Effectiveness of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis

A Meta-analysis of Randomized Controlled Clinical Trials

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Background: The effectiveness of platelet-rich plasma (PRP) injections for knee osteoarthritis and the effects of leukocyte-poor PRP (LP-PRP) versus leukocyte-rich PRP (LR-PRP) are still controversial.

Purpose: To assess the effectiveness of different PRP injections through a direct and indirect meta-analysis of randomized controlled trials.

Study Design: Systematic review; Level of evidence, 1.

Methods: A systematic literature search of electronic databases (PubMed, Cochrane Library, and EMBASE) was performed to locate randomized controlled trials published through March 2019 that compared PRP with control treatment. A random-effects meta-analysis was conducted to synthesize the evidence, and meta-regression analyses were conducted to determine the influence of trial characteristics. An indirect comparison was performed to assess the effects of LP-PRP and LR-PRP compared with hyaluronic acid (HA).

Results: A total of 21 trials were included. A clinically important benefit for pain relief was seen for intra-articular PRP compared with intra-articular saline (standardized mean difference [SMD] = –1.38 [95% CI, –2.07 to –0.70]; $P < .0001$; $I^2 = 37\%$) and corticosteroid solution injection (SMD = –2.47 [95% CI, –3.34 to –1.61]; $P < .00001$; $I^2 = 47\%$). As a result of heterogeneity ($I^2 = 89\%$), there was no conclusive effect compared with HA, even though the pooling effect provided clinically relevant pain relief (SMD = –0.59 [95% CI, –0.97 to –0.21]; $P = .003$). Indirect meta-analysis showed that there was no significant difference between LR-PRP and LP-PRP.

Conclusion: PRP injections are beneficial for pain relief and functional improvement in knee osteoarthritis. Larger, randomized high-quality studies are needed to compare the effects of LP-PRP and LR-PRP.

Keywords: knee osteoarthritis; platelet-rich plasma; meta-analysis; randomized controlled clinical trials; treatment

Osteoarthritis (OA) is one of the most prevalent chronic joint diseases, a leading cause of chronic pain and disability[30] that affects an estimated 25% of adults aged 55 years or older.[33] Despite numerous treatment approaches, treatments to modify the course of the disease have not reached a threshold of efficacy to gain regulatory approval. Furthermore, hyaluronic acid (HA), the most commonly used drug in the treatment of OA, was not recommended in the 2013 American Academy of Orthopaedic Surgeons (AAOS) guidelines because of a lack of significant beneficial evidence.[18] Clinical interest is increasing in the testing of new biological products to improve the efficacy of intra-articular injection treatment.

Platelet-rich plasma (PRP) is an autologous whole-blood extract containing high concentrations of platelets and growth factor, using injections of a patient's own platelets to promote and accelerate the recovery of injured ligaments, muscles, tendons, and joints.[15] Because PRP uses a patient's own immune system to improve OA, this treatment has few adverse effects and requires only a short hospital stay. Because of the potential of PRP to reduce

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inflammation and facilitate tissue repair, PRP and various PRP-derived products are increasingly described as regenerative.[2] Although many clinical trials have been conducted, conclusions about the efficacy of these products are inconsistent. One reason for this inconsistency might be the use of leukocyte-poor PRP (LP-PRP) versus leukocyte-rich PRP (LR-PRP), which have different functions according to the concentration of white cells.[9] Among the 13 meta-analyses that have been performed to date regarding the efficacy of PRP in OA,[§] 11 studies drew positive conclusions,[‖] but 2 recent studies contradicted the evidence of efficacy.[46,50] Meanwhile, this field is gaining widespread attention, and several more comparative studies have been published recently.[¶] Furthermore, most previous meta-analyses did not compare the therapeutic effects of LP-PRP versus LR-PRP.

The purpose of our study was to provide an updated meta-analysis evaluating the different preparations of PRP for the treatment of OA. In addition, we performed an indirect meta-analysis to assess the effectiveness of each PRP category in the treatment of knee OA. We hypothesized that intra-articular PRP would provide better results compared with other intra-articular options and that a significant difference in efficacy would be found when comparing LR-PRP versus LP-PRP for the treatment of OA.

METHODS

This meta-analysis was performed according to the *Cochrane Handbook for Systematic Reviews of Interventions* and is presented based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[16,29] The protocol for this meta-analysis is available in PROSPERO (CRD42019122002).

