	25.03 (23.77 to 26.36)	31.57 (30.17 to 33.03)	-4.10 (-6.32 to -1.87)	-6.54 (-8.92 to -4.15)	-2.44 (-4.36 to -0.52)	<0.001	<0.001	0.013
6 week	8.94 (7.99 to 9.99)	6.88 (6.13 to 7.73)	15.82 (14.26 to 17.55)	-6.88 (-9.07 to -4.69)	-8.94 (-11.18 to -6.70)	-2.05 (-3.33 to -0.78)	<0.001	<0.001	0.002
Womac Total									
Baseline	61.98 ± 10.33	71.15 ± 13.34	65.69 ± 9.60						
3 week	35.77 (34.02 to 37.62)	32.79 (31.15 to 34.52)	41. 52 (39.71 to 43.41)	-5.74 (-8.61 to -2.88)	-8.73 (-11.82 to -5.63)	-2.98 (-5.47 to -0.49)	<0.001	<0.001	0.019
6 week	11.28 (10.09 to 12.62)	8.59 (7.65 to 9.65)	20.32 (18.31 to 22.56)	-9.04 (-11.85 to -6.23)	-11.73(-14.60 to -8.86)	-2.69 (-4.31 to -1.08)	<0.001	<0.001	0.001

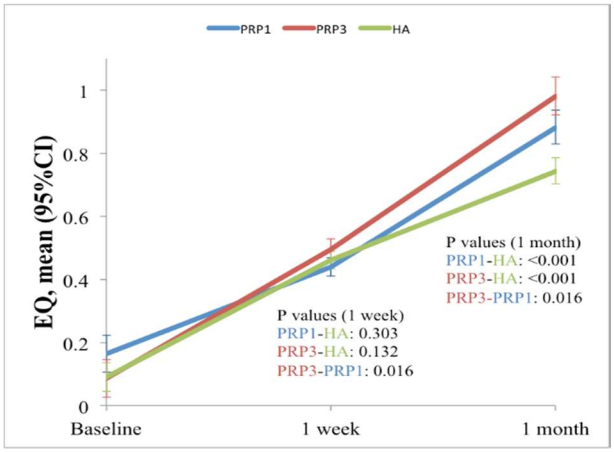
† Baseline data are mean ± standard deviation. Follow-up and difference values are generalized linear mixed models estimated mean (95%CI). The models included group, time, some baseline characteristics (i.e. age, sex, OA grade), baseline value of outcome and group X time interaction as fixed effects. *VAS* Visual Analog Scale, *EQ* European Quality of life, *WOMAC* Western Ontario and Mc Master Universities Osteoarthritis index. ‡ Generalized linear mixed models adjusted (sequential Bonferroni) P value.

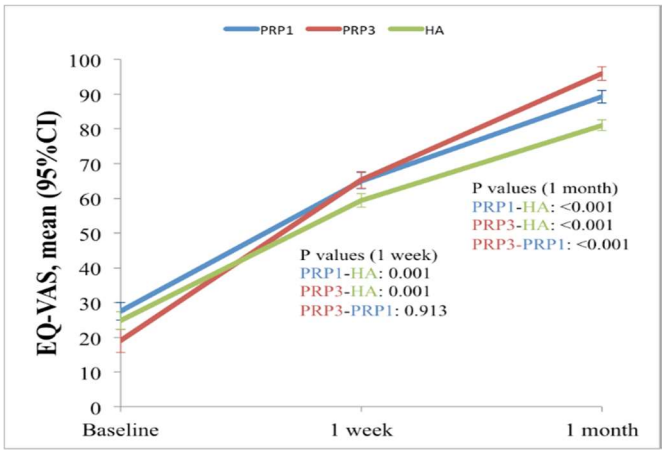
VAS scores in the 6th week. The estimated mean differences were 8.21; 95% CI, 5.54 to 10.87; *p<0.001* between PRP1 and HA groups, 14.89; 95% CI, 11.74 to 18.05; *p<0.001* between PRP3 and HA groups and 6.69; 95 % CI, 3.89 to 9.48; p<0.001 for PRP3 and PRP1 groups (Table 2, Figure 2).

