Knee Surg Sports Traumatol Arthrosc (2016) 24:1665–1677
DOI 10.1007/s00167-015-3784-4

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Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee

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Received: 5 May 2015 / Accepted: 8 September 2015 / Published online: 19 September 2015

Abstract

Purpose To compare the clinical outcomes of osteoarthritis indices (WOMAC and Lequesne scores) and adverse events in the treatment of osteoarthritis (OA) of the knee with platelet-rich plasma (PRP) versus hyaluronic acid (HA) or placebo.

Methods A systematic review and meta-regression were performed to compare outcomes between PRP injections versus HA or placebo. Relevant randomized control trials were identified from Medline and Scopus from date of inception to 13 August 2015.

Results Nine of 551 studies were eligible; 6, 5, 5, 5, 2, 2, 2 and 7 studies were included in pooling of WOMAC total, pain, stiffness and function scores, Lequesne score, IKDC score, EQ-VAS score and adverse events in OA knee patients, respectively. The PRP injections had −15.4 (95 % CI −28.6, −2.3, $p = 0.021$), lower mean WOMAC total scores, and 8.83 (95 % CI 5.88, 11.78, $p < 0.001$), 7.37 (95 % CI 4.33, 10.05, $p = 0.021$) higher mean IKDC and EQ-VAS scores when compared to HA injections. However, PRP injections had no significant differences in WOMAC pain, stiffness and function scores, as well as Lequesne score and adverse events when compared to HA or placebo.

Conclusion In short-term outcomes (≤1 year), PRP injection has improved functional outcomes (WOMAC total scores, IKDC score and EQ-VAS) when compared to HA and placebo, but has no statistically significant difference in adverse events when compared to HA and placebo. This study suggests that PRP injection is more efficacious than HA injection and placebo in reducing symptoms and improving function and quality of life. It has the potential to be the treatment of choice in patients with mild-to-moderate OA of the knee who have not responded to conventional treatment.

Electronic supplementary material The online version of this article (doi:10.1007/s00167-015-3784-4) contains supplementary material, which is available to authorized users.

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Level of evidence I.

Keywords Platelet-rich plasma · Hyaluronic acid · PRP · HA · Meta-analysis · Osteoarthritis

Introduction

Osteoarthritis (OA) is a degenerative joint disease that is common in the elderly population [9, 22]. Treatment goals include pain relief, improvement in knee function, improved quality of life and reduction in disability. Unfortunately, there are currently no pharmacologic agents available that can halt OA progression and reverse any existing damage. Current therapeutic approaches focus on developing less invasive procedures and applying interventions earlier in the disease progression, when the structural changes of OA may still be prevented or delayed [30, 34]. Recent developments in biologic research have highlighted the importance of growth factors in maintenance of normal tissue structure and tissue lesion repair [17, 31]. Several studies describe the use of biological therapies such as platelet-rich plasma (PRP) as effective and safe methods in the treatment of pain and joint dysfunction caused by knee OA. There is an increasing amount of evidence supporting the potential benefits of plasma that is rich in growth factors, which is an autologous PRP that is characterized by leucocytes (rich or poor) [28], pro-inflammatory cytokines and the presence of a specific dose of platelets and growth factors [4]. The use of this autologous biological therapy has been shown to enhance tissue repair and reduce tissue inflammation [3, 29]. Several randomized controlled trials [7, 12, 24, 26, 27, 30, 33] have shown favourable results of intra-articular PRP injections when compared to hyaluronic acid (HA) [7, 12, 26, 30, 33] and placebo injections [24, 27] in patients with cartilage damage and OA of the knee. However, the results also displayed negative outcomes. Five network meta-analyses [6, 8, 16, 18, 19] have been published recently. Four of these meta-analyses [8, 16, 18, 19] that pooled RCTs and comparative studies were inconclusive regarding the efficacy of PRP. The most recently published meta-analysis [6] was a systematic review of overlapping meta-analyses, and this meta-analysis found that although PRP injection improves knee symptoms for up to 12 months, there appears to be an increased risk of adverse reaction associated with its use. All of the meta-analyses did not strictly pool outcomes from studies of high methodological quality (RCTs) as there were very few RCTs available for review at the time. Sources of heterogeneity (e.g. grade of OA, age, sex, BMI and type of PRP) were also not assessed. Additional RCTs [11, 13, 26, 27] have since been published. Therefore, we conducted a systematic review and meta-analysis comparing clinical outcomes when treating osteoarthritis of the knee by injecting intra-articular PRP as compared to hyaluronic acid (HA) or placebo. The clinical outcomes of interest were osteoarthritis indices (WOMAC and Lequesne scores) and adverse events.

Materials and methods

Search strategy

The Medline and Scopus databases were used to identify relevant studies published in English from the date of inception to 13 August 2015. The PubMed and Scopus search engines were used to locate studies using the following search terms: [(osteoarthritis knee OR gonarthrosis OR elderly) AND (platelet rich plasma OR platelet concentrate OR PRP OR platelet derived growth factors OR PRGF) AND (visual analog score OR WOMAC score OR Lequesne score OR pain OR function OR radiographic grading OR X-ray) AND (clinical trial OR RCT OR randomized controlled trial)]. Search strategies for Medline and Scopus are described in the (Appendix in Electronic Supplementary Material). Relevant studies from the reference lists of identified studies and previous systematic reviews were also explored.

Selection of studies

Identified studies were selected by two authors (W.K. and A.A.) and randomly checked by (J.K.). Titles and abstracts were initially screened; full papers were then retrieved if a decision could not be made from the abstracts. The reasons for ineligibility or exclusion of studies were recorded and described (Fig. 1).