Data Sources and Search Strategy

We performed an online systematic search for eligible trials using the electronic databases of PubMed, Cochrane Library, and EMBASE for studies published though March 2019. The detailed search strategy for each database is presented in Appendix Table A1. After the electronic search, we manually extracted relevant articles from the reference lists of included studies or previous systematic reviews.

Eligibility Criteria

To be included in the study, the trials had to fulfill the following 3 criteria: (1) randomized controlled trials comparing various preparations of intra-articular PRP (ie, autologous blood concentration, autologous conditioned plasma, or plasma rich in growth factors) with HA, corticosteroid, or saline in patients with knee OA; (2) minimum follow-up of 6 months; and (3) studies written in English. Studies were excluded if they included duplicate data.

[§]References 6, 8, 21-23, 25, 28, 36, 37, 39, 41, 46, 50.
[‖]References 6, 8, 21-23, 25, 28, 36, 37, 39, 41.
[¶]References 1, 4, 17, 26, 31, 42, 43, 45, 48.

Outcomes and Data Extraction

Data were extracted by 2 reviewers (L.-y.N. and K.Z.), and disagreements were resolved through discussion before the analyses were performed. Extracted data included characteristics of the study design to assess risk of bias, baseline demographic characteristics, PRP preparation method, control group intervention, and follow-up time point. The primary outcome was mean change from baseline to the endpoint in knee pain and physical function. When a study reported more than 1 pain-outcome measure, we gave preference to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale.[27] The secondary outcome was adverse events or complications.

Quality and Risk-of-Bias Assessments

The quality of the included studies was independently evaluated by the same 2 reviewers using the Cochrane Collaboration tool for assessing risk of bias,[16] which consists of 7 areas: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item was graded as low, high, or unclear risk. The included trials were graded as low, high, or moderate quality based on the criteria as described by Zhao et al.[49] Disagreements were discussed and resolved through consensus.

Data and Statistical Analysis

Continuous outcomes were used for statistical efficacy analysis using the Hedge standardized mean difference (SMD) with 95% CIs. Meta-analyses used the random-effects model as the variation of the study characteristics. Heterogeneity was assessed using the I^2 statistic. Meta-regression analyses were performed to assess the influence of trial characteristics (PRP category, spinning approach, activator, number of injections, randomization confirmed, allocation concealment confirmed, sufficient blinding, control group, outcome measure instrument, and follow-up duration) on the treatment effects.

We conducted sensitivity analyses by restricting the analyses to high-quality randomized controlled clinical trials (RCTs), and we also evaluated whether the pooled effects met the threshold for minimal clinically important differences, which have been estimated to be SMDs of 0.39 for WOMAC Pain and 0.37 for WOMAC Function.[27] We also performed a formal, indirect comparison using results from trials that compared LP-PRP or LR-PRP with HA intervention.

The significance of the pooled effects was evaluated by a Z test, and $P < .05$ was considered significant. Possible publication bias was sought by a funnel plot with Egger test. All direct statistical analyses were performed using Review Manager Version 5.3 (Nordic Cochrane Centre) or Stata Version 15.1 (StataCorp), and indirect comparisons were performed using ITC software (Canadian Agency for Drugs and Technologies in Health).

