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ORIGINAL ARTICLE

The effects of platelet-rich plasma injection in knee and hip osteoarthritis: a meta-analysis of randomized controlled trials

Yujie Dong[1] · Butian Zhang[2] · Qi Yang[3] · Jiajing Zhu[2] · Xiaojie Sun[4]

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Abstract

Objective We conducted this updated meta-analysis to evaluate the effects of PRP in patients with knee or hip OA.

Method PubMed, Embase, and Web of Science were searched to identify randomized controlled trials (RCTs) that compared the efficacy of PRP with other intra-articular injections. The outcomes of interest included Western Ontario and McMaster (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analog Scale (VAS), Harris Hip Score (HHS), and International Knee Documentation Committee (IKDC).

Results Twenty-four RCTs with 21 at knee OA and three at hip OA were included in this meta-analysis. The PRP injections significantly improved the WOMAC score, VAS score, IKDC score, and HHS score as compared with comparators. The WOMAC pain, stiffness, and physical function scores were also significantly better in the PRP group than in the control group. Most of the evaluated parameters that favored PRP were observed in knee OA but not in hip OA, at short-term (at 1, 2, 3, 6, 12 months) but not long-term follow-up (at 18 months), in RCTs with low risk of bias.

Conclusions Intra-articular PRP injection provided better effects than other injections for OA patients, especially in knee OA patients, in terms of pain reduction and function improvement at short-term follow-up.

Key Points

- *This updated meta-analysis, based on great sample size and high-quality studies, evaluates the effects of PRP in patients with knee or hip OA.*
- *Intra-articular PRP injection provided better effects than other injections for OA patients.*
- *Most of the evaluated parameters that favored PRP were observed in knee OA at short term (at 1, 2, 3, 6, 12 months).*

Keywords Hip osteoarthritis · Knee osteoarthritis · Platelet-rich plasma

Introduction

Osteoarthritis (OA) is a multifactorial chronic bone and joint disease characterized by articular cartilage degeneration that negatively affects patient mobility and quality of life [1]. It is approximately 20% of patients who were older than 45 years occur OA, which makes it the most common chronic painful condition [2].

Besides the symptoms in knee pain, swelling, and limited mobility, OA can also result in a high prevalence of functional disability. The targets of OA treatment are to relieve pain, improve function and mobility, prevent deformity, and slow the progression of the disease. Currently, there are various of non-surgical treatment modalities that have been applied to treat knee or hip OA, including oral nonsteroidal anti-inflammatory drugs [3], physical therapy, and intra-articular injection of hyaluronic acid (HA) [4], corticosteroids [5], or platelet-rich plasma (PRP) [6].

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✉ Xiaojie Sun
sunxiaojie5413@sina.com

[1] Department of Emergency, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China

[2] Department of Radiology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China

[3] Department of Obstetrics and Gynecology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China

[4] Department of Plastic and Reconstruction Surgery, China-Japan Union Hospital of Jilin University, No. 126 Xiantai Street, Changchun 130033, Jilin, China

PRP, representing a potential biological treatment for knee OA, has been widely used for articular cartilage regeneration [7, 8]. PRP is an autologous blood product that contains high concentrations of a wide range of growth factors that play critical roles in tissue repair [9, 10]. Because of its autologous nature, the PRP treatment avoids any immune reaction or blood transmission disease. Although several published trials reported the promising results of PRP in orthopedic and sports medicine, its clinical application and efficacy still remained uncertain. PRP lacks proper standardization for the number or frequency of injections, as well as the ideal treatment for different stages of gonarthrosis. Several clinical trials reported the favorable results of PRP injection in cartilage damage and knee OA when compared with HA [11–13] and placebo injection [14]. Moreover, recently published systematic reviews and meta-analysis [15–19] also have been carried out to investigate the effects of PRP for knee OA; however, these studies yielded conflicting results [18, 19]. For example, the meta-analysis conducted by Kanchanatawan, W et al. [18] concluded that there was not sufficient evidence to support the effect of PRP in improving the Western Ontario and McMaster (WOMAC) pain, stiffness, and function scores in the treatment of knee OA when compared with HA or placebo. In contrast, another two meta-analyses by Shen, L et al. [20] and Han, Y et al. [19] reported significant beneficial effects of PRP in the WOMAC pain and physical function subscores when compared with HA, saline placebo, ozone, or corticosteroids.

Although these reviews were performed mainly based on the same body of evidence, a first screening suggested that the conflicting findings could be resulted from inconsistent inclusion criteria, differences in risk of bias assessment of included studies, and also errors in data extraction and synthesis. Moreover, both the administration of PRP and comparators have varied greatly among the included studies in previous systematic review and meta-analysis [18–20], such that in some, PRP was compared with HA only [19, 21], whereas in others [17, 18, 20], PRP was compared with saline placebo, HA, ozone, and corticosteroids. By design, these two types of comparisons could address different questions: (1) the efficacy of PRP as compared with HA; (2) the efficacy of PRP as compared with other intra-articular injection regimens. The previous systematic reviews and meta-analysis have not consistently accounted for these fundamental differences, and the treatment estimate may be biasedly analyzed. Moreover, the sources of heterogeneity (age, sex, BMI, and grade of OA) were also not explored in these reviews.

Prompted by these issues outlined above (discrepancies and insufficient methodological quality), as well as the additional RCTs have been published recently in this field, we believe that it is necessary to perform an updated meta-analysis to investigate whether PRP injections are more efficacious than other injections in pain relief and functional improvement for the treatment of patients with knee or hip OA.

Material and methods

Research design

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. We searched medical bibliographic databases to identify articles focusing on the effects of PRP for the treatment of knee or hip OA.

Study search

A comprehensive systematic search was performed in major electronic databases (PubMed, Embase, and Web of Science) from their inception to June 2019. The following search terms were used for searching: (“platelet-rich plasma”[MeSH Terms] OR (“platelet-rich”[All Fields] AND “plasma”[All Fields]) OR “platelet-rich plasma”[All Fields] OR (“platelet”[All Fields] AND “rich”[All Fields] AND “plasma”[All Fields]) OR “platelet-rich plasma”[All Fields]) AND ((“osteoarthritis, hip”[MeSH Terms] OR (“osteoarthritis”[All Fields] AND “hip”[All Fields]) OR “hip osteoarthritis”[All Fields] OR (“hip”[All Fields] AND “osteoarthritis”[All Fields])) OR (“osteoarthritis, knee”[MeSH Terms] OR (“osteoarthritis”[All Fields] AND “knee”[All Fields]) OR “knee osteoarthritis”[All Fields] OR (“knee”[All Fields] AND “osteoarthritis”[All Fields]))). There was no language or publication status restriction. Moreover, the reference lists of reviews and all included studies were manually reviewed to identify other potential articles. We also contact the corresponding authors by email to retrieve original data when important data were not provided in the study.

Inclusion criteria and study selection

Inclusion criteria for this study were as follows: (1) randomized controlled trial (RCT); (2) adult patients had a diagnosis of knee or hip OA; (3) compared the effect of PRP with other injections; (4) provided the outcome measures, including WOMAC, Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analog Scale (VAS), Harris Hip Score (HHS), and International Knee Documentation Committee (IKDC). Exclusion criteria were a cohort study, case-control, or cross-sectional study; review articles, or conference abstracts; or studies did not provide the outcomes of our interest.

The disagreement between investigators was resolved by discussion and consensus.

Data extraction and quality assessment

A standardized Excel form was developed to extract the data. All the data were extracted by two independent investigators and then checked by a third investigator to ensure the accuracy of data. The data of outcome measures, including a mean and standardized deviation of WOMAC, KOOS, VAS, HHS, IKDC, were extracted. The baseline characteristics from each study, such as the first author's name, year of publication, country, sample size, and duration of follow-up, were also extracted. When several publications from the same population or clinical trial were identified, we only included the one that had the most complete data or the latest outcomes.

We used the method recommended by Cochrane Collaboration [23] to assess the risk of bias in an RCT. This method comprises six items, including random sequence generation, allocation concealment; blinding of outcome participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias [23]. In accordance with the quality domains and scoring system, each RCT was classified as being "high" (seriously weakens confidence in results), "low" (unlikely to seriously alter the results), or "unclear" risk of bias [23].

Statistical analysis

Statistical analysis was carried out using the STATA software version 12.0 (Stata Corporation, College Station, TX, USA). Continuous variables were expressed as weight mean difference (WMD) with 95% confidence intervals (CIs), while dichotomous variables were pooled as risk ratio (RR) with 95%CIs.