Inclusion criteria

Randomized controlled trials or quasi-experimental designs comparing clinical outcomes between treatments in primary OA patients knee were eligible if they met the following criteria:

- Compared clinical outcomes between platelet-rich plasma (PRP) with hyaluronic acid, normal saline solution or placebo (no treatment).
- Compared at least one of following outcomes: range of motion, adverse events, function score, osteoarthritis indices including WOMAC total score, WOMAC sub-scores Lequesne algofunctional index (Lequesne scores), IKDC subjective score and EQ-VAS.
- Had sufficient data to extract and pool, i.e. reported mean, standard deviation (SD) and numbers of subjects according to treatments for continuous outcomes; number of patients according to treatment for dichotomous outcomes.

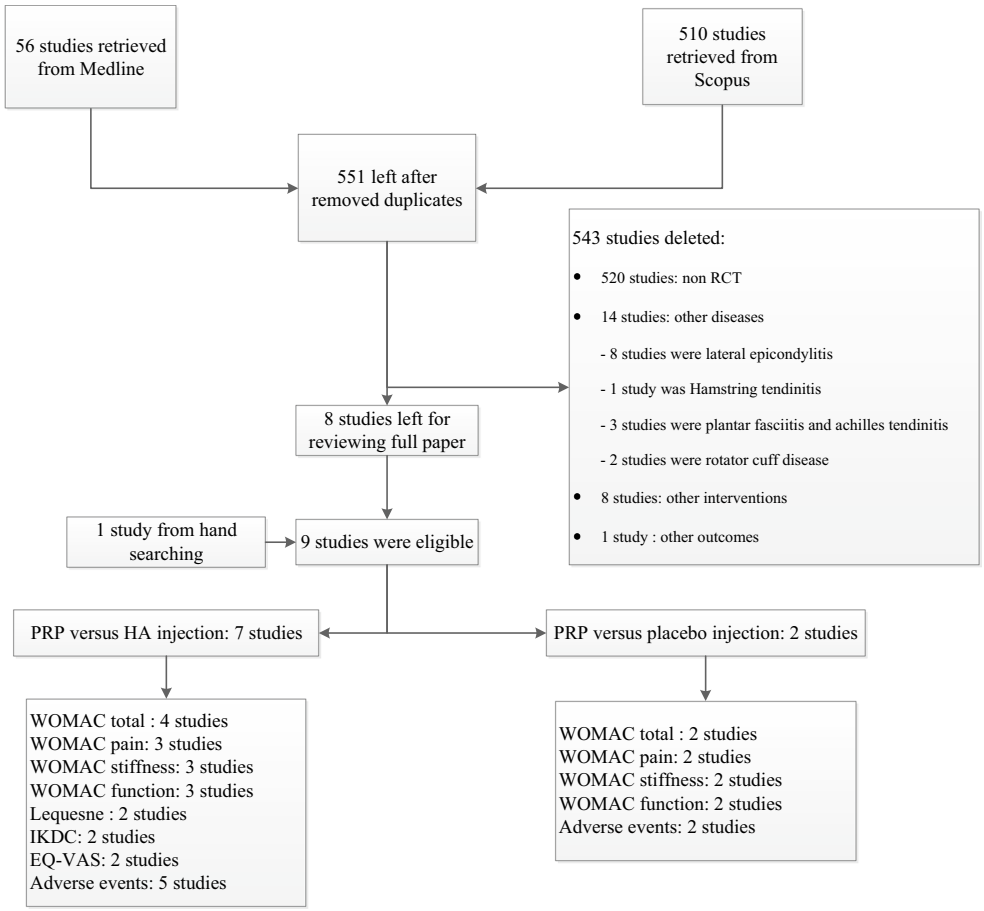

Fig. 1 Flow of study selection

Data extraction

Two reviewers (W.K. and A.A.) independently performed data extraction using standardized data extraction forms. General characteristics of the study (e.g. mean age, gender, body mass index (BMI), duration of OA, type of PRP, pain score, functional scores, osteoarthritis index at baseline) were extracted. The number of subjects, mean and SD of continuous outcomes (i.e. pain by visual analogue score (VAS), WOMAC total and sub-scores, Lequesne scores) between groups were extracted. Cross-tabulated frequencies between treatment and adverse events were also extracted. Any disagreements were resolved by discussion and consensus with a third party (J.K.).

Risk of bias assessment

Two authors (W.K. and A.A.) independently assessed risk of bias for each study. Six study quality domains were considered. These included sequence generation, allocation concealment, blinding (participant, personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias [21]. Disagreements between two authors were resolved by consensus and discussion with a third party (J.K.).

Outcomes

The outcomes of interests were WOMAC total and subscores (i.e. pain, stiffness and function), Lequesne score, EuroQol visual analogue scale (EuroQol-VAS), IKDC subjective scores and adverse events. Methods of measure for these outcomes were used according to the original studies. Briefly, this includes the VAS pain scale from 0 to 10; the WOMAC score that consists of pain (0–20), stiffness (0–8) and function (0–68) with total scores of 0 to 96 [5]; and the Lequesne algofunctional index that measures pain (0–10); maximum distance walked (0–6); and activities of daily living (0–8) with total scores of 0–24 [5, 20]. The EuroQol-VAS is a simple validated and commonly used patient-administered method that assesses pain intensity (0–100). The IKDC subjective evaluation form is commonly used and detects improvement in function and symptoms for knee disorders. The form has three domains: knee

symptoms with seven items; sports and daily activities with ten items; and current knee function with one item. The total score ranges at 0–100, where 100 means the absence of symptoms and no limitation for daily or sporting activities [15]. The adverse events and patient satisfaction levels were recorded as well. Adverse events were considered as composite and separate outcomes of the following: injected site pain, infection and other local complications.

