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Meta-analysis Comparing Platelet-Rich Plasma vs Hyaluronic Acid Injection in Patients with Knee Osteoarthritis

Yanhong Han, MD,*[,a] Hetao Huang, PhD,*[,a] Jianke Pan, PhD,[†,a] Jiongtong Lin, MD,* Lingfeng Zeng, PhD,[†,‡] Guihong Liang, MD,[†,‡] Weiyi Yang, PhD,[†] and Jun Liu, PhD[†,‡]

*The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China; [†]Department of Orthopedics, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [‡]Bone and Joint Research Team of Degeneration and Injury, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, China

[a]Equal contribution

Correspondence to: Jun Liu, PhD, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 111 Dade Road, Guangzhou, China. Tel: 13149092114; fax: 020-81867705; E-mail: liujun3040@126.com.

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Conflicts of interest: We declare that we have no conflicts of interest.

Abstract

Purpose. The purpose of this meta-analysis was to compare platelet-rich plasma (PRP) and hyaluronic acid (HA) in patients with knee osteoarthritis (KOA). **Methods**. Randomized controlled trials (RCTs) comparing the use of PRP and HA in KOA patients were retrieved from each database from the establishment date to April 2018. Outcome measurements were the Western Ontario and McMaster Universities Arthritis Index (WOMAC), visual analog scale (VAS), International Knee Documentation Committee, and Lequesne Index scores and adverse events. The pooled data were evaluated with Review Manager 5.3.5. **Results**. Fifteen RCTs (N = 1,314) were included in our meta-analysis. The present meta-analysis indicated that PRP injections reduced pain more effectively than HA injections in patients with KOA at six and 12 months of follow-up, as evaluated by the WOMAC pain score; the VAS pain score showed a significant difference at 12 months. Moreover, better functional improvement was observed in the PRP group, as demonstrated by the WOMAC function score at three, six, and 12 months. Additionally, PRP injections did not display different adverse event rates compared with HA injections. **Conclusion**. In terms of long-term pain relief and functional improvement, PRP injections might be more effective than HA injections as a treatment for KOA. The optimal dosage, the timing interval and frequency of injections, and the ideal treatment for different stages of KOA remain areas of concern for future investigations.

Key Words: Platelet-Rich Plasma; Osteoarthritis; Knee; Hyaluronic Acid; Randomized Controlled Trials; Randomized Control Trials; Meta-analysis

Introduction

Knee osteoarthritis (KOA) is a progressive joint disease that often involves intra- and periarticular structures [1] and is considered pathology characterized by articular cartilage lesions, synovitis, subchondral sclerosis, and osteophytes [2]. In addition, KOA is one of the most common causes of joint pain and loss of motor function among middle-aged and elderly people in the United States [3,4]. Despite advances in medical technology, no drug or surgical intervention is currently

available for delaying the development of KOA [5]. Oral anti-inflammatory drugs, physiotherapy, topical anti-inflammatory gels, and intra-articular injections are currently routine treatments for patients with symptomatic KOA [5,6]. Nonsurgical treatments, such as exercise and weight loss, are recommended because surgical treatment may lead to increased symptoms and poor functional outcomes [7]. However, compliance with nonsurgical treatment is lower in KOA, and medications, such as simple analgesics and nonsteroidal anti-inflammatory drugs, are often associated with adverse events [8,9]. Many studies have reported that hyaluronic acid (HA) has visco-induction properties and can increase intra-articular lubrication; therefore, intra-articular HA injection is widely used to treat KOA [10]. However, although intra-articular drug therapy is often associated with reduced pain and increased joint function in patients, it is not effective in patients with KOA [11].

In the past decade, the use of autologous growth factors to treat knee osteoarthritis, such as intra-articular injection of platelet-rich plasma (PRP), has received increasing attention [12]. Recent studies have demonstrated that growth factors and other cytokines released by platelets during injury can modulate the inflammatory process and help maintain or regenerate tissue structure [13,14]. The subchondral bone contributes to the cartilage repair process and KOA. PRP is an autologous blood product containing a high concentration of platelets, and it has become an emerging treatment for ligament, tendon, cartilage, and bone injuries in orthopedics and sports medicine [15–18]. The intra-articular injection of PRP as a minimally invasive treatment has been widely used in the treatment of clinically related diseases. Sanchez et al. [19] reported that a new technique for the delivery of PRP is intraosseous infiltration combined with intra-articular injections to treat severe KOA; moreover, no adverse reactions occurred in their study. Many clinical studies have reported good clinical efficacy of PRP injections [20–22], and some previously published systematic reviews and meta-analyses have also suggested that PRP is a safe and effective orthopedic treatment compared with other intra-articular injections [23–27]. However, these reviews did not reach a consensus in terms of the effects of PRP on pain relief and functional recovery and concluded that more high-quality randomized controlled trials (RCTs) are still needed. Previous reviews either included non-RCTs or only analyzed a small number of RCTs (<10), and additional randomized trials have since been published. Therefore, further systematic reviews and meta-analyses are needed to fully investigate the effects of PRP on knee pain relief and functional improvement. Our aim is to identify all prospective RCTs published to date to provide up-to-date insights into the efficacy of PRP in the treatment of KOA.