Statistical heterogeneity between the studies was assessed with Cochrane Q and I^2 statistic [24], in which $P < 0.1$ or $I^2 > 50\%$ were considered to be significant. Depending on the absence or presence of significant heterogeneity, pooled estimates were calculated using a random-effects model [25] or a fixed-effects model [26]. When significant heterogeneity was identified, sensitivity analysis was performed to explore the potential sources of heterogeneity by excluding studies one by one. Subgroup analysis based on disease type, comparators, and treatment duration was performed. Given several confounding factors (mean age, body mass index (BMI), male ratio, grade of OA, history of previous treatment, and symptom duration) that might affect the differences in outcome measures among included studies, we performed meta-regression analysis when the data were available. Publication bias was evaluated by using the Egger [27] and Begger [28] test. Finally, in order to ascertain the robustness of summary treatment effects, we performed meta-analysis confined to RCTs that were at low risk of bias. A P value less than 0.05 was judged as statistically significant, except where otherwise specified.

Results

Search results

A total of 692 publications were identified in the initial search, of which 374 were excluded due to duplications, leaving 318 unique articles for the title/abstract review. Two hundred ninety articles were removed after screening the title and abstract. Then, 28 potential articles were left for full-text information review. Based on the inclusion criteria, 4 of them were removed because of the following reasons: two studies were single-arm design [29, 30], one study did not provide data of our interest [31], and one study did not present available data for analysis [6]. Finally, 24 RCTs [11–14, 32–51] met the inclusion criteria, and were included in this meta-analysis (Fig. 1).

Characteristics of included studies

Table 1 describes the main characteristics of the 24 included RCTs. The majority of studies were from Italy ($n = 7$) [11, 12, 35, 37, 38, 40, 48], with the remaining 3 articles from Spain [34, 41, 46] and Iran [13, 33, 43], 2 articles from China [49, 50], Turkey [32, 39], and USA [44, 47], and 1 article from Australia [36], Brazil [42], India [14], Egypt [45], and Mexico [51]. In total, 42.7% of the study population was male, and 57.3% was female. Among the included studies, 21 articles included knee OA patients [11–14, 32–34, 36, 39–51], and 3 included hip OA patients [35, 37, 38]. The sample size varied greatly, which ranged from 21 to 183 in each study. WOMAC was the most commonly used outcome in 17 of the included studies [11, 13, 14, 33–35, 38, 39, 41, 42, 44, 46–51]. The duration of follow-up was also variable across the trials, with the shortest period of 12 weeks [36] and the longest period of 18 months [49]. PRP protocols used in each trial were greatly different in terms of preparation devices, centrifugations, and the injection regimen of dose and intervals. HA was the most commonly used control in most of the included studies [11–13, 32, 34–42, 45, 47–49], and other comparators in the remaining studies included normal saline [14, 44, 50], acetaminophen [51], and prolotherapy [33].

Two different radiographic OA grading systems were applied in the studies, including 20 studies using Kellgren Lawrence grading (0–IV) [11–13, 32, 33, 35–42, 44–47, 49, 51] and four studies using Ahlback scale(I–V) [14, 34, 48, 50]. In studies with the Kellgren Lawrence classification

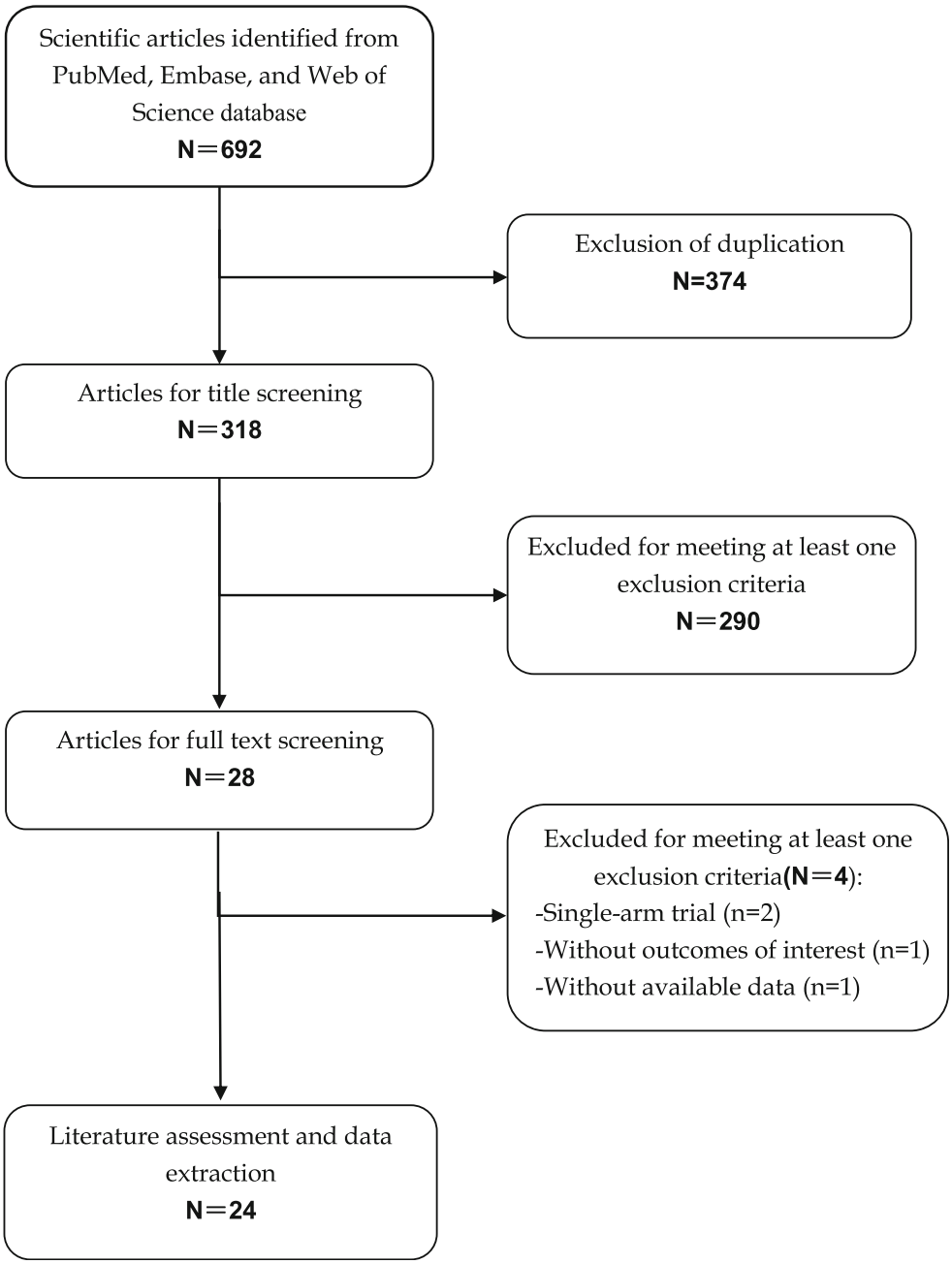

Fig. 1 Eligibility of studies for inclusion in meta-analysis

system, 14.74% of patients had grade I, 47.92% of patients had grade II, 33.89% of patients had grade III, and 3.45% of patients had grade IV, whereas in these studies using Ahlback scale, 60.26% of patients had grade I, 31.09% of patients had grade II, and 8.65% of patients had grade III, and none of the patients had grade IV.

Quality appraisal of included studies

The risk of bias assessment of RCTs is presented in Fig. 2. Overall, ten studies were classified as being at low risk of bias [12, 32, 34, 36, 37, 41, 44, 46–48], five studies as being at unclear risk of bias [35, 39, 40, 49, 51], and the remaining nine studies as being at a high risk of bias [11, 13, 14, 33, 38, 42, 43, 45, 50]. The most common reasons for studies with unclear or high risk of bias were that they did not perform the blind for participants, personnel, or the outcome evaluators.