Statistical analysis

Direct comparisons of continuous outcomes were measured at the end of each study between PRP versus HA and PRP versus placebo and were then pooled using an unstandardized mean difference (UMD). Heterogeneity of the mean difference across studies was checked using the Q statistic, and the degree was quantified using the I^2 statistic. If heterogeneity was present ($p < 0.10$ or the $I^2 > 25$ %), the UMD was estimated using a random effect model; otherwise, a fixed effect model was applied.

For dichotomous outcomes, relative risks (RR) of the adverse reactions of treatment comparisons at the end of each study were estimated and pooled. Heterogeneity was assessed using the same method as mentioned previously. If heterogeneity was present, the Dersimonian and Laird method [1] was applied for pooling; otherwise, the fixed effect model by inverse variance method was applied. Meta-regression was applied to explore the source of heterogeneity [e.g. mean age, percentage of females, body mass index (BMI), OA grading, PRP formulation (injection time, spin approach, leucocyte rich or leucocyte poor) or duration of OA] if data were available. Subgroup or sensitivity analysis was then performed according to the results of meta-regression. Publication bias was assessed using contour-enhanced funnel plots [23, 25] and Egger tests [10]. Asymmetry of the funnel plot may be due to missing data in some studies in which the results that were negative might not have been published and thus could not be identified. The metatrim and fill method was used to estimate the number of studies that might be missing and to adjust the pooled estimate [1]. All analyses were performed using STATA version 13.0 [32]. A p value <0.05 was considered statistically significant, except for the test of heterogeneity where $p < 0.10$ was used.

Results

Fifty-six and 510 studies were identified from Medline and Scopus, respectively (Fig. 1). Fifteen of the studies were duplicates, leaving 551 studies for review of titles and abstracts. Of these, 8 full papers plus 1 study from hand searching were reviewed, leaving a total of 9 studies for data extraction. Characteristics of the 9 studies [7, 11–13, 24, 26, 27, 30, 33] are described in Table 1. Seven studies [7, 11–13, 26, 30, 33] compared PRP with HA. Two studies [24, 27] compared PRP with placebo. The osteoarthritis indices were reported using the WOMAC total score in 6 studies [7, 24, 26, 27, 30, 33], WOMAC sub-scores in 5 studies [24, 26, 27, 30, 33], Lequesne scores in 2 studies [30, 33], IKDC scores in 2 studies [11, 13] and EQ-VAS in 2 studies [11, 13]. Adverse events (composite outcomes of injected site pain, infection and other local complications) were reported in 7 studies [7, 12, 13, 24, 27, 30, 33]. Mean age, BMI and mean follow-up of participants varied from 52.7 to 66.4 years, 26 to 30.9 kg/cm^2 and 6 to 12 months, respectively. Percentages of female gender ranged from 37.6 to 93.5 %. Percentages of patients with osteoarthritis graded by Kellgren–Lawrence (KL) I–II ranged from 50 to 90 %. The PRP formulations that were used by each trial (platelet concentration, leucocytes, activation method and injective protocol) were as follows. The mean platelet counts in all studies were more than 150,000/ul. Four studies were leucocyte-poor (LP) PRP and 5 studies were leucocyte-rich (LR) PRP. Four of the studies were single-spinning preparations of PRP and 5 studies were double-spinning preparations. From the 9 studies [7, 11–13, 24, 26, 27, 30, 33], 3 studies [24, 26, 27] had injected PRP twice, 5 studies [11–13, 30, 33] had injected PRP 3 times, and only one study [7] had injected PRP 4 times. One study [24] compared single injection and double injection with placebo injection. Results showed no statistical or clinical differences between single and double injection groups.

Risk of bias in included studies

Risk of bias assessment is described in Table 2.

Outcomes

WOMAC total scores were compared among 6 studies [7, 24, 26, 27, 30, 33] for PRP injection versus placebo and 4 studies [7, 26, 30, 33] for HA injection versus placebo with a total of 184 and 268 patients in each study, respectively. The pooled unstandardized mean difference (UMD) varied highly across studies ($\chi^2 = 87.96$, $d.f. = 3$, $p < 0.05$, $I^2 = 96.6$ %) and was −15.4 (95 % CI −28.6, −2.3, $p = 0.021$), indicating that the PRP group had statistically significantly improved OA symptoms when compared to the HA group. The PRP group had a minimal clinically significant improvement in WOMAC total score by 12 % when compared to the HA group (Fig. 2; Table 3). None of the co-variables could explain the heterogeneity. There was no evidence of publication bias on Egger's test or contour funnel plot (coefficient = −15.07, SE = 6.89, n.s.). Two studies [24, 27] with a total of 56 and 54 patients compared

