Meta-analysis

Platelet-Rich Plasma Versus Hyaluronic Acid in the Treatment of Knee Osteoarthritis: A Meta-Analysis of 26 Randomized Controlled Trials

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Purpose: To compare the effectiveness and safety of platelet-rich plasma (PRP) and hyaluronic acid (HA) in patients with adult knee osteoarthritis (KOA) and to explore the most effective and safe protocol by using a meta-analysis method. **Methods:** This study was based on Cochrane methodology for conducting a meta-analysis. Only randomized controlled trials with an experimental group that used PRP and a control group that received HA were eligible for this study. The participants were adults who had KOA. The outcome measures were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the visual analog scale (VAS), the EuroQol VAS, the International Knee Documentation Committee, the Tegner score, the Lequesne Scale, the Knee injury Osteoarthritis Outcome Score, satisfaction rate, and adverse events. Subgroup analyses was performed for patients with different doses, types, and times of PRP interventions and grades of OA. The Review Manager Database was used to analyze the included studies. **Results:** Twenty-six randomized controlled trials involving 2430 patients were included. The WOMAC total scores, WOMAC physical function scores, and VAS scores of the PRP group were better than the those of the HA group at 3, 6, and 12 months. The PRP group had better WOMAC pain, WOMAC stiffness, EuroQol VAS, and International Knee Documentation Committee scores than the HA group at 6 and 12 months. There was no significant difference in adverse events between the 2 groups (relative risk 1.21, 95% confidence interval 0.95-1.54; $P = .13$). **Conclusions:** For the nonsurgical treatment of KOA, compared with HA, intra-articular injection of PRP could significantly reduce patients' early pain and improve function. There was no significant difference in adverse events between the 2 groups. PRP was more effective than HA in the treatment of KOA, and the safety of these 2 treatment options was comparable. **Level of Evidence:** Level I, meta-analysis of Level I RCTs.

Osteoarthritis (OA) is the most common articular disease, and it is an important cause of disability in elderly patients.[1,2] The knee is the joint most frequent affected by OA.[3] The increasing number of patients with symptomatic osteoarthritis of the knee (KOA) will continue to place an increasingly larger economic burden on global health care systems.[4] Nonoperative treatments include nonsteroidal anti-inflammatory drugs, weight loss, dietary supplements such as glucosamine and chondroitin sulfate, topical agents, and intra-articular injections of corticosteroids and/or hyaluronic acid (HA).[5-8] Intra-articular injections of HA are often the last treatment options before arthroplasty. However, the efficacy and safety of HA injection for the treatment of KOA remains a matter of conflict. Injection of HA did not diminish the inflammatory process in the joint and sometimes caused adverse reactions.[9-11] In addition, there is no agreement on the use of HA. Chevalier et al.'s research[9] indicated that the use of HA once could significantly improve patients' symptoms. Petrella and Petrella[11] found that continuous injection of HA 3 or 6 times in the knee joint had no statistically significant effect on knee pain or function. Platelet-rich plasma (PRP) is a plasma that is prepared from each patient's own blood, and it has a greater platelet concentration in comparison with normal plasma. Compared with knee arthroplasty, PRP injection is a simple and minimally invasive procedure that provides

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concentrated growth factors for use as an intra-articular injection.[12] Some studies have demonstrated the efficacy of PRP in KOA.[13-15]

There are currently 4 meta-analyses that have compared PRP with HA in the treatment of KOA: Han et al. (15 RCTs),[16] Zhang et al. (13 RCTs),[17] Shen et al. (14 RCTs),[18] and Dai et al. (10 RCTs).[19] They did not achieve consistent results in terms of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS), or International Knee Documentation Committee (IKDC) scores. Four meta-analyses evaluated WOMAC total scores. Zhang et al. and Shen et al. found that the PRP group was better than the HA group in each period (3 months, 6 months, and 12 months). Dai et al.'s research found that PRP was better only at 12 months. Regarding the VAS score, Han et al. found that, compared with the HA group, the PRP group had a greater reduction in the patient pain at 12 months, but no significant difference was found at 1, 3, or 6 months. However, the study of Zhang et al. did not find significant differences between the 2 groups in different periods. Regarding the IKDC score, both Han et al. and Zhang et al. observed better results in the PRP group at 6 months. However, Han et al. did not notice a significant difference between the 2 groups at 2 months. Zhang et al. did not perform an IKDC score analysis at 2 months. The effectiveness of the 2 interventions remains unclear. In recent years, there have been some new and high-quality RCTs.[20-27] The aim of this study was to compare the effectiveness and safety of PRP and HA in adult KOA patients and to explore the most effective and safe protocol by using a meta-analysis method. We hypothesized that, in the treatment of KOA, the use of PRP could reduce pain and improve function more than HA.

Methods

This study was based on the Cochrane methodology for conducting a meta-analysis.[28] The present study was completed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement. There was no registered protocol.

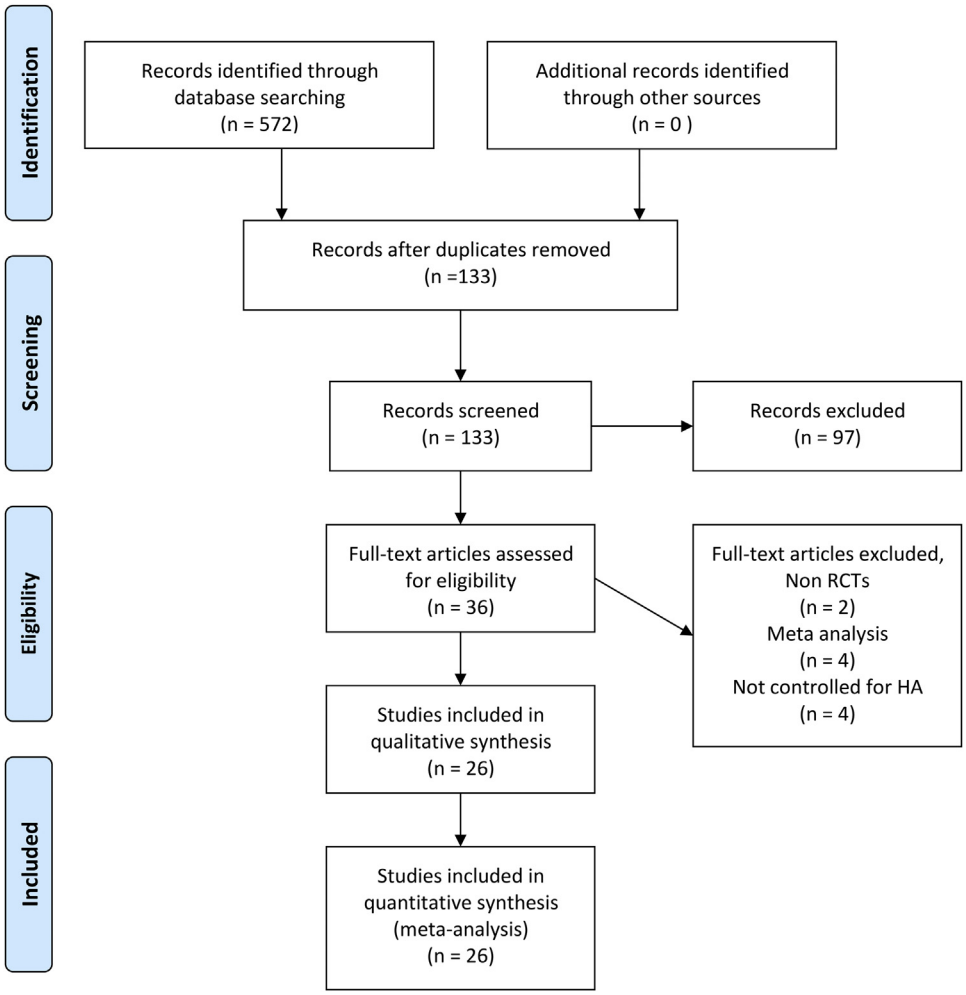

Fig 1. Flowchart of the study selection. (HA, hyaluronic acid; RCT, randomized controlled trial.)