Effects of PRP: comparison with previous meta-analysis and systematic reviews

Shen, LX et al. [20], Kanchanatawan, W et al. [18], and Dold, AP et al. [52] reported that PRP was more effective

Table 1 Baseline characteristics of patients in the trials included in the meta-analysis

Study	Country	Disease type	Treatment regimen	No. of patients	Male/female	Age (mean ± SD, y)	BMI (kg/m^2)	Grade of OA (K-L) (I/II/III/IV)
Cerza, F [11]	Italy	Knee OA	PRP	60	25/35	66.5 ± 11.3	NR	21/24/15/0
			HA	60	28/32	66.2 ± 10.6	NR	25/22/13/0
Filardo, G [12]	Italy	Knee OA	PRP	54	37/17	55	27	NR
			HA	55	31/24	58	26	NR
Raeissadat, SA [13]	Iran	Knee OA	PRP	77	8/69	56.85 ± 9.13	28.20 ± 4.63	6/44/38/12
			HA	62	15/47	61.13 ± 7.48	27.03 ± 4.15	0/47/37/16
Patel, S [14]	India	Knee OA	PRP1	27	11/16	53.11 ± 11.55	26.28 ± 3.23	NA
			PRP2	25	5/20	51.64 ± 9.22	25.81 ± 3.31	NA
			Saline	23	6/17	53.65 ± 8.17	26.21 ± 2.93	NA
Gormeli, G [32]	Turkey	Knee OA	PRP1	44	19/25	53.8 ± 13.4	28.4 ± 4.4	NR
			PRP3	39	16/23	53.7 ± 13.1	28.7 ± 4.8	NR
			HA	39	17/22	53.5 ± 14	29.7 ± 3.7	NR
			Control	40	20/20	52.8 ± 12.8	29.5 ± 3.2	NR
Rahimzadeh, P [33]	Iran	Knee OA	PRP	21	10/11	65.5 ± 6.64	28.6 ± 1.9	NR
			Prolotherapy	21	11/10	64.3 ± 5.31	28.3 ± 1.9	NR
Sánchez, M [34]	Spain	Knee OA	PRP	89	46/43	60.5 ± 7.9	27.9 ± 2.9	NA
			HA	87	45/42	58.9 ± 8.2	28.2 ± 2.7	NA
Di Sante, L [35]	Italy	Hip OA	PRP	21	11/10	71.37 ± 6.03	NR	0/5/16/0
			HA	22	9/13	73.62 ± 7.87	NR	0/7/15/0
Paterson, KL [36]	Australia	Knee OA	PA-PRP	11	8/3	49.94 ± 13.72	27.92 ± 11.94	NR
			HA	10	7/3	52.7 ± 10.3	30.87 ± 5.64	NR
Battaglia, M [37]	Italy	Hip OA	PRP	50	30/21	51 ± 12	26 ± 5	NR
			HA	50	33/17	56 ± 12	27 ± 4	NR
Dallari, D [38]	Italy	Hip OA	PRP	44	20/24	NR	NR	NR
			HA	36	26/10	NR	NR	NR
Duymus, TM [39]	Turkey	Knee OA	PRP	33	1/32	60.4 ± 5.1	27.6 ± 4.6	0/22/11/0
			HA	34	1/33	60.3 ± 9.1	28.4 ± 3.6	0/24/10/0
Filardo, G [40]	Italy	Knee OA	PRP	94	60/34	53.32 ± 13.2	26.6 ± 4	NR
			HA	89	52/37	57.55 ± 11.8	26.9 ± 4.4	NR
Vaquerizo, V [41]	Spain	Knee OA	PRP	48	16/32	62.4 ± 6.6	30.7 ± 3.6	NR
			HA	48	22/26	64.8 ± 7.7	31 ± 4.6	NR
Lana, JF [42]	Brazil	Knee OA	PRP	36	7/29	60.9 ± 7	27.42 ± 6.89	14/16/5/0
			HA	36	3/33	60 ± 6.6	28.24 ± 8.77	17/13/6/0
Angoorani, H [43]	Iran	Knee OA	PRP	27	5/22	62.15 ± 12.14	28.52 ± 3.83	NR
			HA	27	2/25	61.59 ± 8.07	29.21 ± 3.22	NR
Smith, PA [44]	USA	Knee OA	PRP	15	NR	NR	NR	0/8/7/0
			Saline	15	NR	NR	NR	0/10/5/0
Ahmad, HS [45]	Egypt	Knee OA	PRP	45	14/31	56.2 ± 6.8	26.7 ± 3.6	8/17/20/0
			HA	44	14/30	56.8 ± 7.4	26.5 ± 3.5	7/19/18/0
Vaquerizo, V [46]	Spain	Knee OA	PRP1	48	21/27	63.6 ± 6.7	30.1 ± 4	NR
			PRP2	42	15/27	68 ± 8.3	30.8 ± 4.4	NR
Cole, BJ [47]	USA	Knee OA	PRP	49	28/21	55.9 ± 10.4	27.4 ± 3.9	3/26/20/0
			HA	50	20/30	56.8 ± 10.5	29 ± 6.4	0/27/22/1
Lisi, C [48]	Italy	Knee OA	PRP	30	20/10	53.5 ± 15.1	NR	NA
			HA	28	16/12	57.1 ± 10	NR	NA
Su K [49]	China	Knee OA	PRP	27	10/17	50.67 ± 8.7	28.19±	0/16/11/0
			HA	30	12/18	53.13 ± 6.41	28.69 ± 1.13	0/14/16/0
Wu, YT [50]	China	Knee OA	PRP	20	5/15	63.25 ± 6.84	24.14 ± 2.93	NA

Table 1 (continued)

Study	Country	Disease type	Treatment regimen	No. of patients	Male/female	Age (mean ± SD, y)	BMI (kg/m^2)	Grade of OA (K-L) (I/II/III/IV)
			Saline	20	5/15	63.25 ± 6.84	24.14 ± 2.93	NA
Simental-Mendia, M [51]	Mexico	Knee OA	PRP	33	11/22	57.2 ± 8.1	32.2 ± 6.2	11/22/0/0
			Acetaminophen	32	12/20	55.6 ± 11.4	29.5 ± 3.8	12/20/0/0

Abbreviations: *SD*, standard deviation; *OA*, osteoarthritis; *PRP*, platelet-rich plasma; *PA-PRP*, photo-activated PRP; *PRP1*, a single injection of PRP; *PRP2*, 2 injection of PRP; *PRP3*, 3 injection of PRP; *HA*, hyaluronic acid; *BMI*, body mass index; *K-L*, Kellgren and Lawrence grading scale; *NA*, not available

in the treatment of knee OA in pain relief and functional improvement as compared with other injections. However, mistakes were detected in the study inclusion and data extraction in these systematic reviews and meta-analysis. The inclusion criteria in the study design for these reviews were RCTs. However, these reviews included a prospective cohort study by Spakova, T et al. [53] rather than an RCT. Moreover, the effect evaluation of PRP compared with HA was also problematic in the study by Spakova, T et al. [53]. The authors used WOMAC and 11-point pain intensity Numeric Rating Scale to evaluate the effects of PRP and HA at baseline, 3, and 6 months after therapy. However, the baseline measures were not similar between the two groups. Thus, it should be more accurate to compare the changes overall time rather than at the follow-up periods in the outcome measures in both groups. The errors in study inclusion and data extraction may slightly alter Shen, LX [20] and Kanchanatawan, W's [18] conclusion on the effects of PRP on the WOMAC score.

Our study differed from the previous systematic reviews [54, 55], in that, for the same RCTs, more domains were scored with unclear or high risk of bias. The details of the methodological assessment are presented in Fig. 2, whereas none of the previous systematic reviews provided such details, which prevented us from exploring the exact reasons behind the discrepancies. Of note, Di, YL and colleagues [16] assessed two included studies with unclear risk of bias in the blinding of outcome assessment and incomplete outcome, whereas we identified these domains with a high risk of bias. Bennell, KL [17] and Sundaram, K [55] even did not assess the risk of bias. Thus, we could not understand the quality of the included studies in their reviews, as well as whether the evidence of PRP effects was reliable.

WOMAC

Total WOMAC score

For the total WOMAC score, there were 14 studies [11, 13, 38, 39, 41, 14, 44, 51, 33, 46–50] comparing the differences between PRP and comparator groups. Pooled estimate using a random-effects model (I^2 = 97.2%, P < 0.001) showed that PRP was associated with a significantly lower WOMAC score than comparators (WMD = − 10.39, 95%CI − 13.50, − 7.28; P < 0.001) (Fig. 3). We performed a sensitivity analysis by removing the trial with outlier [38], and results showed that the pooled estimate of remaining studies changed a little (WMD = − 12.28, 95%CI − 15.46, − 9.09; P < 0.001), but significant heterogeneity was still present (I^2 = 98.5%, P < 0.001). Further exclusion of any single trial did not change the pooled data and heterogeneity substantially (data not shown).

We performed subgroup analysis based on disease type, comparator, treatment duration, and methodological quality. These results are presented in Table 2.