Table 1 Characteristics of included studies

References	Mean age	Female	BMI	F/U (months)	OA grade (KL I–II)	Injection (times)	Spin approach (PRP)	Platelet conc. (per ml)	LP/LR	PRP preparation	Comparator	Outcome	Level of evidence
Cerza et al. [7]	66.4	55.5	–	6	76.6 %	4 (q1 week)	Single	>150,000	LP	12 ml blood with 1 ml SC −1500 rpm/15 min	Hyalgan	WOMAC total, AE	I
Filardo et al. [12]	57.5	37.6	26.5	12	–	3 (q 1 week)	Double	>150,000	LR	150 ml blood −1480 rpm/6 min −3400 rpm/15 min	Hyalubrix	AE	I
Sanchez et al. [30]	59.7	52.0	28.1	6	49.4 %	3 (q 1 week)	Single	–	LP	36 ml blood with 2 ml SC −5800 rpm/8 min	Euflexxa	WOMAC total, pain, function, stiffness, AE	I
Vaquerizo et al. [33]	63.6	60.4	30.9	12	–	3 (q 2 weeks)	Single	–	LP	36 ml blood with SC −5800 rpm/8 min	Durolane	WOMAC total, pain, function, stiffness, AE	I
Raeissadat et al. [26]	59.0	72.5	27.6	12	60.6 %	2 (q 4 weeks)	Double	>150,000	LR	35–40 ml blood −1600 rpm/15 min −2800 rpm/7 min	Hyalgan	WOMAC total, pain, function, stiffness	I
Patel et al. [24]	52.7	77.1	26.0	6	89.6 %	2 (q 3 weeks)	Single	310,140	LP	100 ml bag with CPD-A1 −1500 rpm/15 min	NSS	WOMAC total, pain, function, stiffness, AE	I
Rayegani et al. [27]	56.4	93.5	27.8	6	64.5 %	2 (q 4 weeks)	Double	>150,000	LR	35–40 ml blood −1600 rpm/15 min −2800 rpm/7 min	Placebo	WOMAC total, pain, function, stiffness, AE	I
Filardo et al. [11]	55.38	38.8	26.75	12	–	3 (q 1 week)	Double	>150,000	LR	150 ml blood −1480 rpm/6 min −3400 rpm/15 min	Hyalubrix	EQ-VAS, IKDC, AE	I
Gormeli et al. [13]	53.6	57.7	29.2	6	65.4	3 (q 1 week)	Double	>150,000	LR	150 ml blood −1500 rpm/6 min −3500 rpm/12 min	Orthovisc	EQ-VAS, IKDC	I

Platelet conc. platelet concentration, *LP* leucocytes poor, *LR* leucocyte rich, *BMI* body mass index, *OA* osteoarthritis, *KL* Kellgren–Lawrence, *q* every, *WOMAC* Western Ontario and Mcmaster score, *AE* adverse events, *G* gravity, *NSS* normal saline solution, *EQ-VAS* EuroQol visual analogue scale, *IKDC* International Knee Documentation Committee, *SC* sodium citrate, *CPD-A1* citrate phosphate dextrose and adenine

Table 2 Risk of bias assessment

References	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective out come report	Free of other bias	Description of other bias
Cerza et al. [7]	Y	N	N	Y	Y	Y	–
Filado et al. [11]	Y	Y	Y	N	Y	N	Per-protocol analysis
Sanchez et al. [29]	Y	Y	Y	N	Y	N	Post-randomization exclusion (16 patients) Per-protocol analysis
Vaquerizo et al. [33]	Y	Y	N	N	Y	N	Per-protocol analysis
Raeissadat et al. [26]	Y	N	N	N	Y	N	Post-randomization exclusion (14 patients) Per-protocol analysis
Patel et al. [24]	Y	Y	Y	N	Y	N	Post-randomization exclusion (3 patients) Per-protocol analysis
Rayegani et al. [27]	Y	N	N	N	Y	N	Per-protocol analysis
Filardo et al. [12]	Y	Y	Y	N	Y	N	Per-protocol analysis
Gormeli et al. [13]	Y	Y	Y	N	Y	N	Per-protocol analysis

Y yes, *N* no, *U* unclear

WOMAC total scores in PRP injection versus placebo in treatment of OA of the knee. The pooled UMD varied highly across studies ($\chi^2 = 12.56$, *d.f.* $= 1$, $p < 0.001$, $I^2 = 93.6$ %) and had a −11.44 (95 % CI −32.81, 9.94, n.s.) lower WOMAC total score in PRP injection when compared to placebo (Fig. 3; Table 3).

WOMAC sub-scores among 5 studies [24, 26, 27, 30, 33] and 3 studies [24, 30, 33] with 224 and 208 patients compared WOMAC pain, stiffness and function scores in PRP versus HA. Two studies [24, 27] compared PRP versus placebo with a total number of 56 and 54 patients in each study.

Mean difference varied highly across studies ($I^2 = 90.5$, 92.9, 95.8 %) with an UMD of −1.95 (95 % CI −4.06, 0.17, n.s.), −0.99 (−2.09, 0.11, n.s.) and −8.02 (−17.45, 1.41, n.s.) showing lower WOMAC pain, stiffness and function scores in PRP when compared to HA, but with no statistically significant results (Table 3). There was no evidence of publication bias by Egger's test for all pooled effects.

Mean difference varied highly across studies ($I^2 = 85.5$, 94.2 %) with an UMD of −2.81 (95 % CI −6.47, 0.84, n.s.) and −8.02 (95 % CI −17.45, 1.41, n.s.) showing lower WOMAC pain and function scores in PRP when compared to placebo, but with no statistically significant results (Table 3). The UMD was homogeneous ($I^2 = 0$) with a value of −0.09 (95 % CI −0.70, 0.53, n.s.), showing that WOMAC stiffness scores were lower in the PRP than the placebo groups, but this was also insignificant. There was no evidence of publication bias by Egger's test and contour funnel plot.

Lequesne score

Two studies [30, 33] with 137 and 135 patients compared the mean Lequesne score between PRP and HA groups (Table 3). Mean difference varied highly across studies ($\chi^2 = 33.40$, *d.f.* $= 1$, $p < 0.05$, $I^2 = 97$ %) with an unstandardized mean difference of −2.82 (95 % CI −8.01, 2.38, n.s.).