Methods

According to the PRISMA criteria, we created a prospective protocol including search strategies, selection criteria, outcome measurements, and methods of statistical analysis before commencing the study. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine. This review is registered in PROSPERO: CRD42018108825.

Search Strategy

A comprehensive search of the PubMed (1966–April 2018), EMBASE (1980–April 2018), and Cochrane library (1966–April 2018) databases was conducted. The search terms included "platelet-rich plasma," "PRP," "knee," "osteoarthritis," "arthritis," and "arthritic." No language exclusions were applied. Manual searches were performed on the references of the identified studies.

Selection Criteria

The inclusion criteria were as follows: 1) RCTs comparing PRP with HA as a treatment for patients with KOA and 2) data that include at least one key outcome indicator, including the Western Ontario and McMaster Universities Arthritis Index (WOMAC), International Knee Documentation Committee (IDKC), visual analog scale (VAS), Lequesne Index, or adverse events.

The exclusion criteria were as follows: 1) retrospective studies, cohort studies, or nonrandomized studies; 2) case reports, letters, editorials, and animal experimental studies; and 3) inability to extract relevant data from the included studies.

Data Extraction

Two authors (YHH and HTH) independently extracted relevant data from the included studies, including authors' names, publication date, patient age and gender, patient body mass index (BMI), sample size, radiographic classification, follow-up period, details of PRP treatment protocols and controls, and related clinical results. In the event that data were missing, we obtained detailed information by contacting the appropriate author.

Quality Assessment

Two authors (YHH and JKP) independently assessed the methodological quality of the included studies using the Cochrane Collaboration Tool for assessing the risk of bias (ROB). Each included study was scored as having a high, low, or unclear ROB according to the following evaluation criteria: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessments, 5) incomplete outcome data, 6) selective reporting, and 7) other sources of bias. Any discrepancies between the reviewers' findings were arbitrated by the appropriate senior experts.

Statistical Analysis

Review Manager 5.3.5 software (Cochrane Collaboration, Oxford, UK) was used for all analyses. Continuous data for the meta-analysis were calculated and are expressed as the mean differences (MDs) with 95% confidence intervals (CIs), and dichotomous data for the meta-analysis are presented as risk ratios (RRs) with 95% CIs. Heterogeneity between studies was estimated with the I^2 test. If the heterogeneity was at an I^2 value of 75% or higher, a random-effects model was used; otherwise, a fixed-effects model was used. P values <0.05 were considered to indicate statistical significance in all the results.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Results

Search Results

Figure 1 shows the flow diagram of study selection. A total of 586 records were identified after the initial literature search. Of these, 296 records were excluded after a thorough screen of the titles and abstracts. Ultimately, the remaining 51 studies were assessed by performing a full-text review, and 15 RCTs [2,21,22,28–39] were included in the meta-analysis.

Study Characteristics

Table 1 shows the characteristics of the included studies. The sample sizes of the studies ranged from 10 to 94, with a total of 1314 individuals; 643 individuals were included in the HA group and 671 individuals in the PRP group. One of the studies [28] had a total follow-up period of three months, seven studies [29,30,34,35,37–39] had follow-up periods of six months, six studies [21,22,31–33,36] had follow-up periods of 12 months, and only one study [2] had a follow-up period of 18 months. With the exception of one study [37], all studies used the Kellgren and Lawrence grading scales to classify the severity of KOA. The patients in most studies had KOA with a severity of class II or III. The demographic characteristics between the two groups in each of the included studies were similar.

The preparation and administration of PRP varied among these studies. Table 2 shows the details of PRP preparation and administration protocols specific to each included study, such as the PRP category, the use of exogenous activators, and the injection regimen, including the doses, times, and intervals.

Assessment of the ROB

The summary of the ROB assessment of all included studies is illustrated in Figure 2. Adequate randomized sequences were generated in 13 studies [2,19,22,28,31–39]. However, two studies [29,30] referred to random assignments but did not report the details of these random assignments. Appropriate allocation concealment was reported in eight studies [21,22,28,31,33,34,37,39], the blinding of participants and personnel was clear in nine studies [21,22,28,31,33,34,37–39], and the blinding of outcome assessors was reported in eight studies [21,22,33–35,37–39]. Incomplete outcome data were not observed in all included studies. In addition, no selective reporting or other obvious sources of bias were identified in these studies.

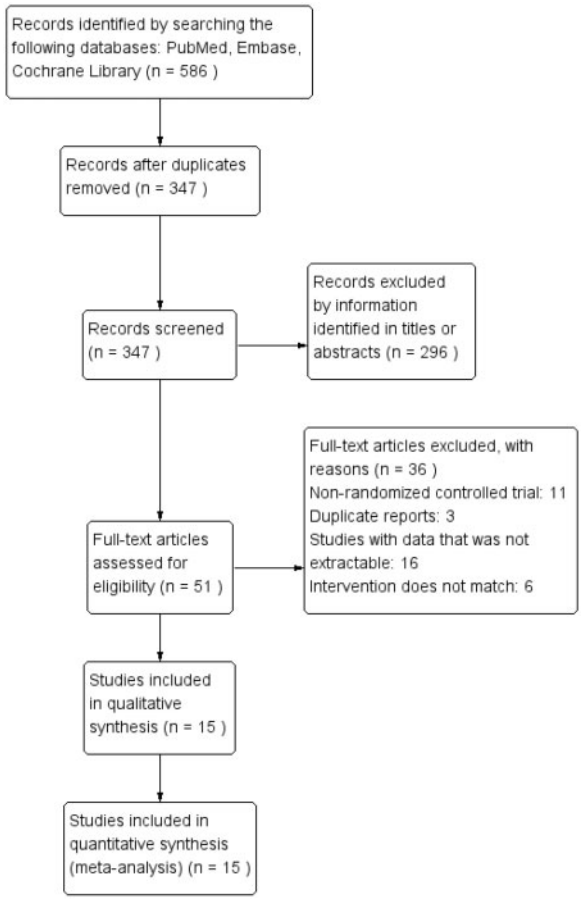

Figure 1. Flow diagram of study selection.