WOMAC pain score

There were 14 studies [13, 14, 33–35, 39, 41, 42, 44, 46, 47, 49–51] reporting the data of WOMAC pain score. The results showed that the WOMAC pain score was significantly lower in the PRP group than in the control group (WMD = − 2.72, 95%CI − 3.32, − 2.12; P < 0.001). There was significant heterogeneity among the included studies (I^2 = 97.9%, P < 0.001). Thus, we performed a sensitivity analysis by excluding the trial with an outlier. However, the heterogeneity was still present (I^2 = 98.0%, P < 0.001), and the pooled data did not change a lot (WMD = − 2.85, 95%CI − 3.45, − 2.26; P < 0.001).

Subgroup analysis results based on disease type, comparator, treatment duration, and methodological quality are presented in Table 2.

WOMAC stiffness score

There were 13 studies [13, 14, 33–35, 39, 41, 42, 44, 46, 49–51] that reported the data of WOMAC stiffness score. Compared with control, PRP significantly reduced the WOMAC stiffness score (WMD = − 0.91, 95%CI − 1.23, − 0.60; P < 0.001). The test for heterogeneity was significant (I^2 = 93.8%, P < 0.001). Thus, a sensitivity analysis was performed. When we deleted the trial with outlier, the overall

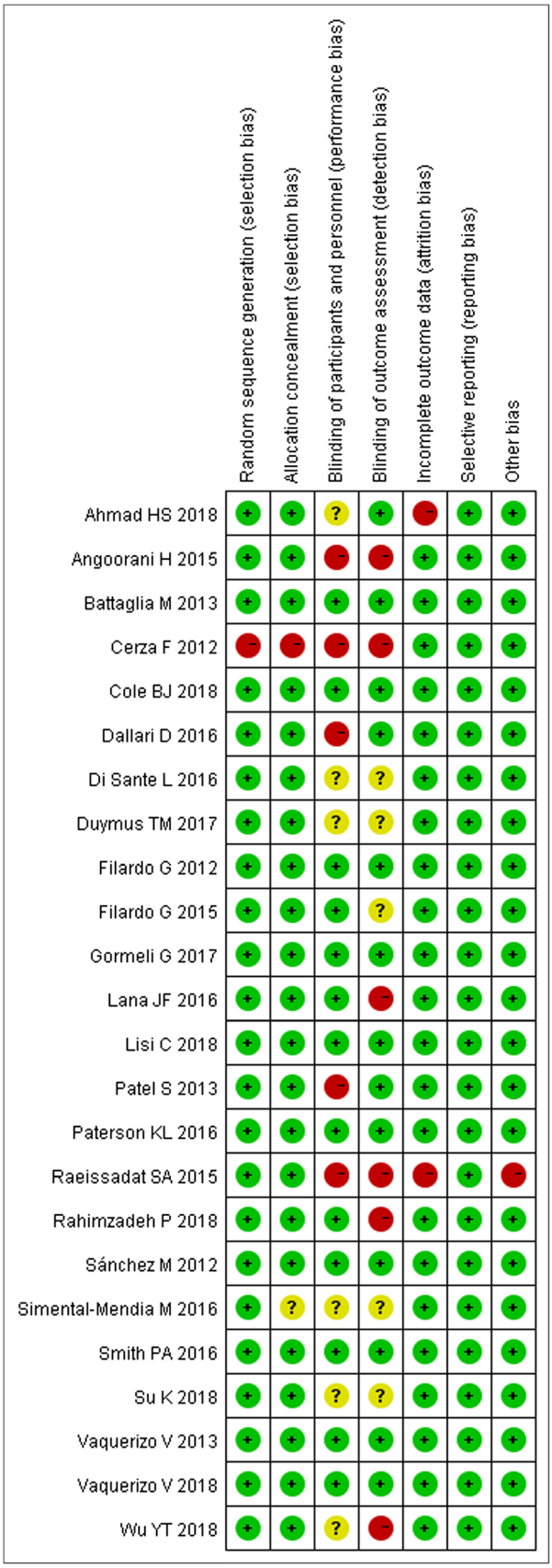

Fig. 2 Risk of bias

estimate changed a little (WMD = − 0.92, 95%CI − 1.24, − 0.61; $P < 0.001$), but the heterogeneity was still present (I^2 = 94.1%, $P < 0.001$).

Subgroup analysis results based on disease type, treatment duration, and methodological quality were presented in Table 2.

WOMAC physical function score

There were 12 studies [13, 14, 33, 34, 39, 41, 42, 44, 46, 49–51] reporting the data of WOMAC physical function score. Pooled data showed that PRP had a significantly decreased score in WOMAC physical function compared with control (WMD = − 9.34, 95%CI − 11.49, − 7.20; $P < 0.001$).

Subgroup analysis results based on treatment duration and methodological quality are presented in Table 2.

VAS

There were 12 studies [14, 33, 35–39, 42, 45, 48, 49, 51] reporting the data of VAS. The pooled estimate showed that the VAS score was significantly lower in the PRP group than in the control group (WMD = − 0.86, 95%CI − 1.20, − 0.52; $P < 0.001$) (Fig. 4).

Subgroup analysis results based on disease type, treatment duration, and methodological quality are presented in Table 2.

KOOS

KOOS symptoms

For KOOS symptoms, there were four studies [12, 36, 40, 43] comparing the difference between PRP with control. The pooled estimate showed that PRP had a similar KOOS symptom score with control (WMD = 1.53, 95%CI − 2.79, 5.85; $P = 0.487$) (Fig. 5). Sensitivity analysis was performed by excluding the trial with outlier [36], the overall estimate changed a little (WMD = 3.11, 95%CI − 0.86, 7.09; $P = 0.125$), but the heterogeneity was still present (I^2 = 86.5%, $P < 0.001$).

Subgroup analysis results based on treatment duration and methodological quality are presented in Table 2.

KOOS pain

There were four studies [12, 36, 40, 43] reporting the data of KOOS pain between PRP and control groups. The pooled estimates using the random-effects model showed that PRP was associated with a similar KOOS pain score with other injections (WMD = 2.30, 95%CI − 0.54, 5.14; $P = 0.113$). Sensitivity analysis was performed by excluding the trial by Paterson, KL et al. [36] with outlier data, and the result suggested that PRP had a significantly higher KOOS pain score

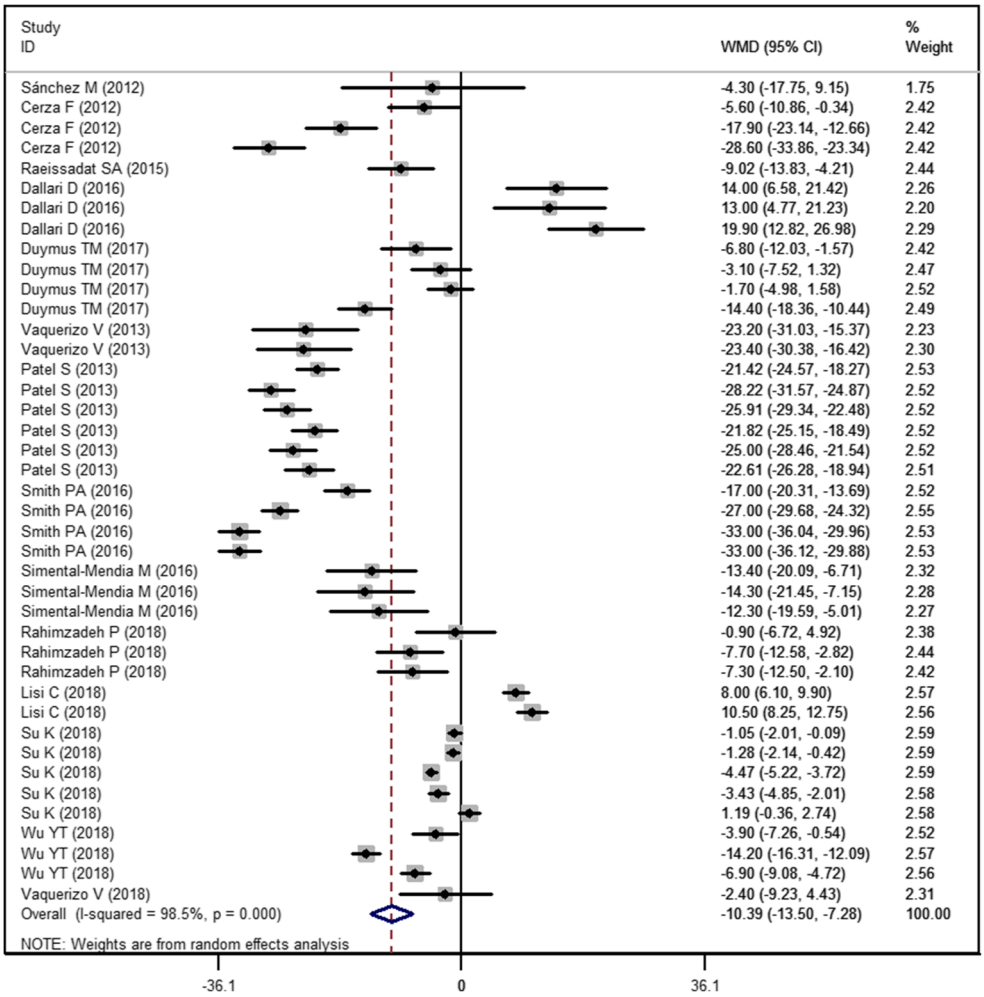

Fig. 3 Forest plot showing the effect of PRP on the total WOMAC score

than control (WMD = 3.27, 95%CI 0.73, 5.81; $P = 0.012$). However, the heterogeneity was still present ($I^2 = 62.8\%$, $P = 0.006$).