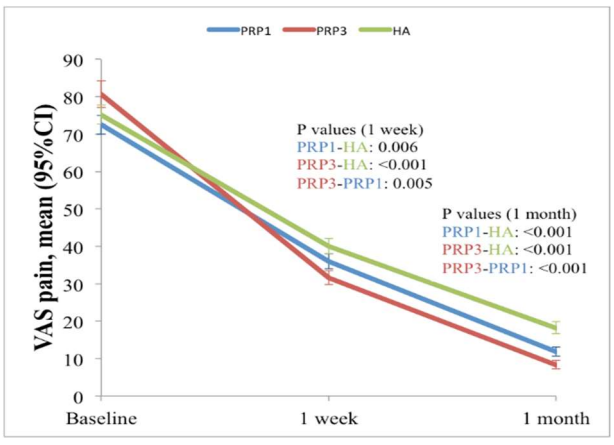
There were statistically significant differences between the PRP1-HA and PRP3-HA groups in the 3rd week for the WOMAC-pain scores in the groups. The estimated mean differences were 1.37; 95% CI, -2.06 to -0.68; *p<0.001* between PRP1 and HA groups, -1.48; 95% CI, -2.24 to -0.71; *p<0.001* between PRP3 and HA groups and -0.11; 95% CI, -0.71 to 0.50; *p=0.729* for PRP3 and PRP1 groups. Differences between the mean WOMAC-pain scores between the groups in the 6th week were identified to be statistically significant between the PRP1-HA and PRP3-HA groups. The estimated mean differences were -1.74; 95% CI, -2.31 to -1.17; *p<0.001* between PRP1 and HA groups, -2.07; 95% CI, -2.66 to -1.48; *p<0.001* between PRP3 and HA groups and -0.33; 95% CI, -0.671 to 0.003; *p=0.052* for PRP3 and PRP1 groups (Table 2, Figure 2).

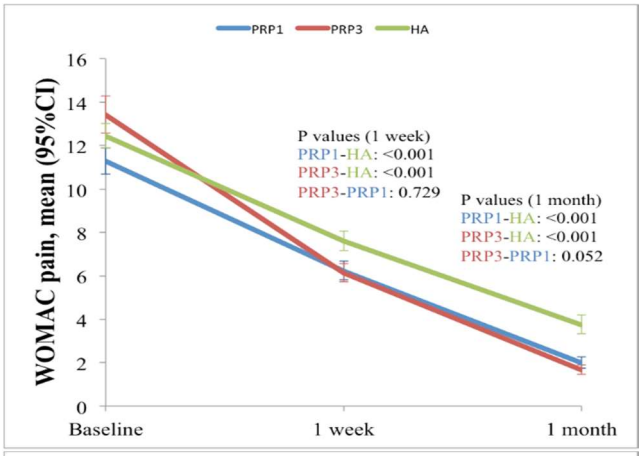
The mean differences between WOMAC-stiffness scores in the groups in the 3rd week were identified to be statistically significant for the PRP1-HA groups. The estimated mean differences were 0.34; 95% CI, -0.63 to -0.06; *p=0.013* between PRP1 and HA groups, -0.25; 95% CI, -0.55 to 0.04; *p=0.104* between PRP3 and HA groups and 0.09; 95% CI, -0.16 to 0.34; *p=0.462* for PRP3 and PRP1 groups. In the 6th week, mean differences between the WOMAC-stiffness scores in the groups were identified to be statistically significant between the PRP3-PRP1 and PRP3-HA groups. The estimated mean differences were -0.16; 95% CI, -0.34 t