Outcomes of the Meta-analysis

WOMAC Pain Score

WOMAC pain scores were reported by three [2,31,32], four [2,31,32,39], six [2,21,31,32,37,38], and five studies [2,21,31,32,36] at one, three, six, and 12 months, respectively. The pooled analysis did not reveal significant differences between the PRP and HA groups at one (MD $= -0.19$, 95% CI $= -0.65$ to 0.27, $I^2 = 67\%$, $P = 0.42$) and three months (MD $= -0.31$, 95% CI $= -1.16$ to 0.54, $I^2 = 88\%$, $P = 0.47$). However, subjects in the PRP group experienced significantly more pain relief than those in the HA group at six (MD $= -1.24$, 95% CI $=$ –1.94 to -0.53, $I^2 = 83\%$, $P = 0.0006$) and 12 months

Table 1. Characteristics of the included studies

Author	Date	Sample Size		Gender (F/M)		Age, y		BMI, kg/m^2		Radiographic Classification (K-L)		Follow-up Periods, mo	Clinical Outcomes
		PRP	HA	PRP	HA	PRP	HA	PRP	HA	PRP	HA		
Paterson et al. [28]	2016	11	10	8/3	7/3	49.9±13.7	52.7±10.3	27.9±11.9	30.8±5.6	II, III	II, III	3	VAS, Adverse events
Li et al. [29]	2011	15	15	6/9	7/8	36∼76	39∼76	19.4∼29.5	17.6∼28.9	I, II, III, IV	I, II, III, IV	6	WOMAC, IDKC, Lequesne Index, Adverse events
Cerza et al. [30]	2012	60	60	25/35	28/32	66.5±11.3	66.2±10.6	NA	NA	I, II, III	I, II, III	6	WOMAC, Adverse events
Cole et al. [31]	2017	49	50	28/21	20/30	55.9±10.4	56.8±10.5	27.4±3.9	29.0±6.4	I, II, III	I, II, III	12	VAS, WOMAC, IDKC
Duymus et al. [32]	2016	33	34	32/1	33/1	60.4±5.1	60.3±9.1	27.6±4.6	28.4±3.6	II, III	II, III	12	VAS, WOMAC
Filardo et al. [33]	2015	94	89	34/60	37/52	53.3±13.2	57.6±11.8	26.6±4.0	26.9±4.4	I, II, III	I, II, III	12	IDKC
Gormeli et al. [34]	2015	39	39	23/16	22/17	57.3±13.1	53.5±14	28.7±4.8	29.7±3.7	I, II, III, IV	I, II, III, IV	6	IDKC
Montanez-Heredia et al. [35]	2016	27	26	15/12	17/9	66.3±8.3	61.5±8.6	29.0±5.5	30.4±4.9	I, II, III	I, II, III	6	Adverse events
Raeissadat et al. [36]	2015	77	62	69/8	47/15	56.9±9.1	61.1±7.5	28.2±4.6	27.0±4.2	I, II, III, IV	I, II, III, IV	12	WOMAC
Sanchez et al. [37]	2012	79	74	46/33	45/29	60.5±7.9	58.9±8.2	27.9±2.9	28.2±2.7	NA	NA	6	WOMAC, Lequesne Index, Adverse events
Vaquerizo et al. [21]	2013	48	42	32/16	26/16	62.4±6.6	64.8±7.7	30.7±3.6	31.0±4.6	II, III, IV	II, III, IV	12	WOMAC, Lequesne Index, Adverse events
Raeissadat et al. [38]	2017	36	33	29/7	27/6	57.0±7.2	59.5±7.5	28.6±2.82	27.5±2.9	II, III	II, III	6	VAS, WOMAC, Adverse events
Su et al. [2]	2018	25	30	14/11	18/12	54.2±6.6	53.1±6.4	28.2±1.4	28.7±1.1	II, III	II, III	18	VAS, WOMAC, Adverse events
Filardo et al. [22]	2012	54	55	17/37	24/31	55	58	27	26	I, II, III	I, II, III	12	IDKC
Louis et al. [39]	2018	24	24	10/14	13/11	53.2±11.7	48.5±11.5	25.6±2.9	27.0±2.9	III, IV	III, IV	6	VAS, WOMAC, Adverse events

BMI = body mass index; HA = hyaluronic acid; IDKC = International Knee Documentation Committee; K-L = Kellgren and Lawrence grading scale; NA = data not available; PRP = platelet-rich plasma; VAS = visual analog scale, WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Table 2. Details of the PRP treatment protocols and the controls