KOOS function

KOOS function was reported in four studies [12, 36, 40, 43]. Pooled analysis using the random-effects model showed that there was no significant difference between PRP and control in terms of KOOS function score (WMD = 2.84, 95%CI − 1.16, 6.85; $P = 0.164$). When we excluded the trial with outlier [36], the pooled result of remaining studies altered a lot (WMD = 4.15, 95%CI 0.41, 7.89; $P = 0.030$), but the heterogeneity was still present ($I^2 = 82.8\%$, $P < 0.001$).

KOOS sport

There were four studies [12, 36, 40, 43] reporting the data of KOOS sport. The pooled estimates showed that patients treated with PRP had a similar KOOS sport score compared with those with other injections (WMD = − 0.73, 95%CI − 3.95, 2.48; $P = 0.655$). Sensitivity analysis by excluding the trial with outlier showed that the summarized estimate did not alter substantially (WMD = − 0.54, 95%CI − 3.51, 2.44; $P = 0.723$), but the heterogeneity changed a little ($I^2 = 45.8\%$, $P = 0.064$).

KOOS quality of life

There were four studies [12, 36, 40, 43] reporting the data of KOOS QoL. Meta-analysis using a fixed-effects model showed that PRP had a significantly higher KOOS QoL score than other injections (WMD = 4.32, 95%CI 3.35, 5.29; $P < 0.001$).

IKDC

Four studies reported the data of IKDC [12, 32, 40, 45]. The aggregated data indicated that the IKDC score was

Table 2 Subgroup analysis results of the outcomes based on disease type, comparator, treatment duration, and methodological quality

	Total WOMAC score	WOMAC pain score	WOMAC stiffness score	WOMAC physical function score	VAS	KOOS symptoms
Disease type						
Knee OA	WMD = − 12.95, 95%CI − 15.46, − 9.09; $P < 0.001$	WMD = − 2.85, 95%CI − 3.45, − 2.28; $P < 0.001$	WMD = − 0.92, 95%CI − 1.24, − 0.61; $P < 0.001$	NA	WMD = − 0.94, 95%CI − 1.30, − 0.58; $P < 0.001$	NA
Hip OA	WMD = 15.95, 95%CI 11.60, 20.30; $P < 0.001$	WMD = 24.60, 95%CI 6.10, 43.10; $P = 0.009$	WMD = 6.93, 95%CI − 8.32, 22.17; $P = 0.373$	NA	WMD = − 0.67, 95%CI − 1.56, 0.22; $P = 0.140$	NA
Comparator						
HA	WMD = − 3.74, 95%CI − 6.35, − 1.14; $P = 0.005$	WMD = − 1.62, 95%CI − 2.15, − 1.10; $P < 0.001$	NA	NA	NA	NA
Normal saline	WMD = − 21.04, 95%CI − 27.48, − 14.58; $P < 0.001$	WMD = − 5.04, 95%CI − 5.99, − 4.10; $P < 0.001$	NA	NA	NA	NA
Acetaminophen	WMD = − 13.35, 95%CI − 17.41, − 9.29; $P < 0.001$	WMD = − 2.22, 95%CI − 3.14, − 1.53; $P < 0.001$	NA	NA	NA	NA
Prolotherapy	WMD = − 5.54, 95%CI − 9.64, − 1.43; $P < 0.001$	WMD = − 1.41, 95%CI − 2.23, − 0.58; $P < 0.001$	NA	NA	NA	NA
Treatment duration						
1 month	WMD = − 3.11, 95%CI − 5.54, − 0.68; $P = 0.012$	WMD = − 0.48, 95%CI − 1.37, − 0.22; $P = 0.008$	WMD = − 0.12, 95%CI − 0.56, − 0.02; $P = 0.04$	WMD = − 1.73, 95%CI − 2.85, − 0.61, $P = 0.002$	WMD = − 0.62, 95%CI − 1.58, − 0.34; $P = 0.004$	WMD = 7.11, 95%CI − 7.15, 21.36; $P = 0.328$
2 months	WMD = − 3.90, 95%CI − 19.26, − 1.45; $P = 0.018$	WMD = − 2.88, 95%CI − 5.14, − 0.63; $P = 0.012$	WMD = − 1.26, 95%CI − 2.73, − 0.21; $P = 0.018$	WMD = − 9.36, 95%CI − 16.80, − 1.92, $P = 0.014$	WMD = − 7.91, 95%CI − 20.91, − 5.10; $P = 0.033$	WMD = 4.39, 95%CI − 2.03, 10.81; $P = 0.180$
3 months	WMD = − 16.38, 95%CI − 25.60, − 7.06; $P = 0.001$	WMD = − 3.98, 95%CI − 5.92, − 2.03; $P < 0.001$	WMD = − 1.15, 95%CI − 1.64, − 0.67; $P < 0.001$	WMD = − 11.15, 95%CI − 17.02, − 5.28, $P < 0.001$	WMD = − 0.83, 95%CI − 1.42, − 0.25; $P = 0.005$	WMD = − 22.30,95%CI −3 6.10, − 8.50; $P = 0.002$
6 months	WMD = − 11.65, 95%CI − 18.31, − 4.99; $P = 0.001$	WMD = − 3.15, 95%CI − 4.35, − 1.95; $P < 0.001$	WMD = − 0.83, 95%CI − 1.53, − 0.13; $P = 0.02$	WMD = − 9.32, 95%CI − 14.30, − 4.33, $P < 0.001$	WMD = − 1.13, 95%CI − 1.86, − 0.40; $P = 0.002$	WMD = 0.77, 95%CI − 3.17, 4.71; $P = 0.701$
12 months	WMD = − 6.96, 95%CI − 17.73, 3.81; $P = 0.205$	WMD = − 2.91, 95%CI − 4.36, − 1.47; $P < 0.001$	WMD = − 1.33, 95%CI − 2.25, − 0.41; $P = 0.004$	WMD = − 11.59, 95%CI − 19.14, − 4.05, $P = 0.003$	WMD = − 1.02, 95%CI − 1.96, − 0.07; $P = 0.035$	WMD = − 0.53, 95%CI − 4.61, 3.55; $P = 0.798$
18 months	WMD = 1.19, 95%CI − 0.36, 2.74; $P = 0.132$	WMD = 0.25, 95%CI − 0.049,0.549; $P = 0.101$	WMD = − 0.17, 95%CI − 0.53, 0.19; $P = 0.353$	WMD = − 2.21, 95%CI − 3.71, − 0.71, $P = 0.004$	WMD = 0.12, 95%CI − 0.05, 0.29; $P = 0.171$	NA
Methodological quality						
Low risk of bias	WMD = − 15.11, 95%CI − 21.39, − 8.83; $P < 0.001$	WMD = − 3.81, 95%CI − 4.63, − 2.30, $P < 0.001$	WMD = − 1.00, 95%CI − 1.40, − 0.60, $P < 0.001$	WMD = − 11.94, 95%CI − 15.35, − 8.52, $P < 0.001$	WMD = − 0.96, 95%CI − 1.54, − 0.38, $P = 0.001$	WMD = 10.70, 95%CI 8.35, 13.05; $P < 0.001$
Unclear risk of bias	WMD = − 4.70, 95%CI − 6.54, 2.85; $P = 0.298$	WMD = − 0.65, 95%CI − 1.23, − 0.07, $P = 0.028$	WMD = − 0.55, 95%CI − 0.84, − 0.26, $P < 0.001$	WMD = − 3.56, 95%CI − 4.73, − 2.40, $P < 0.001$	WMD = − 0.40, 95%CI − 0.69, − 0.11, $P = 0.006$	NA

Table 2 (continued)

	Total WOMAC score	WOMAC pain score	WOMAC stiffness score	WOMAC physical function score	VAS	KOOS symptoms
High risk of bias	WMD = − 2.23, 95%CI − 14.87, 10.41; $P = 0.729$	WMD = − 1.05, 95%CI − 2.16, 0.056; $P = 0.063$	WMD = − 0.95, 95%CI − 1.43, − 0.47, $P < 0.001$	WMD = − 6.32, 95%CI − 9.82, − 2.83, $P < 0.001$	WMD = − 7.82, 95%CI − 11.07, − 4.57, $P < 0.001$	WMD = − 0.75, 95%CI − 3.93, 2.42; $P = 0.641$

Abbreviations: *OA*, osteoarthritis; *WOMAC*, Western Ontario and McMaster; *KOOS*, Knee Injury and Osteoarthritis Outcome Score; *VAS*, Visual Analog Scale; *PRP*, platelet-rich plasma; *PA-PRP*, photo-activated *PRP*; HA, hyaluronic acid; *WMD*, weight mean difference; *CI*: confidence interval; *NA*, not available

significantly improved in the PRP group than in the control group (WMD = 6.95, 95%CI 2.15, 11.74; $P = 0.005$). The test for heterogeneity was significant ($I^2 = 93.3\%$, $P < 0.001$).