Table 1. Characteristics of the Included Studies

Author	Country	Groups	Number	Age, y	Sex M/F, n	BMI	OA Grade	Intervention (Injection Dose, Type, Times, and Intervals)	PRP Preparation	Follow-up, mo	Outcome	QAS	Year
Tavassoli et al[20]	Iran	PRP HA	28 27	66.04 ± 7.58 63.30 ± 8.87	6/22 8/19	29.61 ± 1.64 28.94 ± 2.26	Grade 1-2 (Ahlback)	4-6 mL, fresh, 2 times, 3 weeks 30 mg/2 mL, Hyalgan, 3 times, weekly	About 40 mL of venous blood was drawn from antecubital vein. The blood sample was then centrifuged for 15 min at 1500 rpm, leading to 2 different layers. The plasma was separated and then centrifuged for 7 min at 3500 rpm. The final product was 4-6 mL of PRP.	1, 2, 3	WOMAC, VAS, adverse events	20	2019
Di Martino et al[21]	Italy	PRP HA	85 82	52.7 ± 13.2 57.5 ± 11.7	53/32 47/35	27.2 ± 7.6 26.8 ± 4.3	Grade 1-3 (KL)	5 mL, frozen, 3 times, weekly 30 mg/2 mL, Hyalubrix, 3 times, weekly	A 150-mL unit of peripheral venous blood was harvested from each patient. Two centrifugations were then performed: the first at 1480 rpm for 6 min to separate erythrocytes and the second at 3400 rpm for 15 min to concentrate platelets, which provided 20 mL of PRP divided into 4 units of 5 mL.	2, 6 ,12, 24	IKDC, EQ-VAS, Tegner score, reintervention rate, adverse events	24	2019
Huang et al[22]	China	PRP HA	40 40	54.5 ± 1.2 54.8 ± 1.1	25/15 19/21	25.23 ± 4.15 24.51 ± 3.09	Grade 1-2 (KL)	4 mL, fresh, 1 time 2 mL, NA, 3 times, weekly	Samples of 8 mL of blood were obtained from the cubital vein and centrifuged for 5 min at 1500 g centrifugal force or 3500 pm. After centrifugation, platelet recovery was >80% in 4 mL of PRP.	3, 6, 9, 12	WOMAC, VAS, adverse events	17	2019
Lin et al[23]	China	PRP HA	31 29	61.17 ± 13.08 62.53 ± 9.9	9/22 10/19	23.98 ± 2.62 26.26 ± 2.99	Grade 1-3 (Ahlback)	5 mL, fresh, 3 times, weekly 20 mg/2 mL, HYRUAN plus, 3 times, weekly.	PRP was prepared using RegenKit-THT, which required 10 mL of blood to be drawn and single spun at 1,500 rpm for 8 min. This would yield an average of 5.0mL of PRP with approximately 90% of platelets recovered.	1, 2, 6, 12	WOMAC, IKDC, adverse events	21	2019
Lisi et al[24]	Italy	PRP HA	28 22	53.5 ± 15.1 57.1 ± 10.0	NA	NA	Grade 2-3 (Shahriaree)	NA, Fresh, 3 times, monthly 20 mg/2 mL, Hyalgan, 3 times, monthly	20mL of autologous whole blood was sampled from each patient. The vial was gently centrifuged at 900r/min for 7 min. PRP was collected.	0.5, 6, 12	WOMAC, VAS, AKSS, Lysholm, Tegner, Lequesne, flexion	22	2018

(continued)

Table 1. Continued

Author	Country	Groups	Number	Age, y	Sex M/F, n	BMI	OA Grade	Intervention (Injection Dose, Type, Times, and Intervals)	PRP Preparation	Follow-up, mo	Outcome	QAS	Year
Yu et al[25]	China	PRP HA	104 88	46.2 ± 8.6 51.5 ± 9.3	50/54 48/40	NA	Karnofsky performance status of ≥80%	Baseline stage, the double-blind treatment phase (4-week dose-titration treatment, PRP, 2, 4, 8, 10, 12, and 14 mL, HA, 0.10, 0.15, 0.20, 0.25, and 0.30 mg) and 52-week post-treatment (PRP, 8 mL, HA, 0.2 mg) for patients with knee osteoarthritis who volunteered to complete the ongoing extension study.	NA	12	WOMAC, adverse events	21	2018
Ahmad et al[26]	Egypt	PRP HA	45 44	56.2 ± 6.8 56.8 ± 7.4	14/31 14/30	26.7 ± 3.6 26.5 ± 3.5	Grade 1-3 (KL)	4 mL, fresh, 3 times, 14 days 20 mg/2 mL, NA, 3 times, 14 days	8 mL of peripheral blood was extracted and centrifuged for 9 min at 3500 rpm. Subsequently, 4 mL of PRP were obtained from each patient.	3, 6	VAS, IKDC, ultrasound	20	2018
Buendía -López et al[27]	Spain	PRP HA	33 32	56.15 ± 3.0 56.63 ± 2.9	16/17 15/17	24.9 ± 0.32 24.9 ± 0.41	Grade 1-2 (KL)	5 mL, fresh, 1 time 60 mg/2 mL, DUROLANE, 1 time	Each patient had 60 mL of peripheral blood extracted by venipuncture of the antecubital vein. The first spin step was 1050 rpm for 15 min and for the second spin step, an acceleration of 2000 rpm for 10 min was applied. A total 5 mL of a leukocyte-poor PRP preparation was obtained.	6, 12	WOMAC, VAS, adverse events	18	2018
Louis et al[30]	France	PRP HA	24 24	53.2 ± 11.7 48.5 ± 11.5	14/10 11/13	25.6 ± 2.9 27.0 ± 2.9	Grade ≧2 (KL)	3 mL, fresh, 1 time. 3 mL, DUROLANE, 1 time	52.5 mL (for men) or 37.5 mL (for women) of peripheral blood was collected. First spin was managed with a standard laboratory centrifuged at 130*g* for 15 min. To further concentrate PRP, a second 15-minute spin at 250*g* was performed. 4 mL of PRP was obtained.	1, 3, 6	WOMAC, VAS, adverse events, satisfaction rate	24	2018

(continued)

Table 1. Continued

Author	Country	Groups	Number	Age, y	Sex M/F, n	BMI	OA Grade	Intervention (Injection Dose, Type, Times, and Intervals)	PRP Preparation	Follow-up, mo	Outcome	QAS	Year
Su et al[31]	China	PRP HA	25 30	54.16 ± 6.56 53.13 ± 6.41	11/14 12/18	28.17 ± 1.43 28.69 ± 1.13	Grade 2-3 (KL)	6 mL, fresh, 2 times, 14 days 2 mL, Freda, 5 times, weekly	A total 45-mL venous blood sample was drawn from the antecubital vein. Blood samples were centrifuged at 1480 rpm for 6 min to separate the red blood cells from the buffy coat and the upper plasma layer and centrifuged again at 3400 rpm for 15 min to obtain a 2-part plasma. The upper three-quarter fraction of the plasma was discarded and of the remainder, which contained the approximately 7 mL of concentrated leukocyte-containing PRP.	1, 3, 6, 12, 18	WOMAC, VAS, adverse events	17	2018
Duymus et al[32]	Turkey	PRP HA	33 34	60.4 ± 5.1 60.3 ± 9.1	1/32 1/33	27.6 ± 4.6 28.4 ± 3.6	Grade 2-3 (KL)	5 mL, fresh, 2 times, monthly 40 mg/2 mL, OSTENIL PLUS, 1 time	14 ml of blood was taken from the patients. To concentrate the platelets, the kit was centrifuged at 3700 rpm for 7 min. Finally, 3-4 mL of concentrated PRP was obtained.	1, 3, 6, 12	WOMAC, VAS	18	2017
Cole et al[33]	USA	PRP HA	49 50	55.9 ± 10.4 56.8 ± 10.5	28/21 20/30	27.4 ± 3.9 29.0 ± 6.4	Grade 1-3 (KL)	4 mL, fresh, 3 times, weekly 16 mg/2 mL, Hylan G-F 20, 3 times, weekly	10 mL of blood was drawn and spun at 1500 rpm for 5 min. This yielded approximately 4 mL of PRP for use.	1.5, 3, 6, 12	WOMAC, VAS, IKDC	21	2017
Raeissadat et al[34]	Iran	PRGF HA	36 33	57.0 ± 7.18 59.5 ± 7.54	7/29 6/27	28.6 ± 2.82 27.5 ± 2.9	Grade 2-3 (KL)	5 mL, fresh, 2 times, 3 weeks 20 mg, Hyalgan, 3 times, weekly	35 mL of blood was obtained to prepare PRP. After centrifuging for 15 min at 1600 rpm, 3 layers emerged, including red blood cells, WBCs, and plasma. The 2 uppermost layers underwent another centrifuge for 7 min at 3500 rpm. Our product at this step consisted of 8 mL of plasma with 4.6 times platelet concentration.	2, 6	WOMAC, VAS, Lequesne, adverse events, satisfaction rate	20	2017
Montañez-Heredia et al[35]	Spain	PRP HA	27 26	66.3 ± 8.3 61.5 ± 8.6	12/15 9/17	29.0 ± 5.5 30.4 ± 4.9	Grade 1-3 (KL)	NA, frozen, 3 times, 15 days NA, Adant, 3 times, 15 days	150 mL of whole blood was distributed into 4 Falcon test tubes that were subjected to double centrifugation and cellular testing.	3, 6	VAS, KOOS, EuroQol, adverse events	24	2016