		PRP				HA	
Author	Date	Category	Activation	Injection Dose, Times, and Intervals	Fresh/ Frozen	Type	Injection Dose, Times, and Intervals
Paterson et al. [28]	2016	PA-PRP	Ultraviolet light	3 mL, 3 times, weekly	Fresh	Hylan G-F 20	3 mL, 3 times, weekly
Li et al. [29]	2011	PRP	Calcium chloride	3.5 mL, 3 times, 3 weeks	Fresh	Sofast	2 mL, 3 times, 3 weeks
Cerza et al. [30]	2012	ACP	NA	5.5 mL, 4 times, weekly	Fresh	Hyalgan	20 mg, 4 times, weekly
Cole et al. [31]	2017	PRP	NA	4 mL, 3 times, weekly	Fresh	Hylan G-F 20	16 mg, 3 times, weekly
Duymus et al. [32]	2016	PRP	NO	5 mL, 2 times, monthly	Fresh	Ostenil Plus	40 mg, 1 time, monthly
Filardo et al. [33]	2015	PRP	10% calcium chloride	5 mL, 3 times, weekly	Fresh	Hyalubrix	30 mg, 3 times, weekly
Gormeli et al. [34]	2015	PRP	1 mL of calcium chloride	5 mL, 3 times, weekly	1 fresh/ 2 frozen	Orthovisc	2 mL, 3 times, weekly
Montanez-Heredia et al. [35]	2016	PRP	NA	NA, 3 times, 15 days	Frozen	Adant	NA, 3 times, 15 days
Raeissadat et al. [36]	2015	LR-PRP	NO	4–6 mL, 2 times, 4 weeks	Fresh	Hyalgan	20 mg, 3 times, weekly
Sanchez et al. [37]	2012	PRGF	400 uL of calcium chloride	8 mL, 3 times, weekly	Fresh	Euflexxa	NA, 3 times, weekly
Vaquerizo et al. [21]	2013	PRGF	400 uL of calcium chloride	8 mL, 3 times, weekly	Fresh	Durolane	NA, 1 time
Raeissadat et al. [38]	2017	PRGF	1.5 mL of Rooyagen	5 mL, 2 times, 3 weeks	Fresh	Hyalgan	20 mg, 3 times, weekly
Su et al. [2]	2018	LR-PRP	Calcium chloride	6 mL, 2 times, 14 days	Fresh	Freda	2 mL, 5 times, weekly
Filardo et al. [22]	2012	PRP	NA	5 mL, 3 times, weekly	Frozen	Hyalubrix	NA, 3 times, weekly
Louis et al. [39]	2018	PRP	Calcium chloride	3 mL, 1 time	Fresh	Durolane	3 mL, 1 time

ACP = autologous conditioned plasma; HA = hyaluronic acid; LP-PRP = leukocyte-poor platelet-rich PRP; LR-PRP = leukocyte-rich platelet-rich PRP; NA = data not available; NO = No Activation; PA-PRP = photo-activation and platelet-rich plasma; PRGF = plasma rich in growth factors; PRP = platelet-rich plasma.

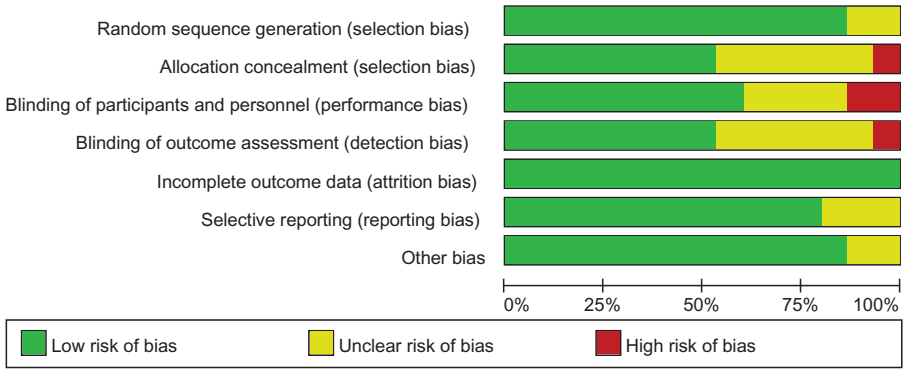

Figure 2. Risk of bias assessment.

(MD = −1.75, 95% CI = −2.50 to −1.01, I^2 = 89%, P < 0.000001). Table 3 presents all of these details.

WOMAC Stiffness Score

WOMAC stiffness scores were reported by two [2,32], three [2,32,39], five [2,21,32,37,38], and four studies [2,21,32,36] at one, three, six, and 12 months, respectively. The pooled analysis did not reveal significant differences between the PRP and HA groups at one (MD = −0.13, 95% CI = −0.41 to 0.15, I^2 = 35%, P = 0.37) and six months (MD = −0.46, 95% CI = −0.92 to 0.01, I^2 = 60%, P = 0.05). However, the subjects in the PRP group experienced significantly greater improvement in knee stiffness than those in the HA group at three (MD = –0.35, 95% CI = −0.63 to −0.08, I^2 = 0%, P = 0.01) and 12 months (MD = −0.99, 95% CI = −1.57 to −0.42, I^2 = 81%, P = 0.0007). Table 3 presents all of these details.