HHS

Two studies [37, 38] reported the data of HHS. Pooled data showed that there was a significant improvement in HHS score in the PRP group than in the control group (WMD = 6.63, 95%CI 5.21, 8.05; $P < 0.001$). The test for heterogeneity was significant ($I^2 = 83.6\%$, $P < 0.001$).

Meta-regression

To further evaluate the influence of potential factors on the total WOMAC score, some meta-regression analyses were performed. Our results suggested that age ($t = 5.32$, $P < 0.001$) (Supplementary figure 1) had a significant impact on the difference in total WOMAC score between PRP and

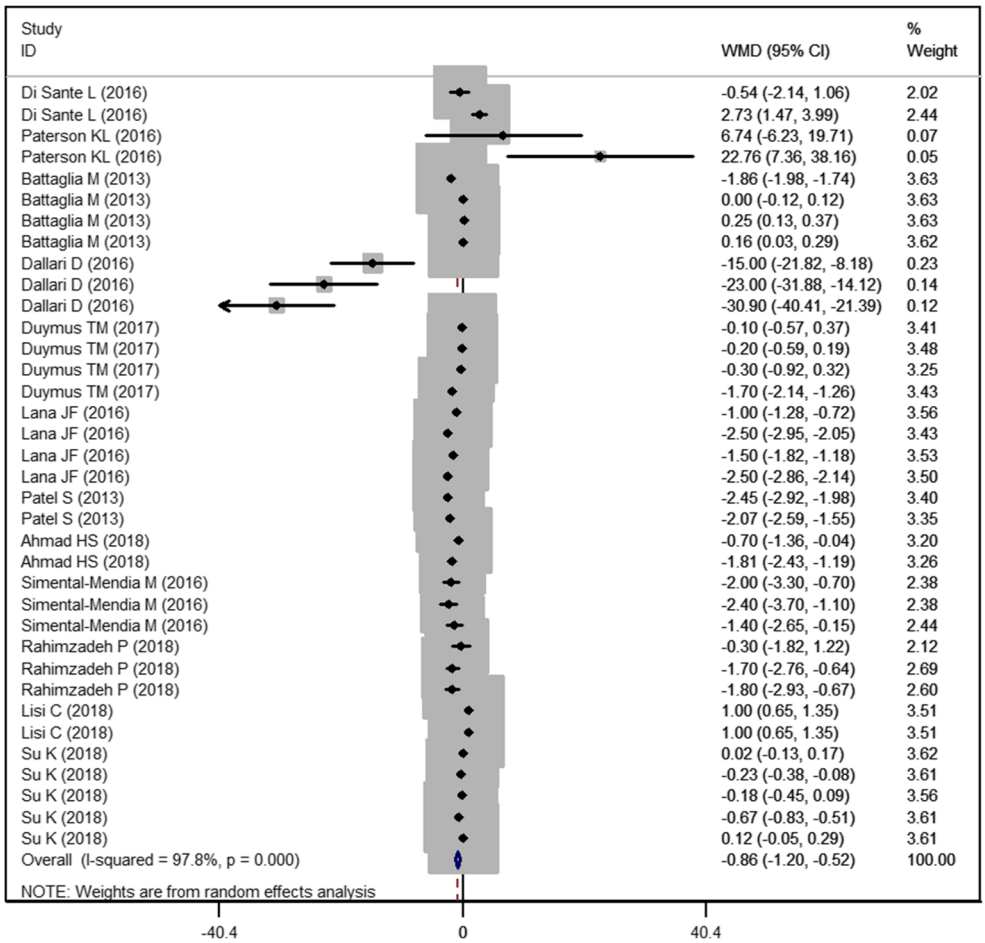

Fig. 4 Forest plot showing the effect of PRP on the VAS score

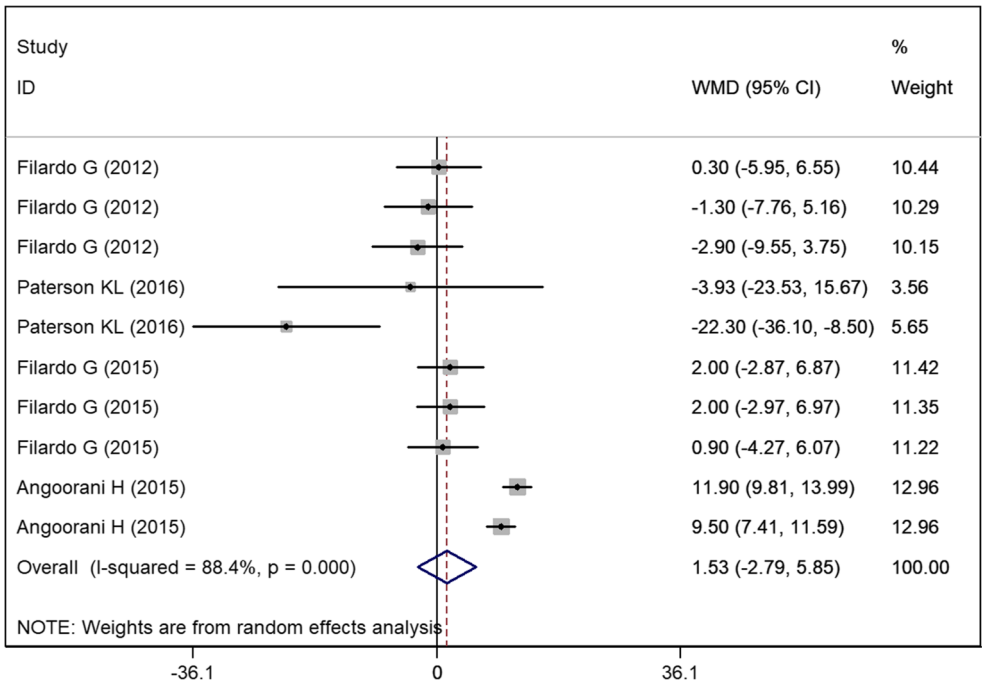

Fig. 5 Forest plot showing the effect of PRP on KOOS symptom score

controls, whereas male sex ($t = -0.87$, $P = 0.392$), BMI ($t = -1.07$, $P = 0.294$), and grade of OA ($t = -0.19$, $P = 0.854$) did not (Supplementary figure 2, 3, 4).

Publication bias

Publication bias was assessed using Begg and Egger's test, in which a P value < 0.05 demonstrated the existence of potential publication bias. As shown by our results, the P values of Begg and Egger's test for all meta-analysis were greater than 0.05, indicating the absence of publication bias among the included studies.

Discussion

PRP has been widely used in several medical fields, such as dentistry, dermatology, and ophthalmology [17]. However, in recent years, there has been an increased use of PRP for the treatment of OA. This present meta-analysis collected the evidence of RCTs to investigate the effects of intra-articular injection of PRP in the treatment of knee and hip OA. The summarized data revealed that PRP significantly improved the WOMAC score, VAS score, IKDC score, and HHS score as compared with comparators. This beneficial effect was only observed at short-term follow-up (1, 2, 3, 6, 12 months), but not at long-term follow-up. Moreover, these positive results were also confirmed in studies with a low risk of bias. However, no significant benefit of PRP was observed over the comparators in terms of the KOOS score.