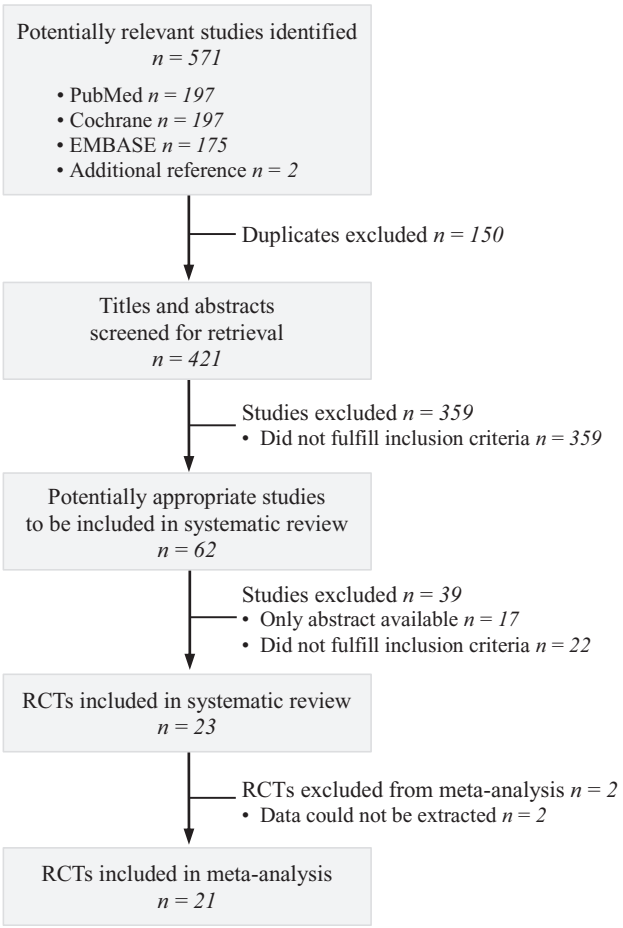


Figure 1. Flowchart of the study-selection process for the meta-analysis. RCT, randomized controlled trial.

RESULTS

Characteristics of the Included Studies

A total of 571 records were retrieved (569 records from database searches and 2 records from previously published meta-analyses[38,44]), and titles and abstracts of these records were screened for inclusion. The full texts of 62 records were read, of which 23 RCTs met eligibility criteria. Ultimately, 21 studies[#] were included in this meta-analysis (Figure 1).

The characteristics of the included studies are shown in Table 1. The RCT by Huang et al[17] included 3 treatment groups, but this did not influence the outcome analysis. Appendix Figure A1 shows the assessment of the risk of bias. Due to ethical issues, 2 studies[4,43] did not implement sufficient blinding; however, we believed that they should be regarded as high-quality research. Overall, the quality of the reported trials was acceptable, with 8 high-quality RCTs.[4,20,24,26,38,40,43,44]

[#]References 1, 4, 5, 7, 11, 14, 17, 20, 24, 26, 31, 32, 34, 35, 38, 40, 42, 43, 44, 45, 48

Efficacy of PRP

Initial meta-regression analyses for pain revealed that a significant cause of heterogeneity ($P < .05$) was the difference in the treatment of control groups (Appendix Table A2). For this reason, we performed subgroup analysis of 3 trials[32,40,45] that reported reduction of pain for the treatment group (n = 87) relative to a saline control group (n = 81), with acceptable statistical heterogeneity ($I^2 = 55\%$; $P = .11$). Pooling the data, we observed a significant effect of PRP treatment on pain (SMD = –1.63 [95% CI, –2.20 to –1.07]; $P < .0001$) (Figure 2A). When we omitted the data by Patel et al,[32] who used a visual analog scale (VAS) score, the pooling effect provided clinically relevant improvements for WOMAC score with low heterogeneity (SMD = –1.38 [95% CI, –2.07 to –0.70]; $P < .0001$; $I^2 = 37\%$) (Figure 2B). Subgroup analysis showed that PRP had a beneficial effect compared with HA or corticosteroid. However, the unexplainable statistical heterogeneity was excessive, and we were unable to identify a particular trial causing this excess variability (Figure 2A). Pooling data with such a high degree of heterogeneity of unknown cause is not advisable. When we omitted 5 trials that used a VAS score,[1,7,17,20,31] the pooling effect demonstrated clinically relevant improvements for WOMAC score in the corticosteroid group, with acceptable heterogeneity (SMD = –2.47 [95% CI, –3.34 to –1.61]; $P < .00001$; $I^2 = 47\%$). As a result of heterogeneity ($I^2 = 89\%$), there was no conclusive effect compared with HA, even though the pooling effect provided clinically relevant pain relief (SMD = –0.59 [95% CI, –0.97 to –0.21]; $P = .003$) (Figure 2B).

We could not identify initial meta-regression analyses for functional improvement that caused the observed significant heterogeneity ($P < .05$) (Appendix Table A2). When we combined all the trials,[**] the overall pooling effect provided clinically relevant functional improvements (SMD = –0.94 [95% CI, –1.27 to –0.60]; $P < .00001$) (Appendix Figure A2).