WOMAC Function Score

WOMAC function scores were reported by two [2,32], three [2,32,39], five [2,21,32,37,38], and four studies [2,21,32,36] at one, three, six, and 12 months, respectively. The pooled analysis showed that the subjects in the PRP and HA groups exhibited similar functional recovery after one month (MD = −2.35, 95% CI = −5.28 to 0.57, I^2 = 59%, P = 0.12) of treatment. However, the subjects in the PRP group performed better than those in the HA group at three (MD = −1.92, 95% CI = −2.57 to −1.27, I^2 = 0%, P < 0.000001), six (MD = −3.71, 95% CI = −7.21 to −0.22, I^2 = 84%, P = 0.04), and

Table 3. Details of PRP treatment protocols and control

Follow-up, mo	WOMAC	No. of Studies	No. of Cases PRP/HA	MD	(95% CI)	Heterogeneity, *P*; I^2	*P* Value of Effect Size, Z (*P*)
1	Pain	3	108/114	–	(–0.65 to 0.27)	0.05; 67%	0.80 (0.42)
	Stiffness	2	58/64	−0.13	(–0.41 to 0.15)	0.21; 35%	0.89 (0.37)
	Function	2	58/64	−2.35	(–5.28 to 0.57)	0.12; 59%	1.57 (0.12)
	Total	3	119/124	−3.81	(–7.98 to 0.36)	0.03; 71%	1.79 (0.07)
3	Pain	4	129/138	−0.31	(–1.16 to 0.54)	<0.0001; 88%	0.72 (0.47)
	Stiffness	3	80/88	−0.35	(–0.63 to −0.08)	0.44; 0%	2.50 (0.01)
	Function	4	80/88	−1.92	(–2.57 to −1.27)	0.80; 0%	5.82 (<0.000001)
	Total	5	155/163	−5.02	(–10.79 to 0.76)	<0.00001; 89%	1.70 (0.09)
6	Pain	6	270/263	−1.24	(–1.94 to −0.53)	<0.0001; 83%	3.42 (0.0006)
	Stiffness	5	221/213	−0.46	(–0.92 to 0.01)	0.04; 60%	1.93 (0.05)
	Function	5	221/213	−3.71	(–7.21 to −0.22)	<0.0001; 84%	2.08 (0.04)
	Total	7	296/288	−10.78	(–17.51 to −4.04)	<0.00001; 94%	3.13 (0.002)
12	Pain	5	232/218	−1.75	(–2.50 to −1.01)	<0.00001; 89%	4.61 (<0.000001)
	Stiffness	4	183/168	−0.99	(–1.57 to −0.42)	0.001; 81%	3.40 (0.0007)
	Function	4	183/168	−8.90	(–14.82 to −2.99)	<0.00001; 94%	2.95 (0.003)
	Total	4	183/168	−12.11	(–20.21 to −4.01)	<0.00001; 94%	2.93 (0.003)