There are a few numbers of systematic review and meta-analysis [17, 18, 20, 56, 57] that have been published with the purpose to investigate the effects of PRP in OA, and their results demonstrated the treatment effect of PRP in improving the functional recovery and pain relief in OA patients. However, these results were obtained based on studies with limited statistical power, methodological errors (inclusion criteria and data extraction), or low quality of evidence. Chang et al. [56] compared the different outcome measurements between PRP and HA for knee OA. However, half of the included studies for analysis were case series, and only 5 of them were RCTs [56]. Laudy et al. [57] pooled ten randomized or non-randomized controlled trials to investigate the effects of PRP on pain relief and functional recovery. Nonetheless, most of their results were obtained based on only 1 or 2 studies because of the small number of RCTs used for data analysis. Another meta-analysis of Kanchanatawan et al. [18] included 9 RCTs to compare the effects of PRP with placebo or HA in knee OA patients. Their results demonstrated better outcomes of PRP in some clinical measures when compared with HA or placebo [18]. This conclusion was limited by the small sample size and medium to high risk of bias of included studies. Shen et al. [20] selected a greater number of RCTs ($n = 14$) for data analysis in patients with knee OA, and their results showed the superior effect of PRP over other intra-articular injections in terms of knee pain and physical function at 3, 6, and 12 months post-injection [20]. However, none of the included RCTs was regarded as being low risk of bias. Blinding to participants, which is crucial controlling placebo effects, has not been successfully

performed in around half the included trials. This is more inclined to result in overestimated effects of PRP. Again, the positive findings might not be reliable since the pooled estimate was calculated based on RCTs with low-quality evidence, and one of the included studies did not meet the inclusion criteria and provided inappropriate method for the measure estimates between PRP and HA.

To address the shortcomings of the previously published meta-analysis, we not only included more recently published RCTs regarding the effect of PRP for knee or hip OA but also performed subgroup analysis based on methodological quality to provide the most rigorous and complete evidence. In addition, in order to explore the potential sources of heterogeneity, which was also observed in the previous meta-analysis, we performed sensitivity analysis and meta-regression analysis. The results revealed that age might have an impact on the difference in the total WOMAC score between PRP and comparators. Another important highlight of our study relates to assessing the long-term effect of PRP in OA patients by comparing it with other intra-injections, which has not been investigated in the previous meta-analysis.

In the present study, we evaluated the effects of PRP in the knee or hip OA patients. Results from RCTs with the knee OA supported the beneficial effect of PRP over other intra-injections, which were consistent with the previous meta-analysis [8, 15, 56–58] whereas in the hip OA, our results only indicated the better effect of PRP in the outcomes of total WOMAC score, but not in some other outcome measurements (such as KOOS score, VAS score). From the studies reporting effects of PRP in hip OA, we found that their results have been conflicting. Dallari et al. [38] reported the significant clinical improvement of PRP in VAS and total WOMAC score at 2 and 6 months, but not at 12 months, as compared with HA. However, in another two RCTs [35, 37] investigating the effects of PRP in hip OA, the authors failed to find the differences between PRP and HA, although functional improvement and pain reduction in PRP was observed, but that was not superior to HA. This might be explained by the limited statistical power owing to the small sample size in the studies [35, 37].

Concerning the duration period of the favorable effect of PRP, it remains uncertain in the previous meta-analysis. Our results demonstrated that PRP was more effective than other intra-articular injections in improving physical function and reducing pain through 1 to 12 months, but not at 18 months. Filardo et al. [59] performed a clinical trial in knee OA to investigate the persistent effect of intra-injection PRP at the 24 months. The results revealed that all the evaluated parameters (including IKDC, EQ-VAS) were significantly lower at the 24 months as compared with that at 12 months, but were still higher than the baseline level [59]. The authors concluded that the median duration of the beneficial effect for PRP was 9 months [59]. The short-term effect of intra-injection PRP suggests that PRP might have a temporary impact on the joint milieu, but have no effects on the joint structure or progression of knee OA.

Although several innovations have been performed in this meta-analysis, the data analyses for some evaluated outcomes are limited by several biases. First, despite no restriction on the language was imposed for the study selection, all the included RCTs were English-language, which might increase the risk of selection bias. Second, there was substantial heterogeneity identified among the included studies; thus, we performed sensitivity analysis and met-regression analysis to explore the potential sources. However, meta-regression analysis was carried out only based on the characteristics of patient population (such as age, gender, BMI, and grade of OA). Some other clinical variables, such as outcome measures and PRP regimens, which might account for the heterogeneity and influence the pooled estimate, were not included for the meta-regression analysis because of the insufficient data across included trials.

In conclusion, intra-articular PRP injection provided better effects than other intra-articular injections for OA patients, especially in those with knee OA, in terms of pain reduction and function improvement at the short-term follow-up (1, 2, 3, 6, 12 months). Further larger scale, double-blinded RCTs are needed to assess the effects of PRP in patients hip OA.

Authors' contributions YD and XS contributed to the study design; all authors collected the data and performed the data analysis; all authors prepared the manuscript.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethics approval and consent to participate Ethics approval and consent to participate are not suitable for a meta-analysis.

Consent for publication Not applicable.

Disclosures None.

References

1. Richmond J, Hunter D, Irrgang J, Jones MH, Snyder-Mackler L, Van Durme D, Rubin C, Matzkin EG, Marx RG, Levy BA, Watters WC 3rd, Goldberg MJ, Keith M, Haralson RH 3rd, Turkelson CM, Wies JL, Anderson S, Boyer K, Sluka P, St Andre J, McGowan R (2010) American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis (OA) of the knee. J Bone Joint Surg Am 92(4):990–993. https://doi.org/10.2106/jbjs.i.00982
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F (2008) Estimates of the prevalence

of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 58(1):26–35. https://doi.org/10.1002/art.23176
3. Verkleij SP, Luijsterburg PA, Bohnen AM, Koes BW, Bierma-Zeinstra SM (2011) NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. Osteoarthr Cartil 19(8):921–929. https://doi.org/10.1016/j.joca.2011.04.013
4. Jevsevar DS (2013) Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg 21(9):571–576. https://doi.org/10.5435/jaaos-21-09-571
5. Hirsch G, Kitas G, Klocke R (2013) Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief–a systematic review. Semin Arthritis Rheum 42(5):451–473. https://doi.org/10.1016/j.semarthrit.2012.08.005
6. Montanez-Heredia E, Irizar S, Huertas PJ, Otero E, Del Valle M, Prat I, Diaz-Gallardo MS, Peran M, Marchal JA, Hernandez-Lamas Mdel C (2016) 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 17(7). https://doi.org/10.3390/ijms17071064
7. Campbell KA, Saltzman BM, Mascarenhas R, Khair MM, Verma NN, Bach BR Jr, Cole BJ (2015) Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. Arthroscopy 31(11):2213–2221. https://doi.org/10.1016/j.arthro.2015.03.041
8. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD (2016) Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. Arthroscopy 32(3):495–505. https://doi.org/10.1016/j.arthro.2015.08.005
9. Amable PR, Carias RB, Teixeira MV, da Cruz PI, Correa do Amaral RJ, Granjeiro JM, Borojevic R (2013) Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther 4(3):67. https://doi.org/10.1186/scrt218
10. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA (2009) Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med 37(11):2259–2272. https://doi.org/10.1177/0363546509349921
11. Cerza F, Carni S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, De Biasi G, Ciuffreda M (2012) Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med 40(12):2822–2827. https://doi.org/10.1177/0363546512461902
12. Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M (2012) Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord 13:229. https://doi.org/10.1186/1471-2474-13-229
13. Raeissadat SA, Rayegani SM, Hassanabadi H, Fathi M, Ghorbani E, Babaee M, Azma K (2015) Knee osteoarthritis injection choices: platelet- rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). Clin Med Insights Arthritis Musculoskelet Disord 8:1–8. https://doi.org/10.4137/cmamd.s17894
14. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A (2013) Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med 41(2):356–364. https://doi.org/10.1177/0363546512471299
15. Anitua E, Sanchez M, Aguirre JJ, Prado R, Padilla S, Orive G (2014) Efficacy and safety of plasma rich in growth factors intra-articular infiltrations in the treatment of knee osteoarthritis. Arthroscopy 30(8):1006–1017. https://doi.org/10.1016/j.arthro.2014.05.021
16. Di Y, Han C, Zhao L, Ren Y (2018) Is local platelet-rich plasma injection clinically superior to hyaluronic acid for treatment of knee osteoarthritis? A systematic review of randomized controlled trials. Arthritis Res Ther 20(1):128. https://doi.org/10.1186/s13075-018-1621-0
17. Bennell KL, Hunter DJ, Paterson KL (2017) Platelet-rich plasma for the management of hip and knee osteoarthritis. Curr Rheumatol Rep 19(5):24. https://doi.org/10.1007/s11926-017-0652-x
18. Kanchanatawan W, Arirachakaran A, Chaijenkij K, Prasathaporn N, Boonard M, Piyapittayanun P, Kongtharvonskul J (2016) Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 24(5):1665–1677. https://doi.org/10.1007/s00167-015-3784-4
19. Han Y, Huang H, Pan J, Lin J, Zeng L, Liang G, Yang W, Liu J (2019) Meta-analysis comparing platelet-rich plasma vs hyaluronic acid injection in patients with knee osteoarthritis. Pain Med 20:1418–1429. https://doi.org/10.1093/pm/pnz011
20. Shen L, Yuan T, Chen S, Xie X, Zhang C (2017) 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 12(1):16. https://doi.org/10.1186/s13018-017-0521-3
21. Ye Y, Zhou X, Mao S, Zhang J, Lin B (2018) Platelet rich plasma versus hyaluronic acid in patients with hip osteoarthritis: a meta-analysis of randomized controlled trials. Int J Surg 53:279–287. https://doi.org/10.1016/j.ijsu.2018.03.078
22. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj 339:b2535. https://doi.org/10.1136/bmj.b2535
23. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 343:d5928. https://doi.org/10.1136/bmj.d5928
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Bmj 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
25. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
26. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22(4):719–748
27. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. Bmj 315(7109):629–634
28. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4):1088–1101
29. Granero-Molto F, Padilla S, Fiz N, Prosper F, Pompei O, Perez JC, Azofra J, Sanchez M, Delgado D, Sanchez P, Muinos-Lopez E, Paiva B (2016) Combination of intra-articular and Intraosseous injections of platelet rich plasma for severe knee osteoarthritis: a pilot study. Biomed Res Int 2016:4868613–4868610. https://doi.org/10.1155/2016/4868613
30. Taniguchi Y, Yoshioka T, Kanamori A, Aoto K, Sugaya H, Yamazaki M (2018) Intra-articular platelet-rich plasma (PRP) injections for treating knee pain associated with osteoarthritis of the knee in the Japanese population: a phase I and IIa clinical trial. Nagoya J Med Sci 80(1):39–51. https://doi.org/10.18999/nagjms.80.1.39
31. Bastos R, Mathias M, Andrade R, Bastos R, Balduino A, Schott V, Rodeo S, Espregueira-Mendes J (2018) Intra-articular injections of expanded mesenchymal stem cells with and without addition of platelet-rich plasma are safe and effective for knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 26(11):3342–3350. https://doi.org/10.1007/s00167-018-4883-9