IKDC subjective scores

Two studies [11, 13] with 133 and 128 patients compared the mean IKDC subjective scores between PRP and HA groups (Table 3; Fig. 4). Mean difference varied highly across studies (*d.f.* $= 1$, $p < 0.001$, $I^2 = 90.7$ %) with an unstandardized mean difference of 8.83 (95 % CI 5.88, 11.78, $p < 0.001$), indicating that the PRP group had

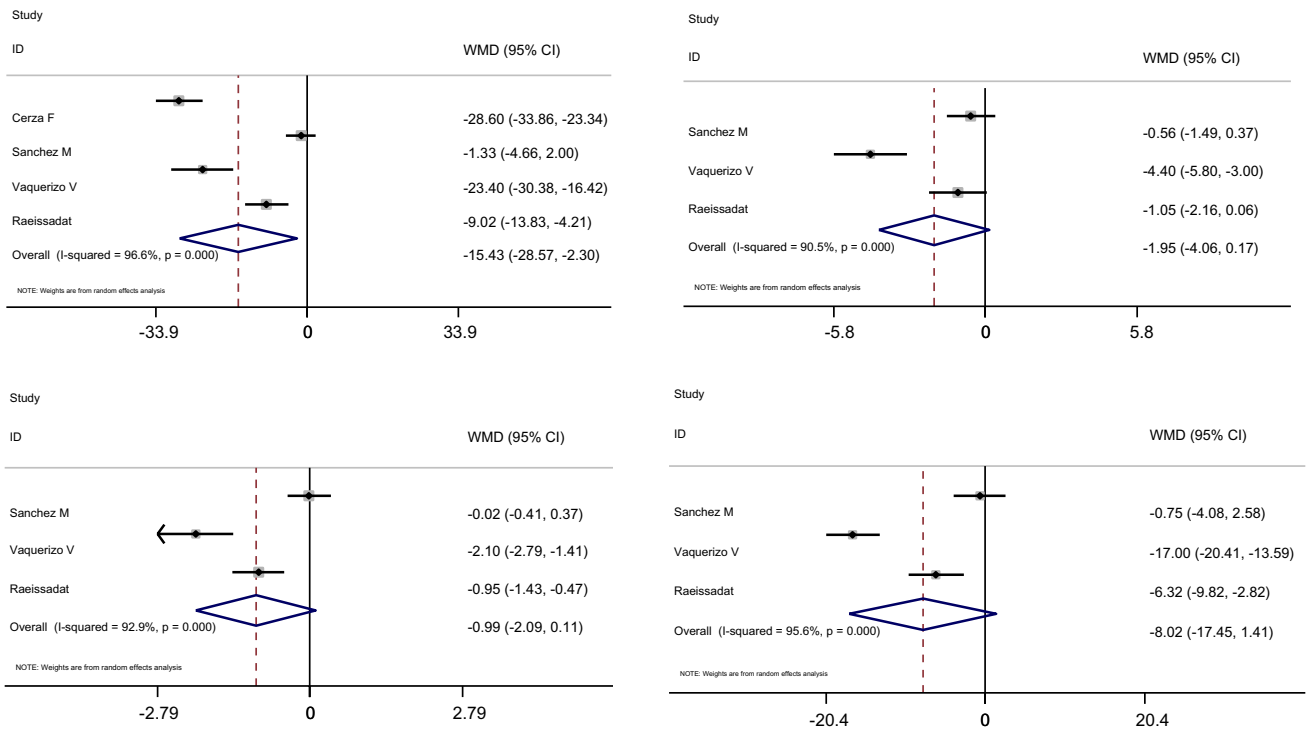

Fig. 2 Forest plot of WOMAC total and sub-score between PRP and HA groups

statistically significantly improved activity post-treatment when compared to the HA group.

EQ-VAS score

Two studies [11, 13] with 133 and 128 patients compared the mean EQ-VAS score between PRP and HA groups (Table 3; Fig. 4). Mean difference varied highly across studies ($d.f. = 1$, $p < 0.05$, $I^2 = 79.9$ %) with an unstandardized mean difference of 7.37 (95 % CI 4.33, 10.05, $p = 0.021$), indicating that the PRP group had statistically significantly better quality of life than the HA group.

Adverse events

Among 7 studies [7, 11, 12, 24, 27, 30, 33], 5 studies [7, 11, 12, 30, 33] compared risk of adverse events in PRP versus HA groups (Table 4; Fig. 5). The remaining two studies [24, 27] compared PRP with placebo groups. The pooled RR of the PRP groups was 0.85 (95 % CI 0.57, 1.28) (n.s.), which showed no statistically significantly lower risk of adverse events when compared to the HA groups. No heterogeneity ($I^2 = 0$) was present. Compared with the placebo groups, the pooled RR of PRP was 6.30 (95 % CI 0.34, 117.48) (n.s.). Neither contour funnel nor Egger's test suggested evidence of publication bias.

Discussion

The most important finding of the present study is that PRP injection for treatment of osteoarthritis of the knee has a statistically significant improvement in outcomes for WOMAC total score, IKDC score and EQ-VAS score when compared to HA injection. In terms of WOMAC pain, stiffness, function scores and Lequesne scores, the PRP group had no statistically significant improvement when compared to both HA and placebo groups. Occurrence of adverse events was not significantly different across all three groups, but the PRP group did have a lower chance of adverse events when compared to the HA group. None of the co-variables [age, sex, BMI, OA grade, PRP formulation (single or double spin, LR or LP, injection protocol)] were sources of heterogeneity. The high heterogeneity may be associated with the varied cellular composition of commercially available PRP preparations; special attention has been devoted to varied leucocyte concentrations in different types of PRP. After subgroup analysis was applied for leucocyte concentration (LP/LR), it was seen that the functional outcome scores and the incidence of adverse events in PRP injections were not affected by leucocyte concentration. We have additional evidence with good methodological quality (RCT) that PRP injection has improved functional outcomes (WOMAC total scores, IKDC score and