(continued)

Table 1. Continued

Author	Country	Groups	Number	Age, y	Sex M/F, n	BMI	OA Grade	Intervention (Injection Dose, Type, Times, and Intervals)	PRP Preparation	Follow-up, mo	Outcome	QAS	Year
Paterson et al[36]	Australia	PRP HA	11 10	49.91 ± 13.72 52.70 ± 10.30	8/3 7/3	27.92 ± 11.94 30.87 ± 5.64	Grade 2-3 (KL)	3 mL, fresh, 3 times, weekly 3 mL, Hylan G-F 20, 3 times, weekly	48.5 mL of the patient's blood was collected using venipuncture, then centrifuged at 2000 rpm for 5 min. The plasma and buffy coat containing platelets was drawn from the top of the sample and centrifuged again at 3000 rpm for 3 min. 3 mL of PRP was obtained.	1, 3	VAS, KOOS, KQoL, functional tests, adverse events	24	2016
Lana et al[37]	Brazil	PRP HA	36 36	60 ± 6.6 60.9 ± 7	7/29 3/33	28.24 ± 8.77 27.42 ± 6.89	Grade 1-3 (KL)	5 ml, fresh, 3 times, 14 days 20 mg/2 mL, EUFLEXXA, 3 times, 14 days	About 60 mL of total blood was drawn from the median or antecubital vein. The first centrifugation was carried out at 300*g* for 5 min. The whole top part of the content is collected, avoiding the collection of erythrocytes. This content continues on to the second centrifugation at a higher speed rotation (700*g* for 17 min). 5 mL of PRP was obtained.	1, 3, 6, 12	WOMAC, VAS, CRP, adverse events	24	2016
Raeissadat et al[38]	Iran	PRP HA	77 62	56.85 ± 9.13 61.13 ± 7.48	8/69 15/47	28.20 ± 4.63 27.03 ± 4.15	Grade 1-4 (KL)	4-6 mL, fresh, 2 times, 4 weeks 20 mg/2 mL, HYALGAN, 3 times, weekly	35-40 mL of blood was first collected from the patient's upper limb cubital vein. The blood sample was then centrifuged for 15 min at 1600 rpm resulting in 3 layers. The buffy coat layer and the plasma layer were later collected and centrifuged for another 7 min at 2800 rpm. The final product was 4-6 mL of PRP containing leukocytes.	1, 6, 12	WOMAC, SF-36,	18	2015

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Table 1. Continued

Author	Country	Groups	Number	Age, y	Sex M/F, n	BMI	OA Grade	Intervention (Injection Dose, Type, Times, and Intervals)	PRP Preparation	Follow-up, mo	Outcome	QAS	Year
Filardo et al[39]	Italy	PRP HA	94 89	53.32 ± 13.2 57.55 ± 11.8	60/34 52/37	26.6 ± 4.0 26.9 ± 4.4	Grade 1-3 (KL)	5 mL, fresh, 3 times, weekly 30 mg/2 mL, Hyalubrix, 3 times, weekly	150-mL unit of peripheral venous blood was harvested from each patient. Then, 2 centrifugations were performed: the first at 1480 rpm for 6 min to separate erythrocytes and the second at 3400 rpm for 15 min to concentrate platelets, which provided 20 mL of PRP divided into 4 small units of 5 mL.	2, 6, 12	IKDC, KOOS, EQ-VAS, Tegner, ROM, Transpatellar circumference, adverse events	22	2015
Görmeli et al[40]	Turkey	PRP HA	39 39	53.7 ± 13.1 53.5 ± 14	16/23 17/22	28.7 ± 4.8 29.7 ± 3.7	Grade 1-4 (KL)	5 mL, 1 fresh/2 frozen, 3 times, weekly 2 mL, ORTHOVISC, 3 times, weekly	150 mL of venous blood was collected under aseptic conditions from the antecubital vein. To collect 20 mL of PRP, 2 centrifugations (the first at 1500 rpm for 6 min and the second at 3500 rpm for 12 min) were performed. The PRP unit was divided into 4 small units of 5 mL each.	6	IKDC, EQ-VAS, satisfaction rate	24	2015
Vaquerizo et al[41]	Spain	PRGF HA	48 48	62.4 ± 6.6 64.8 ± 7.7	16/32 22/26	30.7 ± 3.6 31.0 ± 4.6	Grade 2-4 (KL)	8 mL, fresh, 3 times, 14 days NA, DUROLANE, 1 time	36 mL of peripheral blood was extracted from each patient by venipuncture. The extracted blood was centrifuged at 580*g* for 8 min. Once the blood tubes were centrifuged, we proceeded to physically separate the plasma fractions. The volume of PRGF injected was 8 mL.	6, 12	WOMAC, Lequesne, adverse events	22	2013
Say et al[42]	Turkey	PRP HA	45 45	55.2 ± 7.8 56.2 ± 5.1	5/40 6/39	32.4 ± 4 32.3 ± 3.3	Grade 1-3 (KL)	2.5 mL, fresh, 1 time 25 mg/2.5 mL, NA, 3 times, weekly	A total of 30 cc of peripheral blood was taken from antecubital region of the patients. The tubes were centrifuged at 1800 rpm for 8 min. 2.5 mL of PRP was obtained.	3, 6	KOOS, VAS, adverse events	18	2013
Cerza et al[43]	Italy	PRP HA	60 60	66.5 ± 11.3 66.2 ± 10.6	25/35 28/32	NA	Grade 1-3 (KL)	5.5 mL, fresh, 4 times, weekly 20 mg/2 mL, HYALGAN, 4 times, weekly	NA	1, 3, 6	WOMAC	18	2012

(continued)

Table 1. Continued

Author	Country	Groups	Number	Age, y	Sex M/F, n	BMI	OA Grade	Intervention (Injection Dose, Type, Times, and Intervals)	PRP Preparation	Follow-up, mo	Outcome	QAS	Year
Sánchez et al[44]	Spain	PRGF HA	79 74	60.5 ± 7.9 58.9 ± 8.2	NA	27.9 ± 2.9 28.2 ± 2.7	Grade 1-3 (Ahlback)	8 mL, fresh, 3 times, weekly NA, EUFLEXXA, 3 times, weekly	36 mL of peripheral blood was extracted from each patient by venipuncture. The extracted blood was centrifuged at 580*g* for 8 min. Once the blood tubes were centrifuged, we proceeded to physically separate the plasma fractions. The volume of PRGF injected was 8 mL.	1, 2, 6	WOMAC, Lequesne, Adverse events	23	2012
Filardo et al[45]	Italy	PRP HA	54 55	55 58	37/17 31/24	27 26	Grade 0-3 (KL)	5 mL, frozen, 3 times, weekly NA, Hyalubrix, 3 times, weekly	150 mL of venous blood was extracted from each patient Then, 2 centrifugations (the first at 1480 rpm for 6 min to separate erythrocytes, and a second at 3400 rpm for 15 min to concentrate platelets) produced a unit of PRP. The unit of PRP was divided into 4 small units of 5 mL each.	2, 6, 12	KOOS, EQ-VAS, IKDC, Tegner, adverse events	24	2012
Spaková et al[46]	Slovakia	PRP HA	60 60	52.80 ± 12.43 53.20 ± 14.53	33/27 31/29	27.9 ± 4.1 28.3 ± 4.0	Grade 1-3 (KL)	3 mL, fresh, 3 times, weekly NA, Erectus, 3 times, weekly	The blood (27 mL of venous blood) sample was drawn into tubes. The blood sample was then centrifuged for 15 min at 3200 rpm resulting in the 3 following layers. The buffy coat layer together with the plasma layer was collected and centrifuged for another 10 min at 1500 rpm to separate the leukocytes. The plasma layer was collected, and the third centrifugation step at 3200 rpm for 10 mins was performed to obtain a 2-part plasma. 3 mL of PRP was obtained.	3, 6	WOMAC, NRS, adverse events	22	2012

(continued)