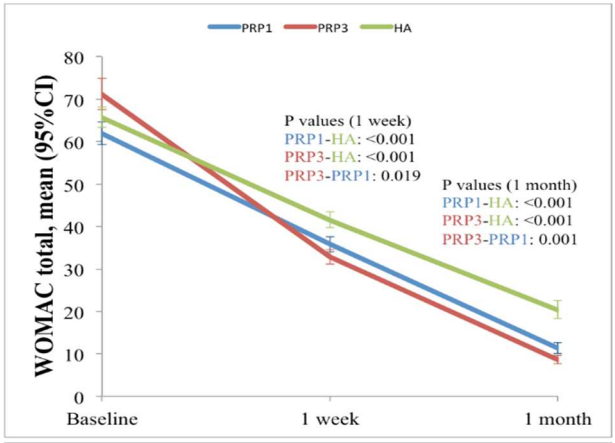
Figure 2. Baseline values are mean (95%CI). Follow-up values are generalized mixed models estimated mean (95%CI). The models included group, time, some baseline characteristics (i.e. age, sex, OA grade), baseline value of outcome and group X time interaction as fixed effects. VAS: Visual Analog Scale, EQ: European Quality of life, WOMAC: Western Ontario and Mc Master Universities Osteoarthritis index. Generalized linear mixed models adjusted (sequential Bonferroni) *P values* are presented.

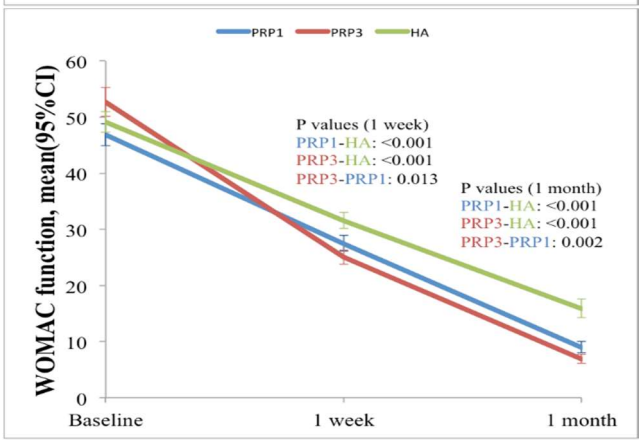


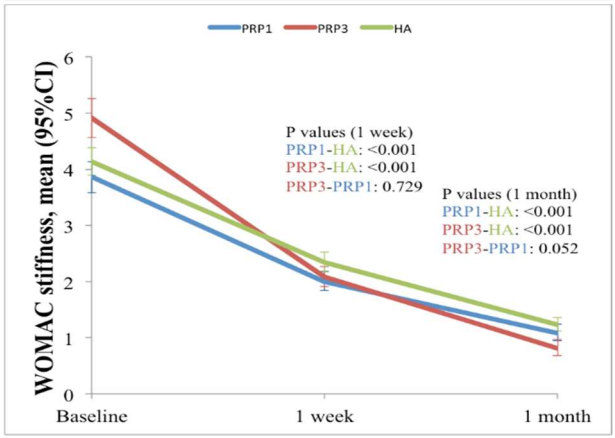












0.03; *p=0.099* between PRP1 and HA groups, 0.43; 95% CI, -0.66 to -0.20*; p<0.001* between PRP3 and HA groups and -0.27; 95% CI, -0.51 to -0.04; *p=0.019* for PRP3 and PRP1 groups (Table 2, Figure 2).

There were statistically significant differences between the groups in the 3rd week for the WOMAC-function scores. The estimated mean differences were -4.10; 95% CI, -6.32 to -1.87; *p<0.001* between PRP1 and HA groups, -6.54; 95% CI, -8.92 to -4.15; *p<0.001* between PRP3 and HA groups and -2.44; 95% CI, -4.36 to –0.52; *p=0.013* for PRP3 and PRP1 groups. Differences between the mean WOMAC-function scores between the groups in the 6th week were identified to be statistically significant. The estimated mean differences were -6.88; 95% CI, -9.07 to -4.69; *p<0.001* between PRP1 and HA groups, -8.94; 95% CI, -11.18 to -6.70; *p<0.001* between PRP3 and HA groups and -2.05; 95% CI, -3.33 to -0.78; *p=0.002* for PRP3 and PRP1 groups (Table 2, Figure 2).