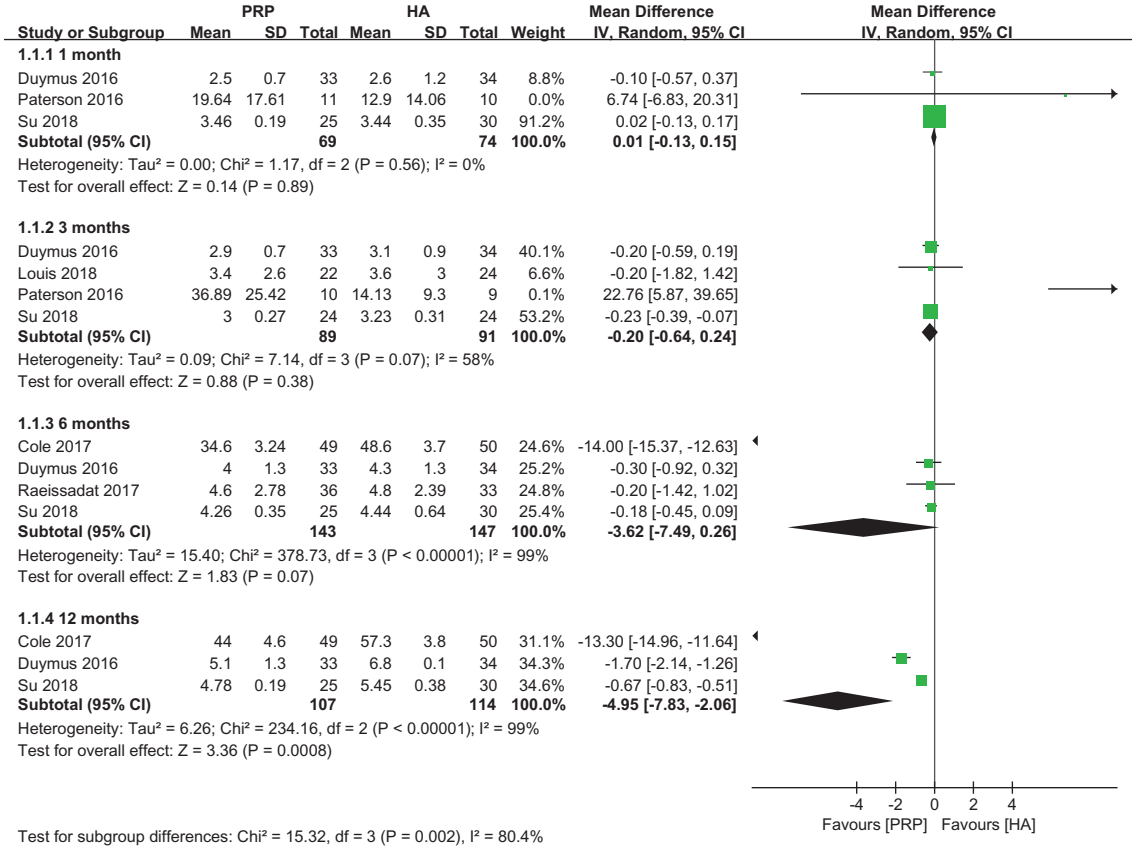

Figure 3. Forest plot and meta-analysis of VAS score.

12 months (MD = −8.90, 95% CI = −14.82 to −2.99, $I^2 = 94\%$, $P = 0.003$). Table 3 presents all of these details.

WOMAC Total Score

WOMAC total scores were reported by three [2,30,32], five [2,29,30,32,39], seven [2,21,29,30,32,37,38], and four studies [2,21,32,36] at one, three, six, and 12 months, respectively. The pooled analysis did not identify significant differences between the PRP and HA groups at one (MD = −3.81, 95% CI = −7.98 to 0.36, $I^2 = 71\%$, $P = 0.07$) and three months (MD = −5.02, 95% CI = −10.79 to 0.76, $I^2 = 89\%$, $P = 0.09$). However, the subjects in the PRP group experienced significantly greater improvement in total scores than those in the HA group at

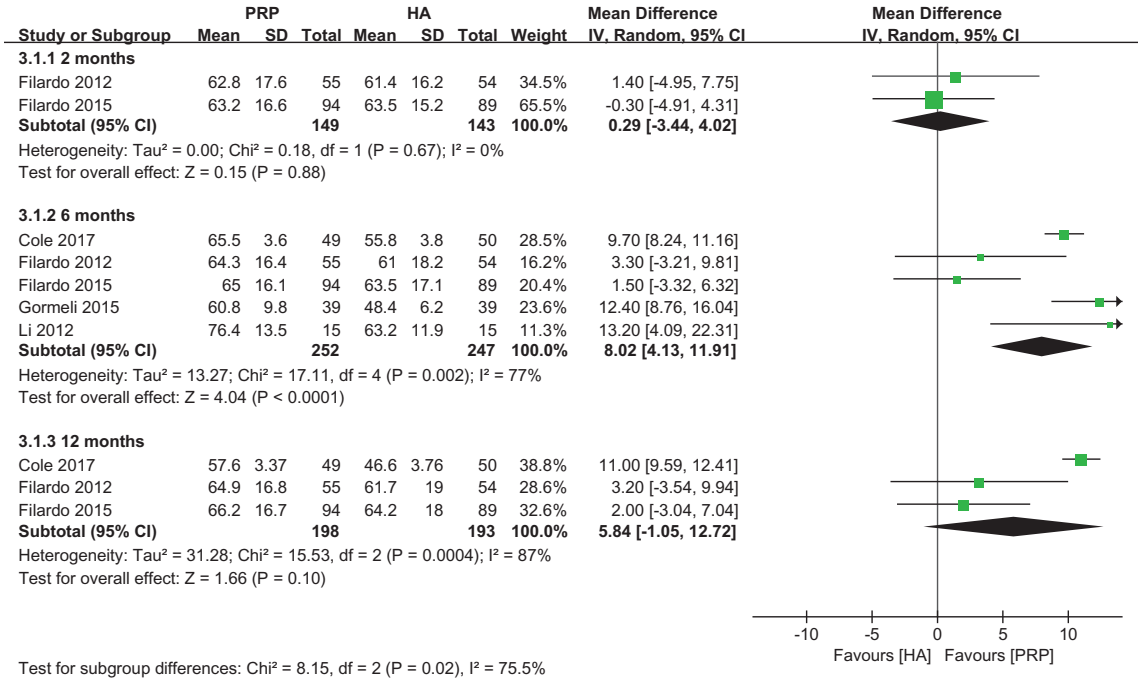

Figure 4. Forest plot and meta-analysis of IDKC.

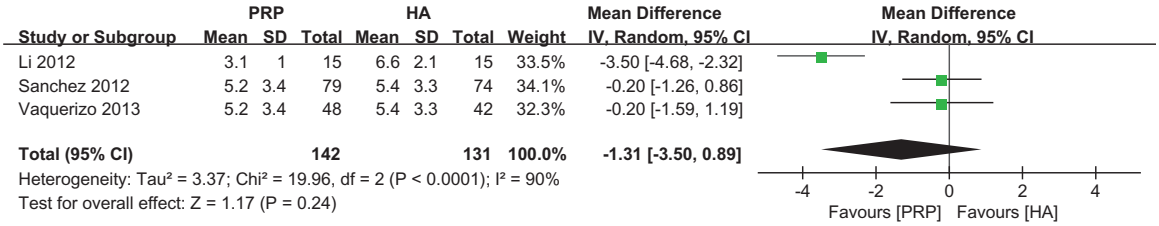

Figure 5. Forest plot and meta-analysis of Lequesne index scores.

six (MD = −10.78, 95% CI = −17.51 to −4.04, I^2 = 94%, P = 0.002) and 12 months (MD = −12.11, 95% CI = −20.21 to −4.01, I^2 = 94%, P = 0.003). All these details are presented in Table 3.