Table 1. Continued

Author	Country	Groups	Number	Age, y	Sex M/F, n	BMI	OA Grade	Intervention (Injection Dose, Type, Times, and Intervals)	PRP Preparation	Follow-up, mo	Outcome	QAS	Year
Kon et al[47]	Italy	PRP	50 50	50.6 ± 13.8	30/20	24.6 ± 3.2	Grade 0-4 (KL)	5 mL, 1 fresh/2 frozen, 3 times, 14 days	150 mL of venous blood was extracted from each patient Then, 2 centrifugations (the first at 1480 rpm for 6 min to separate erythrocytes, and a second at 3400 rpm for 15 min to concentrate platelets) produced a unit of PRP. The unit of PRP was divided into 4 small units of 5 mL each.	2, 6	EQ-VAS, IKDC, adverse events, satisfaction rate	18	2011
		HA		54.9 ± 12.6	25/25	24.8 ± 3.5		30 mg/2 mL, NA, 1 time					

AKSS, American Knee Society Score; BMI, body mass index; CRP, C-reactive protein; EQ-VAS, EuroQol visual analog scale; EuroQol, European Quality of Life Scale; F, female; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KL, Kellgren–Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; KQoL, Knee Quality of Life; M, male; NA, not available; NRS, numeric rating scale; OA, osteoarthritis; QAS, quality assessment score; PRGF, plasma-rich in growth factor; PRP, platelet-rich plasma; ROM, range of motion; SF-36, Short form-36; VAS, visual analog scale; WBC, white blood cells; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Search Strategy

The published literature was searched using the electronic MEDLINE (1950 to December 2019), Allied and Complementary Medicine (1985 to December 2019), EMBASE (1974 to December 2019), CINHAL (1982 to December 2019), Cochrane Library (2019), China National Knowledge Infrastructure (1994 to December 2019), Scopus (2019), and Biomed Central (2019) databases. No language or date restrictions were applied. The Medical Subject Headings and key word search adopted was "platelet rich plasma" AND "hyaluronic acid" OR "knee osteoarthritis." The unpublished literature was searched using the electronic OpenSIGLE (System for Information on Grey Literature in Europe) database, the World Health Organization International Clinical Trials Registry Platform, the Current Controlled Trials database, the UK Clinical Research Network Portfolio Database, and the National Technical Information Service database from their inception to December 1, 2019. Finally, the reference lists of all full-text papers identified as pertinent to the study were reviewed for any unidentified studies.

Inclusion and Eligibility Criteria

Only RCTs were eligible for this study, with an experimental group that received PRP and a control group that received HA. The participants were adults who had KOA. Subgroup analyses were performed for patients with different doses, types, and times of PRP interventions and different grades of OA. Exclusion criteria consisted of (1) history of other joint diseases in the knee, such as rheumatoid arthritis or gout; (2) history of knee surgery; (3) history of knee fracture; (4) intra-articular injection of other drugs, such as HA over the previous 1 year; or (5) contraindications for intra-articular injection, such as thrombocytopenia, coagulopathy, articular infection of knee, skin infection at the injection site, or impairment of immunity.

Study Selection

Two authors (J.T., H.C., the 2 authors are attending physicians and have worked over 8 years) independently applied the search strategy to select references from these databases. The titles and abstracts of the retrieved articles were reviewed independently. When there was a doubt, the full text was retrieved for further scrutiny. The same 2 authors independently assessed each full study report to see whether it met the review's inclusion criteria, and authors were contacted for more information and clarification of the data, as necessary. Any disagreement was discussed with the senior authors (L.Z., W.H.), and when consensus could not be reached, that study was excluded. A list of all pertinent papers satisfying these criteria was then constructed by each reviewer to compile an agreed list of studies for inclusion.

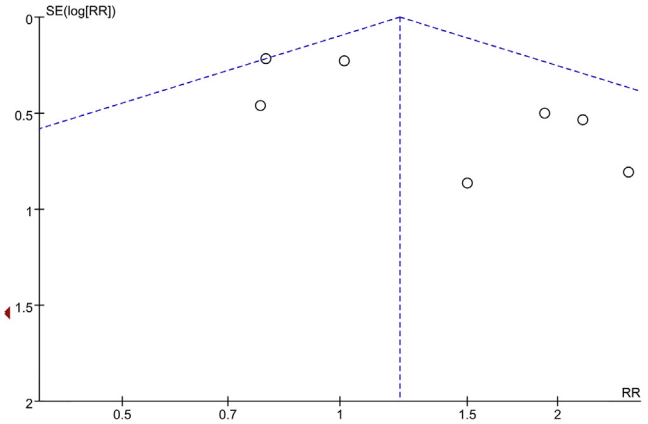

Fig 2. Trials of PRP versus HA: funnel plot of adverse events. (HA, hyaluronic acid; PRP, platelet-rich plasma; RR, relative risk; SE, standard error.)

Data Abstraction

A data-extraction form was designed and agreed upon by the authors, and a pilot test of 3 articles was performed to ensure its consistency. Initially, 2 authors (J.T., H.C.) independently extracted the data, which were later reviewed jointly to produce agreed upon and accurate data. Disagreements were resolved by consensus or consultation with the senior authors (L.Z., W.H.). The data extracted included sample size, study design, subject age, sex, body mass index, number of surgeons operating, surgical technique, interventions, the results, and follow-up period.

Outcomes

The outcome measures were WOMAC score, VAS score, EuroQol visual analog scale (EQ-VAS) score, IKDC score, Tegner score, the Lequesne Scale, the Knee injury and Osteoarthritis Outcome Score (KOOS), the American Knee Society Score, reintervention rate, C-reactive protein, Short Form-36 score, the Numeric rating scale, Knee Quality of Life, and the European Quality of Life Scale (EuroQol), satisfaction rate, and adverse events.

Quality Assessment

To assess the methodologic quality of the included studies, the authors used a modification of the generic evaluation tool used by the Cochrane Bone, Joint and Muscle Trauma Group.[29] The methodologic quality of each trial was scored and ranged from 0 to 24. Any disagreement was resolved by the senior authors.

Statistical Analysis

The Review Manager Database (RevMan version 5.3, Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to analyze the included studies. Continuous data for each arm in a particular study were expressed as the mean and standard deviation, and the treatment effect was expressed as the mean differences (MD). Dichotomous data for each arm in a particular study were expressed as proportions or risks, and the treatment effect was expressed as the relative risk (RR). Missing data were sought from the authors. When this was not possible or when data were missing through loss to follow-up, intention-to-treat principles were used. Statistical heterogeneity was assessed using the value of I^2 and the result of the χ^2 test. A P value of $< .1$ and an I^2 value $>50\%$ were considered suggestive of statistical heterogeneity, prompting a random effects modeling estimate. Otherwise, a fixed-effects approach was used. Conversely, a nonsignificant χ^2 test result (a P value ≥ 0.1 and an I^2 value $\leq 50\%$) only suggested that there was no evidence of heterogeneity: it did not imply that there was necessarily homogeneity, as there may have been insufficient power to be able to detect heterogeneity. When the data allowed, we performed subgroup analyses of the trials.

Results

A total of 572 abstracts and titles were reviewed. Of these, 26 satisfied the eligibility criteria and were included in the meta-analysis.[20-27,30-47] A flowchart is provided in Figure 1. The number of patients included in these studies ranged from 21 to 192. A total of 2430 patients were enrolled in the studies. The details are shown in Table 1. The RCTs were relatively well designed, and the quality assessment score was high for most of them, with a mode of 24, and a range of 17 to 24; some studies received the highest possible score. Only 8 studies had a score less than 20. A funnel plot based on the most frequently cited outcome was broadly symmetrical, indicating minimal publication bias (Fig 2). Twenty of the 26 included studies provided data on adverse events, but only 7 dots are shown in the funnel plot. There are 3 on the left and 4 on the right, with a relatively even distribution.

Adverse Events

In all, 20 trials including 1908 patients provided useful data on adverse events (Fig 3). The number of adverse events in the PRP and HA groups was 109 of 970 participants and 84 of 938 participants, respectively. There was no significant difference in adverse events between the 2 groups (RR 1.21, 95% CI 0.95-1.54; $P = .13$). Eighty-three of 193 cases clearly stated the type of adverse events. Most of the patients (64/83) had mild pain and swelling. There were 8 cases of stiffness and heaviness and 2 cases of pseudoseptic reactions.