Table 3 Mean differences between PRP, HA and placebo

References	(A) WOMAC total score					
	PRP			HA		
	N	Mean	SD	N	Mean	SD
Cerza et al. [7]	60	36.5	17.9	60	65.1	10.6
Sanchez et al. [29]	89	23.7	11.31	87	25.03	11.25
Vaquerizo et al. [33]	48	30.8	15.5	48	54.2	19.2
Raeissadat et al. [26]	87	18.44	14.35	73	27.46	16.36
UMD (95 % CI)	−15.43 (95 % CI −28.57, −2.30), $p = 0.021$					
	PRP			Placebo		
Patel et al. [24]	25	30.48	9.27	23	53.09	20.16
Rayegani et al. [27]	31	19.13	9.71	31	19.92	14.21
UMD (95 % CI)	−11.44 (95 % CI −32.81, 9.94), $p = 0.294$ (n.s.)					
	(B) WOMAC pain					
	PRP			HA		
Sanchez et al. [29]	89	4.82	3.1	87	5.38	3.16
Vaquerizo et al. [33]	48	6.3	3.3	48	10.7	3.7
Raeissadat et al. [26]	87	4.03	3.36	73	5.08	3.71
UMD (95 % CI)	−1.95 (95 % CI −4.06, 0.17), $p = 0.071$ (n.s.)					
	PRP			Placebo		
Patel et al. [24]	25	6.18	2.17	23	10.87	4.49
Rayegani et al. [27]	31	4.2	3.08	31	5.16	4.5
UMD (95 % CI)	−2.81 (95 % CI −6.47, 0.84), $p = 0.132$ (n.s.)					
	(C) WOMAC stiffness					
	PRP			HA		
Sanchez et al. [29]	89	2.02	1.23	87	2.04	1.43
Vaquerizo et al. [33]	48	2.6	1.4	48	4.7	2
Raeissadat et al. [26]	87	1.19	1.4	73	2.14	1.66
UMD (95 % CI)	−0.99 (95 % CI −2.09, 0.11), $p = 0.077$ (n.s.)					
	PRP			Placebo		
Patel et al. [24]	25	1.88	1.12	23	2.76	2.06
Rayegani et al. [27]	31	0.83	1.28	31	0.83	1.31
UMD (95 % CI)	−0.09 (95 % CI −0.70, 0.53), $p = 0.781$ (n.s.)					
	(D) WOMAC function					
	PRP			HA		
Sanchez et al. [30]	89	16.86	10.81	87	17.61	11.7
Vaquerizo et al. [33]	48	21.9	11.3	48	38.9	4.2
Raeissadat et al. [26]	87	13.19	10.39	73	19.51	11.9
UMD (95 % CI)	−8.02 (95 % CI −17.45, 1.41), $p = 0.096$ (n.s.)					
	PRP			Placebo		
Patel et al. [24]	25	22.4	6.5	23	39.46	12.65
Rayegani et al. [27]	31	14.1	9.12	31	13.93	13.4
UMD (95 % CI)	−8.44 (95 % CI −25.33, 8.45), $p = 0.327$ (n.s.)					

Table 3 continued

	(E) Lequesne score					
	PRP			HA		
Sanchez et al.	89	16.86	10.81	87	17.61	11.7
Vaquerizo et al.	48	21.9	11.3	48	38.9	4.2
UMD (95 % CI)	−2.82 (95 % CI −8.01, 2.38), $p = 0.287$ (n.s.)					
	(F) IKDC subjective scores					
	PRP			HA		
Filardo et al. [11]	39	60.8	9.8	39	48.4	6.2
Gormeli et al. [13]	94	66.2	16.7	89	64.2	18
UMD (95 % CI)	8.83 (95 % CI 5.88, 11.78), $p < 0.001$					
	(G) EuroQol-VAS					
	PRP			HA		
Filardo et al. [12]	39	71.4	10.8	39	60.8	7.2
Gormeli et al. [13]	94	77.6	11.1	89	73.4	15.2
UMD (95 % CI)	7.37 (95 % CI 4.43, 10.05), $p = 0.021$					

PRP platelet-rich plasma, *HA* hyaluronic acid, *UMD* unstandardized mean difference, *WOMAC* Western Ontario and Mcmaster score, *SD* standard deviation, *IKDC* International Knee Documentation Committee, *EQ-VAS* EuroQol visual analogue scale, *n.s.* non-significant