32. Gormeli G, Gormeli CA, Ataoglu B, Colak C, Aslanturk O, Ertem K (2017) 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 25(3):958–965. https://doi.org/10.1007/s00167-015-3705-6
33. Rahimzadeh P, Imani F, Faiz SHR, Entezary SR, Zamanabadi MN, Alebouyeh MR (2018) The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. Clin Interv Aging 13:73–79. https://doi.org/10.2147/cia.s147757
34. Sanchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, Garcia Gutierrez A, Albillos J, Garate R, Aguirre JJ, Padilla S, Orive G, Anitua E (2012) 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 28(8):1070–1078. https://doi.org/10.1016/j.arthro.2012.05.011
35. Di Sante L, Villani C, Santilli V, Valeo M, Bologna E, Imparato L, Paoloni M, Iagnocco A (2016) Intra-articular hyaluronic acid vs platelet-rich plasma in the treatment of hip osteoarthritis. Med Ultrason 18(4):463–468. https://doi.org/10.11152/mu-874
36. Paterson KL, Nicholls M, Bennell KL, Bates D (2016) Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: a double-blind, randomized controlled pilot study. BMC Musculoskelet Disord 17:67. https://doi.org/10.1186/s12891-016-0920-3
37. Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S (2013) Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics 36(12):e1501–e1508
38. Dallari D, Stagni C, Rani N, Sabbioni G, Pelotti P, Torricelli P, Tschon M, Giavaresi G (2016) 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 44(3):664–671. https://doi.org/10.1177/0363546515620383
39. Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN (2017) Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc 25(2):485–492. https://doi.org/10.1007/s00167-016-4110-5
40. Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E (2015) Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. Am J Sports Med 43(7):1575–1582. https://doi.org/10.1177/0363546515582027
41. Vaquerizo V, Plasencia MA, Arribas I, Seijas R, Padilla S, Orive G, Anitua E (2013) 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 29(10):1635–1643. https://doi.org/10.1016/j.arthro.2013.07.264
42. Lana JF, Weglein A, Sampson SE, Vicente EF, Huber SC, Souza CV, Ambach MA, Vincent H, Urban-Paffaro A, Onodera CM, Annichino-Bizzacchi JM, Santana MH, Belangero WD (2016) 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 12(2):69–78
43. Angoorani H, Mazaherinezhad A, Marjomaki O, Younespour S (2015) Treatment of knee osteoarthritis with platelet-rich plasma in comparison with transcutaneous electrical nerve stimulation plus exercise: a randomized clinical trial. Med J Islam Repub Iran 29:223
44. Smith PA (2016) Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: an FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial. Am J Sports Med 44(4):884–891. https://doi.org/10.1177/0363546515624678
45. Ahmad HS, Farrag SE, Okasha AE, Kadry AO, Ata TB, Monir AA, Shady I (2018) Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. Int J Rheum Dis 21(5):960–966. https://doi.org/10.1111/1756-185x.13315
46. Vaquerizo V, Padilla S, Aguirre JJ, Begona L, Orive G, Anitua E (2018) Two cycles of plasma rich in growth factors (PRGF-Endoret) intra-articular injections improve stiffness and activities of daily living but not pain compared to one cycle on patients with symptomatic knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 26(9):2615–2621. https://doi.org/10.1007/s00167-017-4565-z
47. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA (2017) 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 45(2):339–346. https://doi.org/10.1177/0363546516665809
48. Lisi C, Perotti C, Scudeller L, Sammarchi L, Dametti F, Musella V, Di Natali G (2018) Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Clin Rehabil 32(3):330–339. https://doi.org/10.1177/0269215517724193
49. Su K, Bai Y, Wang J, Zhang H, Liu H, Ma S (2018) 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 37(5):1341–1350. https://doi.org/10.1007/s10067-018-3985-6
50. Wu YT, Hsu KC, Li TY, Chang CK, Chen LC (2018) Effects of platelet-rich plasma on pain and muscle strength in patients with knee osteoarthritis. Am J Phys Med Rehabil 97(4):248–254. https://doi.org/10.1097/phm.0000000000000874
51. Simental-Mendia M, Vilchez-Cavazos JF, Pena-Martinez VM, Said-Fernandez S, Lara-Arias J, Martinez-Rodriguez HG (2016) Leukocyte-poor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis. Arch Orthop Trauma Surg 136(12):1723–1732. https://doi.org/10.1007/s00402-016-2545-2
52. Dold AP, Zywiel MG, Taylor DW, Dwyer T, Theodoropoulos J (2014) Platelet-rich plasma in the management of articular cartilage pathology: a systematic review. Clin J Sport Med 24(1):31–43. https://doi.org/10.1097/01.jsm.0000432855.85143.e5
53. Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A (2012) Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil 91(5):411–417. https://doi.org/10.1097/PHM.0b013e3182aab72
54. Tietze DC, Geissler K, Borchers J (2014) The effects of platelet-rich plasma in the treatment of large-joint osteoarthritis: a systematic review. Phys Sportsmed 42(2):27–37. https://doi.org/10.3810/psm.2014.05.2055
55. Sundaram K, Vargas-Hernandez JS, Sanchez TR, Moreu NM, Mont MA, Higuera CA, Piuzzi NS (2019) Are subchondral intraosseous injections effective and safe for the treatment of knee osteoarthritis? A systematic review. J Knee Surg 32:1046–1057. https://doi.org/10.1055/s-0039-1677792
56. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS (2014) Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. Arch Phys Med Rehabil 95(3):562–575. https://doi.org/10.1016/j.apmr.2013.11.006

57. Laudy AB, Bakker EW, Rekers M, Moen MH (2015) Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. Br J Sports Med 49(10):657–672. https://doi.org/10.1136/bjsports-2014-094036
58. Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, Gandhi R, Takhar K, Lum G, Chahal J (2013) The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy 29(12):2037–2048. https://doi.org/10.1016/j.arthro.2013.09.006
59. Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M (2011) Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc 19(4):528–535. https://doi.org/10.1007/s00167-010-1238-6