WOMAC Total Score

WOMAC total scores were reported by 3, 7, 8, and 7 studies at 1, 3, 6, and 12 months, respectively (Fig 4). The analysis did not identify a significant difference between the PRP and HA groups after 1 month (MD −3.81, 95% CI −7.98 to 0.36; $P = .07$) of

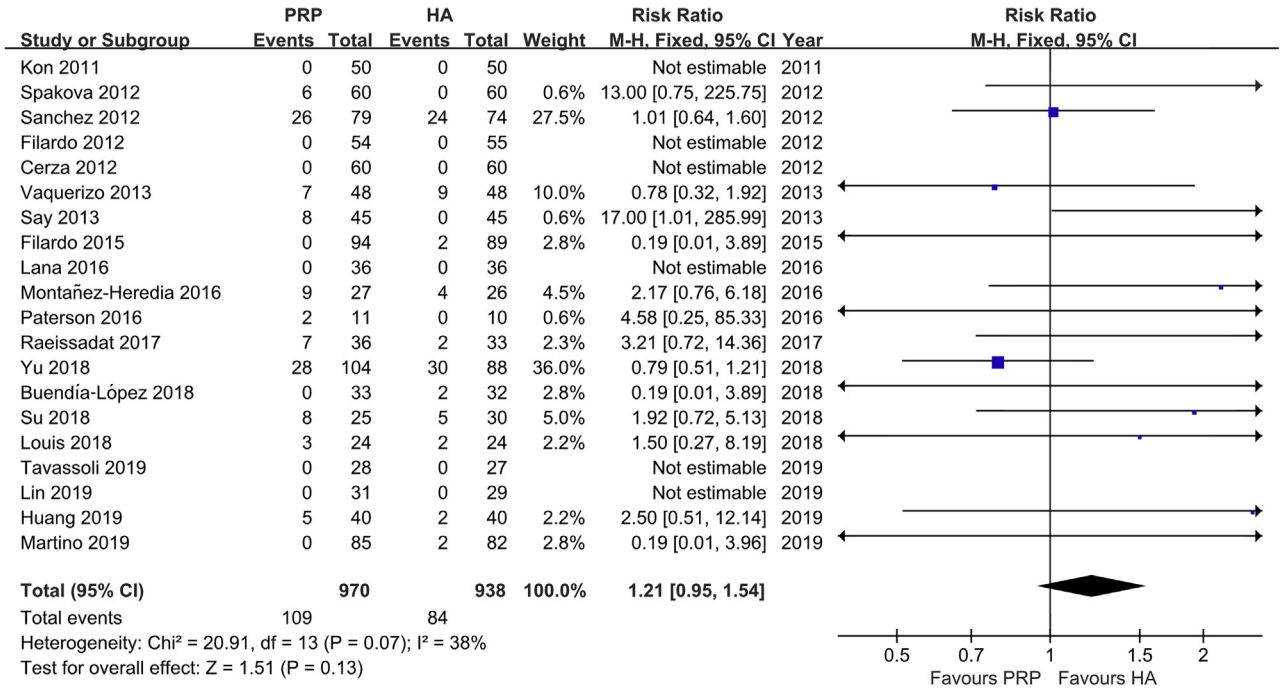

Fig 3. Trials of PRP versus HA: forest plot of adverse events. (CI, confidence interval; HA, hyaluronic acid; M-H, Mantel-Haenszel; PRP, platelet-rich plasma.)

treatment. However, the subjects in the PRP group performed better than those in the HA group at 3 (MD −5.04, 95% CI −8.82 to −1.26; $P = .009$), 6 (MD −8.52, 95% CI −11.17 to −5.87; $P < .00001$), and 12 months (MD −10.52, 95% CI −13.77 to −7.27; $P < .00001$).

WOMAC Pain Score

WOMAC pain scores were reported by 3, 5, 6, and 7 studies at 1, 3, 6, and 12 months, respectively. Table 2 presents all of these details. The outcomes did not reveal a significant difference between the PRP and HA groups at 1 (MD −0.03, 95% CI −0.42 to 0.35; $P = .86$) or 3 months (MD 0.03, 95% CI −0.31 to 0.38; $P = .85$). However, subjects in the PRP group experienced significantly more pain relief than those in the HA group at 6 (MD −1.17, 95% CI −1.99 to −0.35 $P = .005$) and 12 months (MD −1.62, 95% CI −2.26 to −0.98; $P < .00001$).

WOMAC Stiffness Score

There was no significant difference in WOMAC stiffness scores between the 2 groups after 1 (MD −0.13, 95% CI −0.41 to 0.15; $P = .37$) and 3 months (MD −0.26, 95% CI −0.51 to 0.00; $P = .05$) of treatment. However, the PRP group improved more than the HA group at 6 (MD −0.39, 95% CI −0.74 to −0.04; $P = .03$) and 12 months (MD −0.84, 95% CI−1.16 to −0.53; $P < .00001$) (Table 2).

WOMAC Physical Function Score

WOMAC physical function scores were reported in 2 studies and showed that patients treated with PRP and HA had similar functional recovery after 1 month of treatment (MD −2.35, 95% CI −5.28 to 0.57; $P = .12$). However, PRP performed better than HA at 3 (MD −1.90, 95% CI −2.54 to −1.26; $P < .00001$), 6 (MD −3.15, 95% CI −4.95 to −1.35; $P = .0006$), and 12 months (MD −7.32, 95% CI −9.98 to −4.66; $P < .00001$) (Table 2).

VAS and EQ-VAS Scores

VAS scores for pain were reported by 2, 6, 7, and 5 studies at 1, 3, 6, and 12 months. The details are shown in Table 2. The results showed that the PRP group had less pain than the HA group after 3, 6, and 12 months of treatment. EQ-VAS scores were reported at 2, 6, and 12 months. The results showed that the improvement of knee pain was better in the PRP group than in the HA group at 6 and 12 months.

IKDC Score

IKDC scores were reported by 1, 6, 7, and 4 studies at 1, 3, 6, and 12 months, respectively (Table 2). The subjects in the PRP group performed better than those in the HA group at 6 (MD 7.67, 95% CI 3.91-11.43; $P < .0001$) and 12 months (MD 5.70, 95% CI 0.98-10.42; $P = .005$).

Tegner Score

There was no significant difference in Tegner scores between the 2 groups after 2 and 6 months of treatment. However, the PRP group improved more than the HA group at 12 (MD 0.34, 95% CI 0.01 to 0.66; p = 0.04) (Table 2).