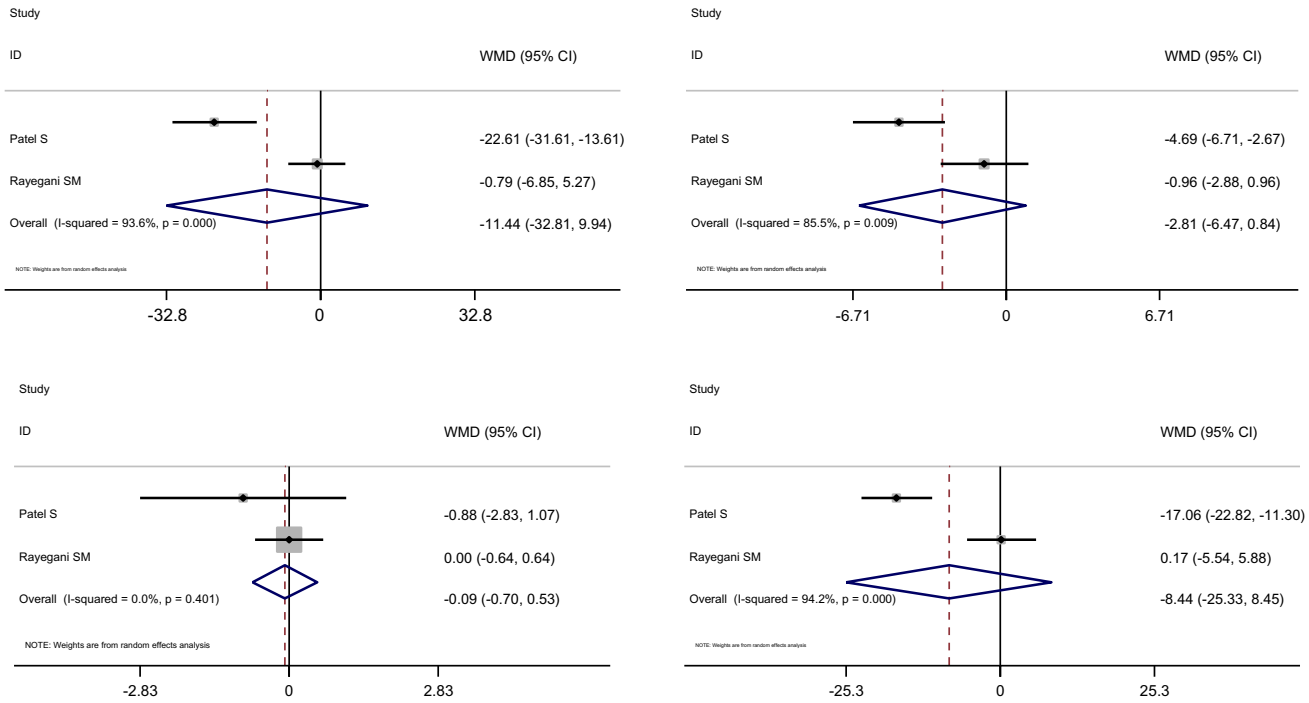

Fig. 3 Forest plot of WOMAC total and sub-score between PRP and placebo groups

EQ-VAS) when compared to HA and placebo, but there is no difference in terms of adverse events when comparing PRP to HA or placebo. According to this study, PRP injection can be considered as a safe and useful treatment of choice in select patients with mild-to-moderate degrees of OA who fail to respond to other current treatments such as lifestyle modification, exercise and physical modalities.

From previous systematic reviews [2, 18, 19, 28], it has been concluded that PRP reduces pain and improves the osteoarthritis indices (WOMAC total score, WOMAC

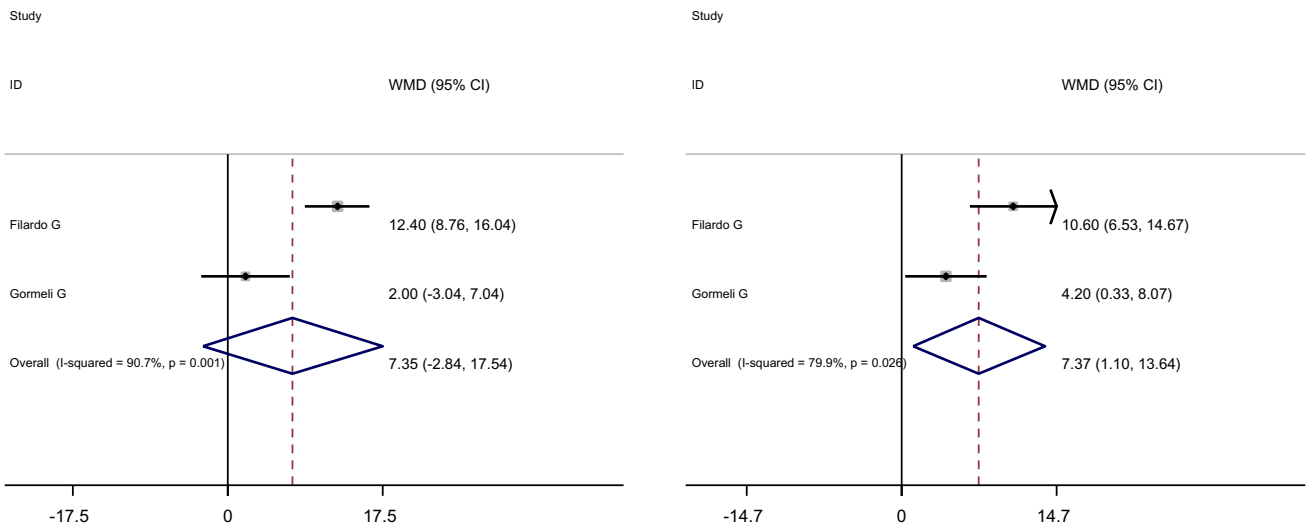

Fig. 4 Forest plot of IKDC score and EQ-VAS score between groups

Table 4 Comparisons of dichotomous outcomes between PRP, HA and placebo

References	Adverse effect						RR	95 % CI
	PRP		HA		Placebo			
	Yes	No	Yes	No	Yes	No		
Cerza et al. [7]	0	60	0	60	–	–	1.00	0.02, 49.60
Filardo et al. [11]	0	54	0	55	–	–	1.02	0.21, 50.41
Sanchez et al. [29]	24	65	26	61	–	–	0.90	0.56, 1.44
Vaquerizo et al. [33]	7	41	9	39	–	–	0.78	0.32, 1.92
Filardo et al. [12]	0	96	2	94	–	–	0.20	0.01, 4.11
Pooled RR							0.85	0.57, 1.28 (n.s)
Patel et al. [24]	11	14	–	–	0	23	21.12	1.31, 339.82
Rayegani et al. [27]	0	31	–	–	0	31	1.00	0.02, 48.87
Pooled RR							6.30	0.34, 117.38 (n.s)