Sensitivity Analysis

Performing a sensitivity analysis that was restricted to high-quality RCTs, we were unable to identify a particular cause of the observed excess variability and heterogeneity in the statistical data (Figure 3). When the high-quality trials were pooled with all controls, we found a significant effect of PRP treatment for pain relief (SMD = –0.87 [95% CI, –1.32 to –0.41]; $P = .0002$; $I^2 = 85\%$) and a clinically relevant functional improvement (SMD = –0.95 [95% CI, –1.55 to –0.36]; $P = .002$; $I^2 = 87\%$). This did not meaningfully change the magnitude or direction of the overall effect.

Indirect Comparison of the Effect of LP-PRP and LR-PRP

We chose the HA group for an indirect comparison analysis. For each outcome variable, a forest plot representing every possible treatment comparison was created. These results

[**]References 4, 11, 24, 26, 34, 35, 38, 40, 42-45, 48.

TABLE 1
Characteristics of the Included Studies[a]

Lead Author (Year)	Sample Size		PRP Type	Spinning Approach	Activator	No. of Injections	Control Group	Outcome Measure	Follow-up, mo
	PRP	Control							
Cerza (2012)[5]	60	60	LP	Single	NR	4	HA	WOMAC Pain subscale	6
Sánchez (2012)[38]	89	87	LP	Single	$CaCl_2$	3	HA	WOMAC Pain and Function subscales, adverse events	6
Patel (2013)[32]	27	23	LP	Single	$CaCl_2$	1	Saline	VAS	6
Vaquerizo (2013)[44]	48	48	LP	Single	$CaCl_2$	3	HA	WOMAC Pain and Function subscales, adverse events	6, 12
Raeissadat (2015)[34]	77	62	LR	Double	No	3	HA	WOMAC Pain and Function subscales	12
Forogh (2016)[14]	24	24	LR	Double	$CaCl_2$	1	CS	VAS	6
Lana (2016)[24]	36	36	LR	Double	Thrombin	3	HA	WOMAC Pain and Function subscales, VAS, adverse events	6, 12
Smith (2016)[40]	15	15	LP	Single	NR	3	Saline	WOMAC Pain and Function subscales, adverse events	6, 12
Cole (2017)[7]	49	50	LP	Single	NR	3	HA	WOMAC Pain subscale	6,12
Duymus (2017)[11]	33	34	LR	Single	No	2	HA	WOMAC Pain and Function subscales, VAS	6, 12
Joshi Jubert (2017)[20]	35	30	LP	Double	No	1	CS	VAS, adverse events	6
Raeissadat (2017)[35]	36	33	LR	Double	$CaCl_2$	2	HA	WOMAC Pain and Function subscales, VAS	6
Ahmad (2018)[1]	45	44	LR	Single	NR	3	HA	VAS, adverse events	6
Buendía-López (2018)[4]	33	32	LP	Double	$CaCl_2$	1	HA	WOMAC Pain and Physical Function subscales, VAS, adverse events	6, 12
Uslu Guvendi (2018)[43]	19	17	LR	Single	NR	3	CS	WOMAC Pain and Function subscales	6
Louis (2018)[26]	24	24	LR	Double	$CaCl_2$	1	HA	WOMAC Pain and Function subscales, VAS, adverse events	6
Nabi (2018)[31]	33	34	LR	Double	NR	3	CS	VAS, adverse events	6
Su (2018)[42]	25	30	LR	Double	$CaCl_2$	2	HA	WOMAC Pain and Function subscales, VAS, adverse events	6, 12, 18
Wu (2018)[45]	20	20	LR	Single	NR	1	Saline	WOMAC Pain and Function subscales, adverse events	6
Yu (2018)[48]	104	88	LR	NR	NR	1	HA	WOMAC Pain and Function subscales, adverse events	12
Huang (2019)[17]	40	40 (HA); 40 (CS)	LP	Single	No	3	HA; CS	VAS, adverse events	12

[a]CS, corticosteroid; HA, hyaluronic acid; LP, leukocyte poor; LR, leucocyte rich; NR, not reported; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

are summarized in Figure 4, showing no significant effect on pain relief (SMD = –0.33 [95% CI, –1.02 to 0.36]) and functional improvement (SMD = 0.21 [95% CI, –0.56 to 0.98]).