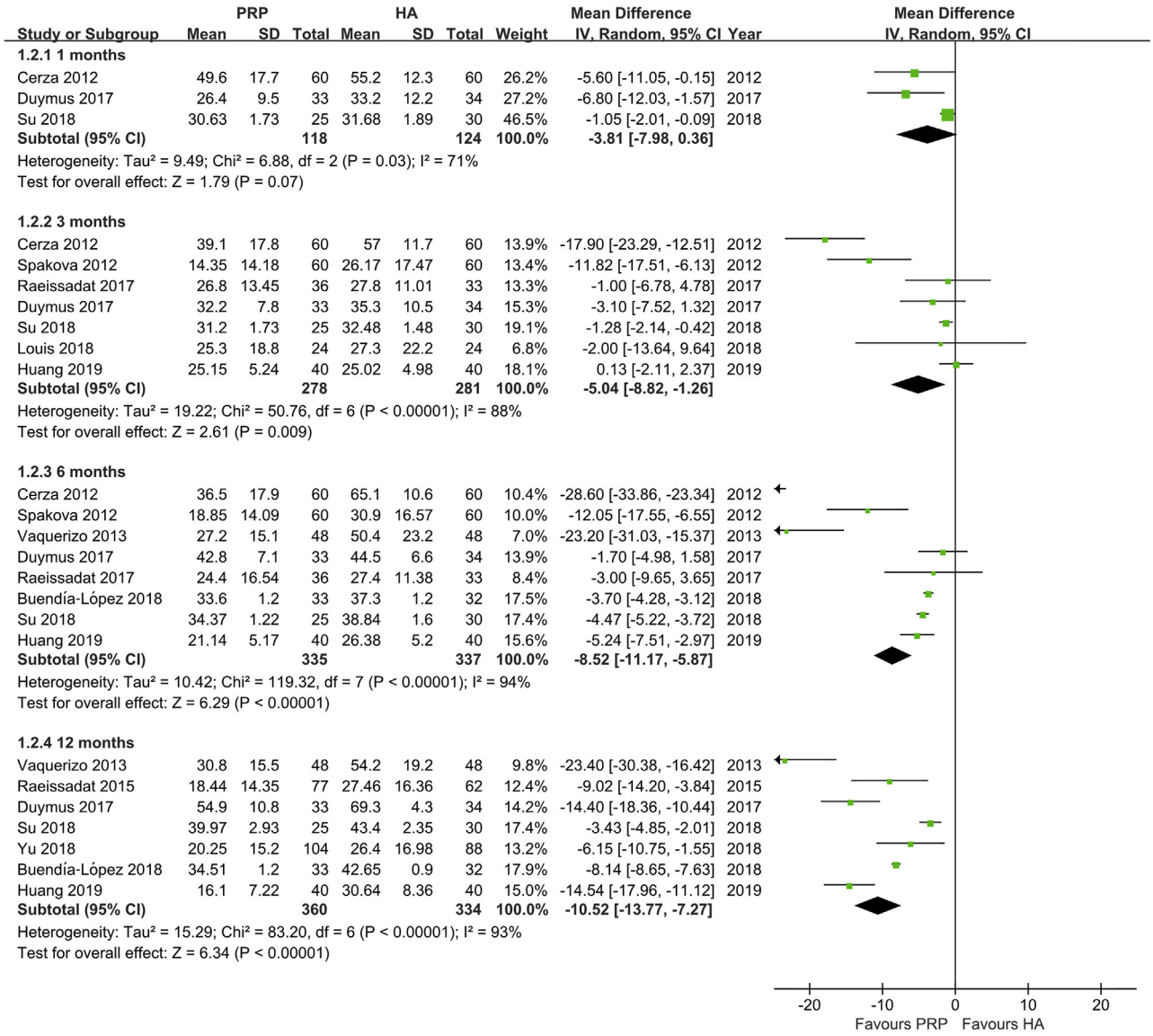

Fig 4. Trials of PRP versus HA: forest plot of WOMAC total score. (CI, confidence interval; HA, hyaluronic acid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

Lequesne Scale and KOOS Score

The Lequesne Scale was reported at 6 months and KOOS scores were reported at 2, 6, and 12 months (Table 2). There were no significant differences in these results between the 2 groups.

Satisfaction Rate

This outcome measure was available in 4 studies (293 patients). There was no significant difference in the satisfaction rate between the 2 groups (RR 1.14, 95% CI 0.99-1.31; $P = .08$) (Fig 5).

Discussion

This meta-analysis showed that the WOMAC total, WOMAC physical function, and VAS scores of the PRP group were better than those of the HA group at 3, 6, and 12 months. The PRP group performed better than the HA group in terms of WOMAC pain, WOMAC stiffness, EQ-VAS, and IKDC scores at 6 and 12 months. The PRP group had more mild joint pain and swelling after using PRP, but there was no significant difference in adverse events between the 2 groups ($P = .13$). The reason why the results of the Lequesne Scale, KOOS scores, and satisfaction rate were not statistically significant was perhaps due to the smaller number of included studies that evaluated these outcomes. Therefore, we believed that compared with the use of HA in patients with KOA, PRP could produce better clinical efficacy in the early and middle stages, and the safety was comparable. In addition, although we performed subgroup analyses of the different doses (<5 mL and ≥5 mL), types (fresh and frozen) and times (1 time and 2 times or

Table 2. Summary of Other Analysis Results of PRP Versus HA

Other Analysis	Studies	Patients	Mean Difference [95% CI]	Heterogeneity	Other Analysis	Studies	Patients	Mean Difference [95% CI]	Heterogeneity
WOMAC Pain 1 mo	3	107/114	−0.03 [−0.42, 0.35]; $P = .86$	$I^2 = 16\%$; $P = .30$	IKDC 6 mo	7	362/356	7.67 [3.91-11.43]; $P < .0001$	$I^2 = 61\%$; $P = .02$
WOMAC Pain 3 mo	5	167/171	0.03 [−0.31, 0.38]; $P = .85$	$I^2 = 0\%$; $P = .76$	IKDC 12 mo	4	228/223	5.70 [0.98-10.42]; $P = .005$	$I^2 = 41\%$; $P = .16$
WOMAC Pain 6 mo	6	224/227	−1.17 [−1.99, −0.35]; $P = .005$	$I^2 = 85\%$; $P = .00001$	Tegner 2 mo	2	179/171	0.30 [−0.01, 0.61]; $P = .06$	$I^2 = 0\%$; $P = 1.00$
WOMAC Pain 12 mo	7	369/344	−1.62 [−2.26, −0.98]; $P < .00001$	$I^2 = 84\%$; $P = .00001$	Tegner 6 mo	1	94/89	0.20 [−0.23, 0.63]; $P = .37$	Not applicable
WOMAC Stiffness 1 mo	2	58/64	−0.13 [−0.41, 0.15]; $P = .37$	$I^2 = 35\%$; $P = .21$	Tegner 12 mo	2	148/144	0.34 [0.01-0.66]; $P = .04$	$I^2 = 0\%$; $P = .77$
WOMAC Stiffness 3 mo	4	118/121	−0.26 [−0.51, 0.00]; $P = .05$	$I^2 = 44\%$; $P = .15$	Lequesne 6 mo	2	127/122	−0.20 [−1.03, 0.63]; $P = .64$	$I^2 = 0\%$; $P = .00$
WOMAC Stiffness 6 mo	5	175/177	−0.39 [−0.74, −0.04]; $P = .03$	$I^2 = 68\%$; $P = .01$	KOOS Pain 2 mo	3	159/154	−0.20 [−4.31, 3.91]; $P = .92$	$I^2 = 49\%$; $P = .14$
WOMAC Stiffness 12 mo	6	320/294	−0.84 [−1.16, −0.53]; $P < .00001$	$I^2 = 75\%$; $P = .001$	KOOS Pain 6 mo	2	148/144	0.30 [−3.97, 4.57]; $P = .89$	$I^2 = 0\%$; $P = .81$
WOMAC Physical function 1 mo	2	58/64	−2.35 [−5.28, 0.57]; $P = .12$	$I^2 = 59\%$; $P = .12$	KOOS Pain 12 mo	2	148/144	−0.32 [−4.73, 4.10]; $P = .89$	$I^2 = 0\%$; $P = .91$
WOMAC Physical function 3 mo	4	118/121	−1.90 [−2.54, −1.26]; $P < .00001$	$I^2 = 0\%$; $P = .90$	KOOS Symptoms 2 mo	3	159/154	−4.02 [−13.55, 5.51]; $P = .41$	$I^2 = 80\%$; $P = .007$
WOMAC Physical function 6 mo	5	175/177	−3.15 [−4.95, −1.35]; $P = .0006$	$I^2 = 88\%$; $P < .00001$	KOOS Symptoms 6 mo	2	148/144	0.77 [−3.17, 4.71]; $P = .70$	$I^2 = 0\%$; $P = .43$
WOMAC Physical function 12 mo	6	320/294	−7.32 [-9.98, −4.66]; $P < .00001$	$I^2 = 91\%$; $P < .00001$	KOOS Symptoms 12 mo	2	148/144	−1.09 [−5.17, 2.99]; $P = .60$	$I^2 = 0\%$; $P = .50$
VAS 1 mo	2	58/64	0.01 [−0.13, 0.15]; $P = .89$	$I^2 = 0\%$; $P = .63$	KOOS Daily activity 2 mo	3	159/154	−1.26 [−8.16, 5.64]; $P = .72$	$I^2 = 63\%$; $P = .06$
VAS 3 mo	6	208/210	−0.54 [−1.03, −0.05]; $P = .03$	$I^2 = 81\%$; $P < .00001$	KOOS Daily activity 6 mo	2	148/144	1.12 [−3.24, 5.47]; $P = .61$	$I^2 = 0\%$; $P = .81$
VAS 6 mo	7	266/268	−0.77 [−1.24, −0.29]; $P = .002$	$I^2 = 84\%$; $P < .00001$	KOOS Daily activity 12 mo	2	148/144	0.22 [−4.38, 4.83]; $P = .93$	$I^2 = 0\%$; $P = .90$
VAS 12 mo	5	180/186	−0.99 [−1.54, −0.45]; $P = .0003$	$I^2 = 84\%$; $P < .00001$	KOOS Sport 2 mo	3	159/154	−0.71 [−11.54, 10.12]; $P = .90$	$I^2 = 64\%$; $P = .06$
EQ-VAS 2 mo	3	229/221	4.32 [−0.09, 8.73]; $P = .05$	$I^2 = 67\%$; $P = .05$	KOOS Sport 6 mo	2	148/144	4.32 [−2.13, 10.77]; $P = .19$	$I^2 = 0\%$; $P = .94$
EQ-VAS 6 mo	4	268/260	6.22 [1.72-10.72]; $P = .007$	$I^2 = 74\%$; $P = .009$	KOOS Sport 12 mo	2	148/144	2.17 [−4.31, 8.65]; $P = .51$	$I^2 = 0\%$; $P = .75$
EQ-VAS 12 mo	2	179/171	4.64 [1.86-7.42]; $P = .001$	$I^2 = 0\%$; $P = .75$	KOOS Quality of life 2 mo	3	159/154	0.06 [−4.97, 5.09]; $P = .98$	$I^2 = 44\%$; $P = .17$
IKDC 1 mo	1	31/29	0.04 [−7.70, 7.78]; $P = .99$	Not applicable	KOOS Quality of life 6 mo	2	148/144	−0.63 [−6.02, 4.76]; $P = .82$	$I^2 = 0\%$; $P = .97$
IKDC 3 mo	6	359/349	3.27 [−0.21, 6.75]; $P = .07$	$I^2 = 54\%$; $P = .06$	KOOS Quality of life 12 mo	2	148/144	0.42 [−5.15, 5.99]; $P = .88$	$I^2 = 0\%$; $P = .81$