VAS

VAS scores for pain were reported by three [28,32], four [2,28,32,39], four [2,31,32,38], and three studies [2,31,32] at one, three, six, and 12 months, respectively. Therefore, a subgroup meta-analysis was performed to compare the VAS scores for pain based on the length of follow-up. No significant differences were observed between the PRP and HA groups at one (MD = 0.01, 95% CI = −0.13 to 0.15, I^2 = 0%, P = 0.89), three (MD = −0.20, 95% CI = −0.64 to 0.24, I^2 = 58%, P = 0.38), and six months (MD = −3.62, 95% CI = −7.49 to 0.26, I^2 = 99%, P = 0.07). However, the treatment in the PRP groups exhibited better efficacy than that in the HA groups at 12 months (MD = −4.95, 95% CI = −7.83 to −2.06, I^2 = 99%, P = 0.0008) (Figure 3).

IDKC

IDKC scores were reported by two [22,33], five [22,29,31,33,34], and three studies [22,31,33] at two, six, and 12 months, respectively. Therefore, a subgroup meta-analysis was performed to compare the IDKC scores based on the length of follow-up. No significant differences were observed between the PRP and HA groups at two (MD = 0.29, 95% CI = −3.44 to 4.02, I^2 = 0%, P = 0.88) and 12 months (MD = 5.84, 95% CI = −1.05 to 12.72, I^2 = 87%, P = 0.10). However, the subjects in the PRP group had significantly better IDKC scores than those in the HA group at six months (MD = 8.02, 95% CI = 4.13 to 11.91, I^2 = 77%, P < 0.0001) (Figure 4).

Lequesne Index

Lequesne Index scores were reported by three studies [21,29,37], with 142 patients treated with PRP and 131 with HA. The pooled analysis did not reveal a significant difference between the PRP and HA groups at six months (MD = −1.31, 95% CI = −3.50 to 0.89, I^2 = 90%, P = 0.24) (Figure 5).

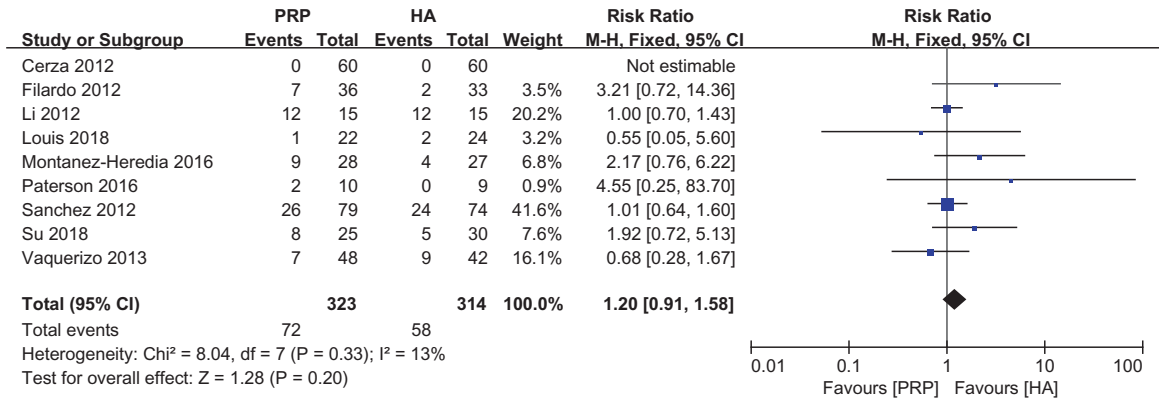

Figure 6. Forest plot and meta-analysis of adverse events.

Adverse Events

Adverse events were reported by nine studies [2,21,28–30,35,37–39], with 323 patients treated with PRP and 314 with HA. The pooled analysis did not detect a significant difference between the PRP and HA groups (RR = 1.20, 95% CI = 0.91 to 1.58, I^2 = 13%, P = 0.20) (Figure 6).

Discussion

As a common degenerative joint disease, KOA is the second leading cause of loss of joint function [4], which causes enormous economic and social burdens worldwide [40]. The understanding of KOA in terms of etiology and pathogenesis remains unclear [41]; the main pathological changes involve components around the joints and degeneration of articular cartilage [42].

HA is mainly composed of important factors such as D-glucosamine and N-acetyl-D-glucosamine, and these factors play an important role in nourishing cartilage and protecting joints [43]. HA is degraded and diluted by exudates, resulting in a decrease in the molecular weight and endogenous concentration of HA in the knee joint cavity of patients with KOA. These changes reduce the viscoelasticity of the knee cartilage and reduce the knee's ability to resist mechanical stress and damage [11,44]. Many clinical studies have also shown that HA can effectively relieve knee pain and improve knee function [45–47]. However, some researchers have shown that HA does not improve regeneration of damaged cartilage, particularly in elderly patients with severe KOA [44,48]. PRP is highly concentrated autologous plasma containing a variety of growth factors that promote the healing of ligaments, tendons, and bones, including platelet-derived growth factor, transforming growth factor–b, vascular endothelial growth factor, basic fibroblast growth factor, and bioactive proteins [49–51]. As a vector for large growth factors [52], PRP promotes tissue repair [53] and is increasingly used to treat KOA. PRP plays an important role in mesenchymal stem cell proliferation and cartilage formation through a combination of various growth factors [54]. It has been reported that PRP may have a positive effect on inducing migration, proliferation, and differentiation of precursor cells in cartilage. Therefore, PRP can effectively repair the damaged cartilage of the knee joint [55] while reducing the effects of knee pain and inflammatory responses [56]. These effects of PRP make it a new drug treatment for KOA.