The mean difference between WOMAC-total scores in the groups in the 3rd week were identified to be statistically significant. The estimated mean differences were -5.74; 95% CI, -8.61 to -2.88; *p<0.001* between PRP1 and HA groups, -8.73 95% CI, -11.82 to -5.63; *p<0.001* between PRP3 and HA groups and -2.98; 95% CI, -5.47 to -0.49; *p=0.019* for PRP3 and PRP1 groups.

In the 6th week, mean differences between the WOMAC-total scores in the groups were identified to be statistically significant. The estimated mean differences were -9.04; 95% CI, -11.85 to -6.23; *p<0.001* between PRP1 and HA groups, -11.73; 95% CI, -14.60 to -8.86; *p<0.001* between PRP3 and HA groups and -2.69; 95% CI, -4.31 to -1.08; *p=0.001* for PRP3 and PRP1 groups (Table 2, Figure 2).

Discussion

The study found statistically significant differences between the PRP1-HA groups in all parameters except EQ5, between PRP3-HA groups in all parameters except EQ5 and WOMAC stiffness, and between PRP3-PRP1 groups in all parameters except EQVAS, WOMAC pain and WOMAC stiffness in the 3rd week; and statistically significant differences between the PRP1-HA groups in all parameters except WOMAC stiffness; between PRP3-HA groups in all parameters; and between PRP3-PRP1 groups in all parameters except WOMAC pain in the 6th week.

The targets of treatment for KOA include controlling pain, minimizing physical limitations, increasing quality of life and if possible, stopping progression of pathological processes [3-6]. Treatment should be specifically organized according to each individual based on patient expectations, disease severity, activity level and presence of comorbid diseases [3-6]. The minimal invasive treatments of intraarticular HA and PRP administration are commonly used treatment alternatives. Though many studies have been published about both treatment methods, effects and efficacy are still controversial [8-12].

In KOA treatment, just as with IA PRP injection, the use of autologous growth factors is increasing [16]. PRP is the most convenient agent to obtain when compared with products containing other autologous growth factors. PRP contains factors like platelet-derived insulin-like growth factor, fibroblast growth factor, platelet-derived growth factor, epidermal growth factor and venous endothelial growth factor. These factors obtained from PRP may change the inflammatory process and have been shown to assist in preserving and regenerating tissue structure [17,18]. Due to these features, PRP is used in many different areas, not just for joint pathologies [19]. PRP contributes to the repair processes in subchondral bone and cartilage in KOA [20]. It reduces the negative effects of knee pain and inflammatory response [21]. Many reviews have reported positive clinical effects of PRP injection. PRP was shown to reduce pain and improve osteoarthritis indices (WOMAC total score, WOMAC subscores and Lequesne score) in KOA patients [22-29].

PRP injection is observed to be effective in early symptomatic OA knees. Outcomes after treatment show a clear reduction in pain in the 12th month compared to situation before treatment and continued improvement in knee functions [22]. A study of patients with moderate stage KOA administered a single injection of PRP and two and three doses of PRP at two-week intervals and analyzed results at the end of the 6th month. In conclusion, they showed that for improvement in functional status and pain, a minimum of two injections were required [30]. A study of late stage (stage IV) KOA patients with single dose PRP and single dose steroid injection identified that the daily life activities, pain and QoL scores were similar in the two groups in the 6th month, with a significant improvement compared to initially [31].

A meta-analysis included many studies researching the clinical effect of PRP and stated that PRP was effective for KOA treatment but there was no clear evidence about dose or frequency. In this study, Vilchez-Cavazos et al. assessed 6-month outcomes and stated that single dose PRP had similar levels of improvement in terms of pain to multiple PRP doses; however, multiple dose PRP groups had more significant improvement in terms of joint functions [32]. Patel et al. compared efficacy at the end of the 6th month for 1 and 2 doses of

PRP with single-dose saline injection and showed that PRP injections ensured better improvement compared to saline injections in terms of WOMAC scores; however, there was no difference between the two PRP injections [33]. Görmeli et al. showed that three doses of PRP injection provided significantly better improvement compared with a single injection for early OA (stage I, II, III) patients; however, in advanced OA patients (stage IV) there was no difference between the groups [11]. In our study, early and moderate stage KOA patients (stage I, II, III) had the short-term effects of PRP injection investigated and both PRP groups had independent improvement identified in terms of pain (VAS), quality of life scores (EQ-5D) and daily life activities (WOMAC). The group with 3 consecutive PRP injections were identified to have significant improvement in the 3rd and 6th weeks compared to the PRP1 group.