EQ-VAS, EuroQol visual analog scale; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; PRP, platelet- rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

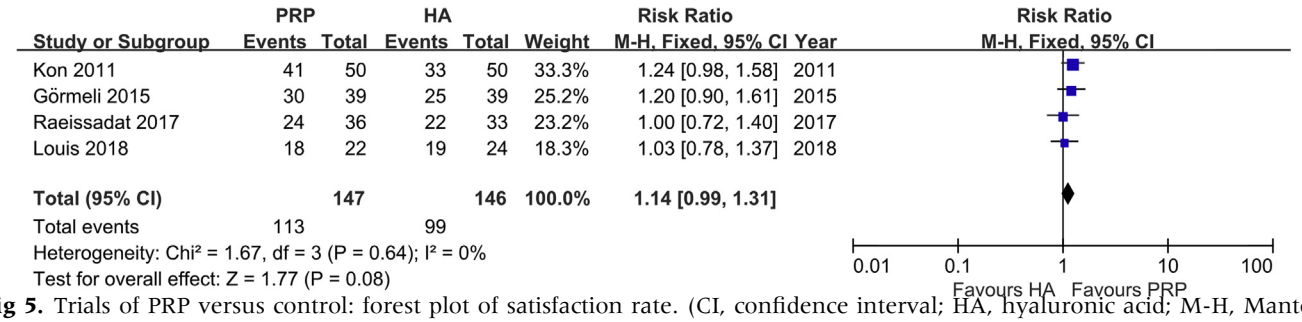

Fig 5. Trials of PRP versus control: forest plot of satisfaction rate. (CI, confidence interval; HA, hyaluronic acid; M-H, Mantel-Haenszel; PRP, platelet-rich plasma.)

more) of PRP interventions and the grade of OA, no meaningful results were found.

Previously, 4 meta-analyses compared the use of PRP and HA in the treatment of KOA: Han et al. (15 RCTs),[16] Zhang et al. (13 RCTs),[17] Shen et al. (14 RCTs),[18] and Dai et al. (10 RCTs).[19] The meta-analysis study by Han et al.[16] showed that the WOMAC total scores of the PRP group were better at 6 and 12 months, and the VAS scores were better at 12 months. However, our analysis showed that the WOMAC total and VAS scores of the PRP group were better than those of the HA group at 3, 6, and 12 months. Zhang et al.[17] found that no significant differences were found between the 2 groups in WOMAC stiffness, VAS, or EQ-VAS scores. This meta-analysis found that the WOMAC stiffness and EQ-VAS scores in the PRP group were better than those in the HA group at 6 and 12 months. Han et al.'s and Zhang et al.'s IKDC scores were better in the PRP group at 6 months, and there was no significant difference between the 2 groups at 12 months. Our IKDC scores showed that patients recovered better in the PRP group at 6 and 12 months. Dai et al. found that the results of the WOMAC total, WOMAC pain, and WOMAC physical function scores of the PRP group were better than those of the HA group only at 12 months.[19] These findings were inconsistent with our results. The reason might be that they had included fewer studies. Our meta-analysis included a total of 26 RCTs. The meta-analysis by Shen et al.[18] found that the WOMAC total, WOMAC pain, and WOMAC physical function scores of the PRP group were better those for the HA group from 3 to 12 months. After reading the full text, we found that of the 14 studies included by Shen et al., 12 compared PRP with HA, and the other 2 compared PRP with saline. The inclusion of studies with different control groups might have affected the results of the analysis. Three of the 4 previous meta-analyses analyzed adverse events, and the result was consistent with ours. No significant differences in adverse events were found between the 2 groups (Han: RR 1.20, 95% CI 0.91-1.58, $P = .20$; Shen: RR 1.40, 95% CI 0.80-2.45, $P = .24$; and Dai: RR 0.63, 95% CI 0.20-1.98, $P = 0.43$). Nonetheless, we found a trend for more adverse events in the PRP group, although most were mild joint pain and swelling.

This meta-analysis not only statistically showed the PRP group was better than HA group but also proved the clinically significant differences in both the WOMAC total and IKDC scores between the 2 groups. Angst et al.[48] found that the minimal clinically important difference (MCID) in the WOMAC total measure was 6% of the maximal value. Greco et al.[49] indicated that the MCID in the IKDC score was an absolute change of 6.3 at 6 months. Our results of WOMAC total scores showed that the PRP group clearly surpassed the MCID (difference of 6 points) compared with the HA group at 6 (MD −8.52) and 12 (MD −10.52) months. In addition, the IKDC score of the PRP group showed clinically significant ascendancy compared with the HA group, with a change of 7.67 at 6 months.

In the past few years, an increasing number of researchers have noticed the potential of PRP in the treatment of various musculoskeletal diseases, such as rotator cuff tears, lateral epicondylitis, patellar tendinopathy, OA, and Achilles tendon repair.[50-54] However, in the current clinical guidelines of orthopaedic surgeons, the use of PRP injection for KOA patients is uncertain.[55,56] The use of PRP in the treatment of degenerative KOA has increased in recent years, given its apparent high margin of safety and ease of production and administration.[57] Contrasting scientific evidence exists regarding PRP injections for KOA, with the efficacy of PRP injections widely reported.[58] Enhanced effectiveness of PRP for pain treatment and knee joint function compared to HA and positive outcomes in all stages of knee OA (early, middle and late), have all been reported.[14,19] These results could have been due to the immediate and sustained release of growth factors over a prolonged period, which enhanced healing and resulted in sustained clinical effects.[59] PRP has been shown to have both anti-inflammatory effects through both growth factors such as transforming growth factor-β and insulin-like growth factor 1, and the stimulatory effects on mesenchymal stem cells and fibroblasts.[60] Unfortunately, there are many variations in PRP preparation, and a lack of standardization in preparation-related factors, such as speed and duration of centrifugation, leads to wide ranges of platelet and leukocyte

concentrations. Unifying the most effective PRP preparation process might be the direction of future research.

In this meta-analysis, only RCTs were eligible, and only data from one experimental group that used of PRP and a control group that received HA were extracted from a multigroup comparison study. Significant heterogeneity among the included studies was demonstrated when the WOMAC total, WOMAC pain, WOMAC stiffness, WOMAC physical function, VAS, EQ-VAS and IKDC scores were evaluated. Although we conducted subgroup analyses and sensitivity analysis on these results with significant heterogeneity, no significant differences were found. This phenomenon could not be well explained by the differences in the treatment protocols, enrolled patients, interventions, or OA grades in each study, and could not be simply considered to be caused by 1 or 2 studies. Rather, the authors of this study believed that the sample size differences, patient characteristics variations, inclusion and exclusion criteria diversity, differences between treating centers in terms of management protocols and logistics, and different strategies for measuring outcomes may be responsible for such heterogeneity. For these results with significant heterogeneity, we chose the random effects approach in this meta-analysis. Even so, the reliability would still be affected.

Limitations

Limitations of this meta-analysis include the small sample size and short follow-up time of each study and the significant heterogeneity in the WOMAC total, WOMAC pain, WOMAC stiffness, WOMAC physical function, VAS, EQ-VAS, and IKDC scores. In addition, no sufficient data were available to analyze the American Knee Society Score, reintervention rate, C-reactive protein, Short Form-36, Numeric rating scale, Knee Quality of Life, or EuroQOL scores.

Conclusions

For the nonsurgical treatment of KOA, compared with HA, intra-articular injection of PRP could significantly reduce patients' early pain and improve function. There was no significant difference in adverse events between the 2 groups. PRP was more effective than HA in the treatment of KOA, and the safety of these 2 treatment options was comparable.