Most of the previous systematic reviews have shown that PRP is an effective alternative treatment for long-term relief of knee pain and improved joint function in KOA patients. However, the previous conclusions were reached on the basis of a small number of RCTs [23–26,27,57], and thus, the time effect of PRP injection therapy on KOA has not been fully investigated. Chang et al. [58] found that patients receiving PRP injections showed better, longer-lasting improvements than patients receiving HA treatment; however, most of the studies that were included in the analysis were case series, and only five were RCTs. Laudy et al. [27] pooled 10 trials, including six RCTs, and found that PRP injections were more effective than placebo or HA injections for alleviating pain symptoms and improving joint motor function in KOA patients. Another recent meta-analysis [11] included 13 studies (10 RCTs) and synthesized the WOMAC scores to compare the efficacy of PRP injections with that of HA injections. Based on a large number of RCTs, this study evaluated the effects of PRP treatment on knee joint pain and physiological function at different times after injection.

In our study, the data from 15 RCTs showed that long-term pain relief and functional improvement in the PRP group were superior to those in the HA group. Divergent results were observed in the WOMAC, VAS, IKDC, and Lequesne Index scores, as well as in the occurrence of adverse events. The principal findings of this study were that within one to three months postinjection, subjects in the PRP group and HA group had similar experiences with respect to pain relief (WOMAC pain score and VAS pain score) and functional improvement (WOMAC total score, WOMAC function score, and IKDC score). In addition, no significant differences in

the Lequesne Index were observed between the PRP and HA groups after six months. However, subjects in the PRP group experienced significantly better pain relief (WOMAC pain score and VAS pain score) and functional improvement (WOMAC function score, WOMAC total score, and IKDC score) between six and 12 months postinjection than those in the HA group. In addition, the HA and PRP groups did not display different adverse event rates.

Heterogeneity was different between all measured parameters, indicating that the effects were inconsistent throughout the studies. Based on a careful review and evaluation of all included studies, we found some common problems. First, the pathology of KOA in the PRP and HA groups was different among all these included studies, and the distribution of KOA severity among the studies varied between grades I and IV (K-L grading scale). As shown in the studies by Chang et al. [58] and Filardo et al. [59], PRP has a better effect on patients with early or moderate forms of KOA but has a limited effect on patients with advanced forms of KOA. Therefore, patients with different stages of KOA may not exhibit the same responses to PRP or HA treatment [11].

Additionally, the number of injections and the length of the time between the two injections also varied among all these included studies. Among the studies that included multiple injections, an interval of two weeks was used in the studies by Montanez-Heredia et al. [35] and Su et al. [2], three weeks was adopted by Li et al. [29] and Raeissadat et al. [38], and one month was adopted by Duymus et al. [32] and Raeissadat et al. [36]. In the study by Gormeli et al. [34], no differences were observed between patients who received an HA injection and those who received a single-dose PRP injection, whereas the patients receiving multiple-dose PRP experienced greater improvement than the patients receiving either of the other two treatments. However, Patel et al. [53] concluded that a single dose of PRP injection and a double dose of PRP injection had the same therapeutic effect. The study by Görmeli et al. [34] further confirmed this conclusion in patients with advanced KOA, as there was no difference between treatment methods. These findings might provide guidance for future treatment options, because a consensus regarding treatment methods is currently unavailable.

As this study was a systematic review, it inevitably had certain limitations. Limitations exist in the recommendation of routine PRP injections as a treatment for KOA because the composition of PRP remains uncertain. Different types of PRP preparations have been used; thus, these preparations differ in the platelet counts, growth factor concentrations, and leukocyte counts depending on the patient characteristics and the preparation kit. Furthermore, the interval between injections and the optimal dosage are still areas of concern in the future because they might exert an effect on the postinjection process, and there are currently no published studies supporting any specific injection protocol. In the present study, insufficient data were available for us to conduct a subgroup analysis to confirm whether multiple injections are necessary for patients with different stages of KOA.

Conclusions

Based on the current evidence, the use of PRP to treat KOA has a positive effect on pain levels and functional outcomes. In addition, PRP injections do not display different adverse event rates compared with HA injections. There is a lack of clarity regarding the number and frequency of PRP injections required to achieve maximum results and in the ideal treatment regimens for different severities of KOA.

Authors' Contributions

Conceived and designed the experiments: Yanhong Han and Jun Liu; performed the experiments: Jianke Pan, Weiyi Yang, and Lingfeng Zeng; analyzed the data: Hetao Huang, Jiongtong Lin, and Guihong Liang; wrote the paper: Yanhong Han and Jianke Pan.

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