Significant problems experienced with PRP administration may be listed as obtaining PRP solution amounts, platelet concentration in contents, use of tubes and kits with different features, homogenization of obtained PRP and user experience [34,35]. In our study, a PRP kit abiding by standardization as determined by the Turkish Ministry of Health and international standards and with safety certification was used. The PRP solutions for administration were prepared by an experienced health staff with clinical training and administered by a single clinician.

Patients with HA injection, assessed in many studies for knee treatments, were not identified to have any difference compared to patients with single-dose PRP injection. Patients with multiple PRP doses were identified to have greater improvement than patients with one of the other two treatments administered [34, 36-40].

In the literature, though studies comparing PRP and HA injections and meta-analyses have generally emphasized that IA PRP administration is more effective compared to HA administration in terms of pain and functional improvement [23, 27, 29, 41-43], a few meta-analyses have reported the opposite view [44, 45]. PRP injection was shown to be more effective in reducing symptoms in mild and moderate (stage I, II, III) KOA patients who do not respond to traditional treatment and in improving function and quality of life compared to HA injection and placebo in many studies in the literature [42, 46-49].

Görmeli et al. in a study of PRP and HA injections showed that there were significant degrees of improvement in early OA (stage I, II, III) patients in terms of pain and function improvement; however, there was no difference between the groups for advanced OA (stage IV) patients [34]. Zhang et al. compared pain, function and quality of life indices after PRP and HA injections and showed that patients in different stages of KOA did not show the same response to PRP or HA treatment [12]. Kon et al. investigated three homogeneous patient groups treated with PRP, low-molecular weight HA and high molecular weight HA and concluded that autologous PRP injections had longer duration of efficacy compared to HA injections and improved joint functions [47]. In our study, early and moderate stage (stage I, II, III) KOA patients had single dose and triple dose of PRP and high-molecular weight HA administered IA. There are standardization problems with PRP kits and the treatment performed with these kits and with HA preparations. Products offered for use may be obtained with different technological methods, have different molecular weights and doses, and have problems like being straight or cross-linked causing different treatment outcomes

and complications to be encountered. In our study, all patients had PRP kit and HA preparations administered with the same brands and features. No infection or allergic reactions were encountered during follow-up. In the 3rd and 6th weeks after injections, scores indicating pain, quality of life and daily life activities were improved in all groups. This improvement was identified to be at more significant levels in the PRP groups compared to the HA group. When the PRP groups are compared, all scores in the PRP3 group were significantly better than the PRP1 group. In our study, we think the short-term efficacy of PRP injections is due to symptomatic amelioration occurring with physiological variations effective on pain in the intra/periarticular region, rather than positive changes to the pathologic degeneration process in the joint structure or knee OA. However, the improvement after PRP treatment compared to HA treatment, more pronounced after three doses of PRP, leads to consideration that the regeneration process begins in the short term. In order to reveal regenerative changes after PRP administration, it is necessary to perform moderate and long-term follow-up with radiological and histopathological investigations needed to prove these changes.

The nonrandomized design, the patient follow-up duration being limited to 6 weeks, and not showing the presence of regeneration after the administered treatments with histopathologic and/or imaging methods may be listed as important limitations of our study. Also, the lack of recording the adherence to home exercise program is another limitation: patients who adhered to home exercise program might have been better improvements than those who did not adhere to it.

Conclusions

Intraarticular PRP injections (single or three doses) were found to be more beneficial in the short term in terms of pain and functional improvement than HA injection and administration of three consecutive doses of PRP may be more effective compared to single-dose PRP administration in KOA patients

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Ethical statement: *All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants prior to being included in the study.*

The study was approved by Usak University Medical School Ethics Committee, decision number 31-5-13, dated 2018/04/25.

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