n.s. non-significant

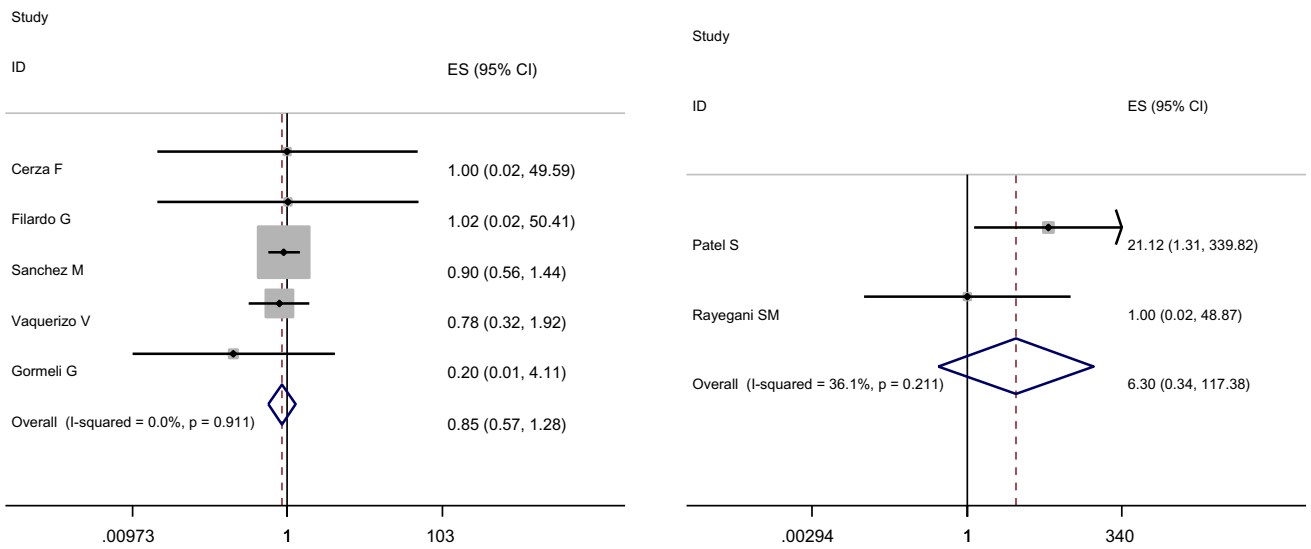

Fig. 5 Forest plot of adverse event between groups

Table 5 Evidence profile for PRP and HA

Outcome	No. studies	No. subjects	I^2 (%)	Pooled effects	Evidence profile	Quality of evidence
WOMAC total	4	284 versus 268	96.6	−15.43 (−28.57, −2.30)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) High heterogeneity and no publication bias	2B[a]
WOMAC pain	3	224 versus 208	90.5	−1.95 (−4.06, 0.17)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) Quite imprecise estimated effects with no clinical impacts High heterogeneity and no publication bias	2B
WOMAC stiffness	3	224 versus 208	92.9	−0.99 (−2.09, 0.11)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) Quite imprecise precise estimated effects High heterogeneity and without publication bias	2B
WOMAC function	3	224 versus 208	95.8	−8.02 (−17.45, 1.41)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) Quite imprecise estimated effects High heterogeneity and without publication bias	2B
Lequesne	2	137 versus 135	97	−2.82 (−8.01, 2.38)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) Quite imprecise estimated effects No heterogeneity and without publication bias	2B
EQ-VAS	2	133 versus 128	79.9	7.24 (4.43, 10.05)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) Quite imprecise estimated effects No heterogeneity and without publication bias	2B
IKDC	2	133 versus 128	90.7	8.83 (5.88, 11.78)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) Quite imprecise estimated effects No heterogeneity and without publication bias	2B
Adverse events	5	290 versus 289	0	0.85 (0.57, 1.28)	Few methodological limitations (i.e. did not describe method of randomizations, allocation concealment) Quite imprecise estimated effects No evidence of heterogeneity and publication bias	2B

2B = Intermediate-strength recommendation may be applicable to some patients depending on circumstances or society

[a] May be able to upgrade due to strength of effects and if no presence of publication bias

sub-score and Lequesne score) in osteoarthritis knee patients. Two meta-analyses were done from four systematic reviews, in which one [28] compared clinical outcomes and rates of adverse events between LP-PRP and LR-PRP. However, some of the outcomes had only one or two studies pooled, and non-RCT studies were included in the reviews.

This study has several strengths. First of all, 9 RCTs were included in the pooling of relevant clinical outcomes

(i.e. WOMAC total score and sub-scores, Lequesne index, IKDC score, EQ-VAS score and adverse events) of PRP injection versus HA injection or placebo. Secondly, possible causes of heterogeneity were explored if covariate data at baseline [e.g. mean age, percentage of females, follow-up times, OA grading, times and type of PRP injection (single- or double-spinning approach, leucocyte poor or leucocyte rich)] were available. Publication bias for each outcome was also assessed.

There are some limitations in this study. When PRP injection was compared to placebo, the results of the PRP group were better than the placebo group in the WOMAC total and sub-scores, but this was not statistically significant. This was also true for the sub-WOMAC scores in PRP compared to HA. In order to reach statistical significance, the number of subjects that compared PRP to HA or placebo should be increased. All studies had a mean follow-up time of approximately 6 months to 1 year. Therefore, long-term effects of PRP and HA are still unknown. The quality of evidence was also assessed for each outcome [14] (Table 5) and showed intermediate strength for all outcomes.

Conclusion

For short-term outcomes (≤1 year), PRP injection has improved functional outcomes (WOMAC total scores, IKDC score and EQ-VAS) when compared to HA and placebo, but no difference in adverse events when compared to HA or placebo. This study suggests that PRP injection is more efficacious than HA injection and placebo in reducing symptoms, improving function and improving quality of life in patients with mild-to-moderate OA of the knee who have not responded to conventional treatment and therefore can be considered as a treatment of choice.

Acknowledgments All authors declare no funding sources or sponsor involvement in the study design, collection, analysis and interpretation of the data, writing of the manuscript and in submission of the manuscript for publication.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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