Acknowledgment

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References

1. Migliore A, Giovannangeli F, Granata M, Laganà B. Hylan g-f 20: Review of its safety and efficacy in the management of joint pain in osteoarthritis. *Clin Med Insights Arthritis Musculoskelet Disord* 2010;3:55-68.
2. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1145-1153.
3. Wood AM, Brock TM, Heil K, Holmes R, Weusten A. A review on the management of hip and knee osteoarthritis. *Int J Chronic Dis* 2013;845015:10.
4. Curl WW, Krome J, Gordon ES, Rushing J. Cartilage injuries: A review of 31,516 knee arthroscopies. *Arthroscopy* 1997;13:456-460.
5. Strand V, McIntyre LF, Beach WR, Miller LE, Block JE. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: A systematic review and meta-analysis of randomized, saline-controlled trials. *J Pain Res* 2015;8:217-228.
6. Riecke BF, Christensen R, Christensen P, et al. Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: A pragmatic randomized clinical trial. *Osteoarthritis Cartilage* 2010;18:746-754.
7. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. *Semin Arthritis Rheum* 2014;43:701-712.
8. McAlindon TE, Bannuru RR, Sullivan MC, et al. Response to Letter to the Editor entitled "Comments on 'OARSI guidelines for the non-surgical management of knee osteoarthritis'." *Osteoarthritis Cartilage* 2014;22:890-891.
9. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis* 2010;69:113-119.
10. Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* 2006;14:154-162.
11. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol* 2006;33:951-956.
12. Piuzzi NS, Ng M, Kantor A, et al. What is the price and claimed efficacy of platelet-rich plasma injections for the treatment of knee osteoarthritis in the United States? *J Knee Surg* 2019;32:879-885.
13. Kavadar G, Demircioglu DT, Celik MY, Emre TY. Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: A randomized prospective study. *J Phys Ther Sci* 2015;27:3863-3867.
14. Kanchanatawan W, Arirachakaran A, Chaijenkij K, et al. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc* 2016;24:1665-1677.
15. Joshi Jubert N, Rodríguez L, Reverté-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis a prospective, randomized, double-blinded clinical trial. *Orthop J Sports Med* 2017;5:2325967116689386.
16. Han Y, Huang H, Pan J, et al. Meta-analysis comparing platelet-rich plasma vs hyaluronic acid injection in

patients with knee osteoarthritis. *Pain Med* 2019;20:1418-1429.
17. Zhang HF, Wang CG, Li H, Huang YT, Li ZJ. Intra-articular platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: A meta-analysis. *Drug Des Devel Ther* 2018;12:445-453.
18. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: Systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res* 2017;12:16.
19. Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: A meta-analysis of randomized controlled trials. *Arthroscopy* 2017;33:659-670.
20. Tavassoli M, Janmohammadi N, Hosseini A, Khafri S, Esmaeilnejad-Ganji SM. Single- and double-dose of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: A randomized controlled trial. *World J Orthop* 2019;10:310-326.
21. Di Martino A, Di Matteo B, Papio T, et al. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: Results at 5 years of a double-blind, randomized controlled trial. *Am J Sports Med* 2019;47:347-354.
22. Huang Y, Liu X, Xu X, Liu J. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis: A prospective randomized controlled study. *Orthopade* 2019;48:239-247.
23. Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular injection of platelet-rich plasma is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: A randomized, double-blind, triple-parallel, placebo-controlled clinical trial. *Arthroscopy* 2019;35:106-117.
24. Lisi C, Perotti C, Scudeller L, et al. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. *Clin Rehabil* 2018;32:330-339.
25. Yu W, Xu P, Huang G, Liu L. Clinical therapy of hyaluronic acid combined with platelet-rich plasma for the treatment of knee osteoarthritis. *Exp Ther Med* 2018;16:2119-2125.
26. Ahmad HS, Farrag SE, Okasha AE, et al. Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. *Int J Rheum Dis* 2018;21:960-966.
27. Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín MÁ. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: A randomized controlled trial. *J Orthop Traumatol* 2018;19:3.
28. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions. Version 4.2.5*. West Sussex: John Wiley & Sons, 2008.
29. Handoll H, Elstub L, Elliott J, et al. Cochrane Bone, Joint and Muscle Trauma Group. About the Cochrane collaboration (Cochrane Review Groups (CRGS)) 2008;Issue 4. Art. No: MUSKINJ.
30. Louis ML, Magalon J, Jouve E, et al. Growth factors levels determine efficacy of platelets rich plasma injection in knee osteoarthritis: A randomized double blind non-inferiority trial compared with viscosupplementation. *Arthroscopy* 2018;34:1530-1540.
31. Su K, Bai Y, Wang J, Zhang H, Liu H, Ma S. Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis. *Clin Rheumatol* 2018;37:1341-1350.
32. Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN. Choice of intra-articular injection in treatment of knee osteoarthritis: Platelet-rich plasma, hyaluronic acid or ozone options. *Knee Surg Sports Traumatol Arthrosc* 2017;25:485-492.
33. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: A prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. *Am J Sports Med* 2017;45:339-346.
34. Raeissadat SA, Rayegani SM, Ahangar AG, Abadi PH, Mojgani P, Ahangar OG. Efficacy of intra-articular injection of a newly developed plasma rich in growth factor (PRGF) versus hyaluronic acid on pain and function of patients with knee osteoarthritis: A single-blinded randomized clinical trial. *Clin Med Insights Arthritis Musculoskelet Disord* 2017;10:1179544117733452.
35. Montañez-Heredia E, Irízar S, Huertas PJ, et al. Intra-articular injections of platelet-rich plasma versus hyaluronic acid in the treatment of osteoarthritic knee pain: A randomized clinical trial in the Context of the Spanish National Health Care System. *Int J Mol Sci* 2016;17:E1064.
36. Paterson KL, Nicholls M, Bennell KL, Bates D. Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: A double-blind, randomized controlled pilot study. *BMC Musculoskelet Disord* 2016;17:67.
37. Lana JF, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med* 2016;12:69-78.
38. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord* 2015;8:1-8.
39. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: A randomized controlled trial. *Am J Sports Med* 2015;43:1575-1582.
40. Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2017;25:958-965.
41. Vaquerizo V, Plasencia MÁ, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the

treatment of patients with symptomatic osteoarthritis: A randomized controlled trial. *Arthroscopy* 2013;29:1635-1643.
42. Say F, Gürler D, Yener K, Bülbül M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Cech* 2013;80:278-283.
43. Cerza F, Carnì S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 2012;40:2822-2827.
44. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070-1078.
45. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord* 2012;13:229.
46. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil* 2012;91:411-417.
47. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. *Arthroscopy* 2011;27:1490-1501.
48. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimally clinically important difference of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. *Arthritis Rheum* 2001;45:384-391.
49. Greco NJ, Anderson AF, Mann BJ, et al. Responsiveness of the International Knee Documentation Committee Subjective Knee Form in comparison to the Western Ontario and McMaster Universities Osteoarthritis Index, modified Cincinnati Knee Rating System, and Short Form 116 K-Y. LIN ET AL. 36 in patients with focal articular cartilage defects. *Am J Sports Med* 2010;38:891-902.
50. Andriolo L, Altamura SA, Reale D, Candrian C, Zaffagnini S, Filardo G. Nonsurgical treatments of patellar tendinopathy: Multiple injections of platelet-rich plasma are a suitable option: a systematic review and meta-analysis. *Am J Sports Med* 2019;47:1001-1018.
51. Di Sante L, Villani C, Santilli V, et al. Intra-articular hyaluronic acid vs platelet-rich plasma in the treatment of hip osteoarthritis. *Med Ultrason* 2016;18:463-468.
52. Vannabouathong C, Del FG, Sales B, et al. Intra-articular injections in the treatment of symptoms from ankle arthritis: A systematic review. *Foot Ankle Int* 2018;39:1141-1150.
53. Le ADK, Enweze L, DeBaun MR, Dragoo JL. Current clinical recommendations for use of platelet-rich plasma. *Curr Rev Musculoskelet Med* 2018;11:624-634.
54. Dallari D, Stagni C, Rani N, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis: a randomized controlled study. *Am J Sports Med* 2016;44:664-671.
55. Jevsevar DS, Brown GA, Jones DL, et al. The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. *J Bone Joint Surg Am* 2013;95:1885-1886.
56. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartilage* 2014;22:363-388.
57. Smith PA. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis. *Am J Sports Med* 2016;44:884-891.
58. Rahimzadeh P, Imani F, Faiz SH, Entezary SR, Zamanabadi MN, Alebouyeh MR. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. *Clin Interv Aging* 2018;13:73-79.
59. Dhillon MS, Patel S, John R. PRP in OA knee-update, current confusions and future options. *Sicot-J* 2017;3:27.
60. Southworth TM, Naveen NB, Tauro TM, Leong NL, Cole BJ. The use of platelet-rich plasma in symptomatic knee osteoarthritis. *J Knee Surg* 2019;32:37-45.