Adverse Events

We identified 13 RCTs that reported the incidence of adverse events.[††] Of these, 6 studies observed zero adverse events in PRP groups.[4,20,24,31,40,45] Although the other RCTs mentioned a few occurrences of adverse events, no significant difference was found between the PRP and control groups (Appendix Table A3).

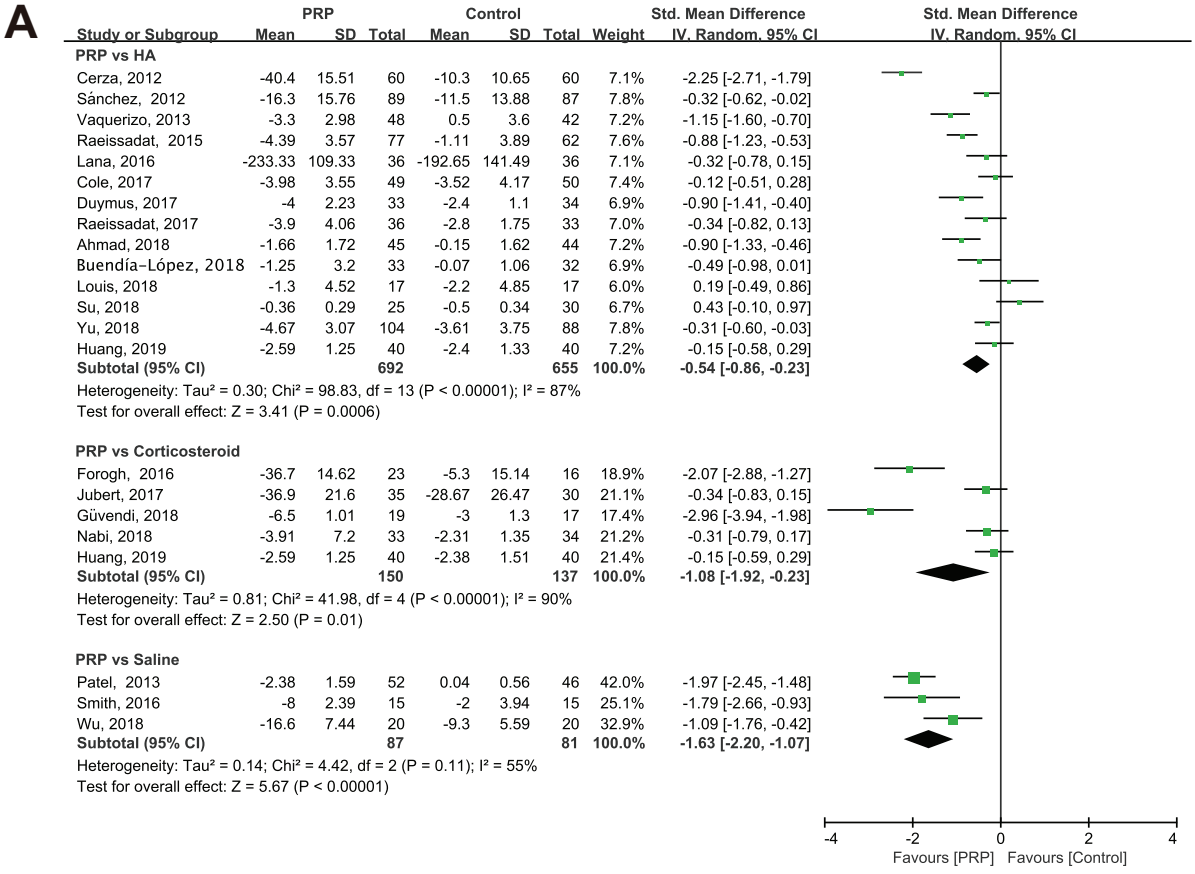
[††]References 1, 4, 17, 20, 24, 26, 31, 38, 40, 42, 44, 45, 48.

Publication Bias

An Egger test[12] was used to determine whether the effect sizes had been inflated by publication bias. The *P* values of the Egger test were .100 for WOMAC Pain and .016 for WOMAC Function (Appendix Table A4), indicating some inflation of effect sizes due to selective publication.

DISCUSSION

Current evidence, which includes that from well-designed, double-blind trials, suggests that PRP may be an effective treatment for patients with OA of the knee. However, drawing general conclusions is complicated because of unexplained statistical heterogeneity. Statistically relevant



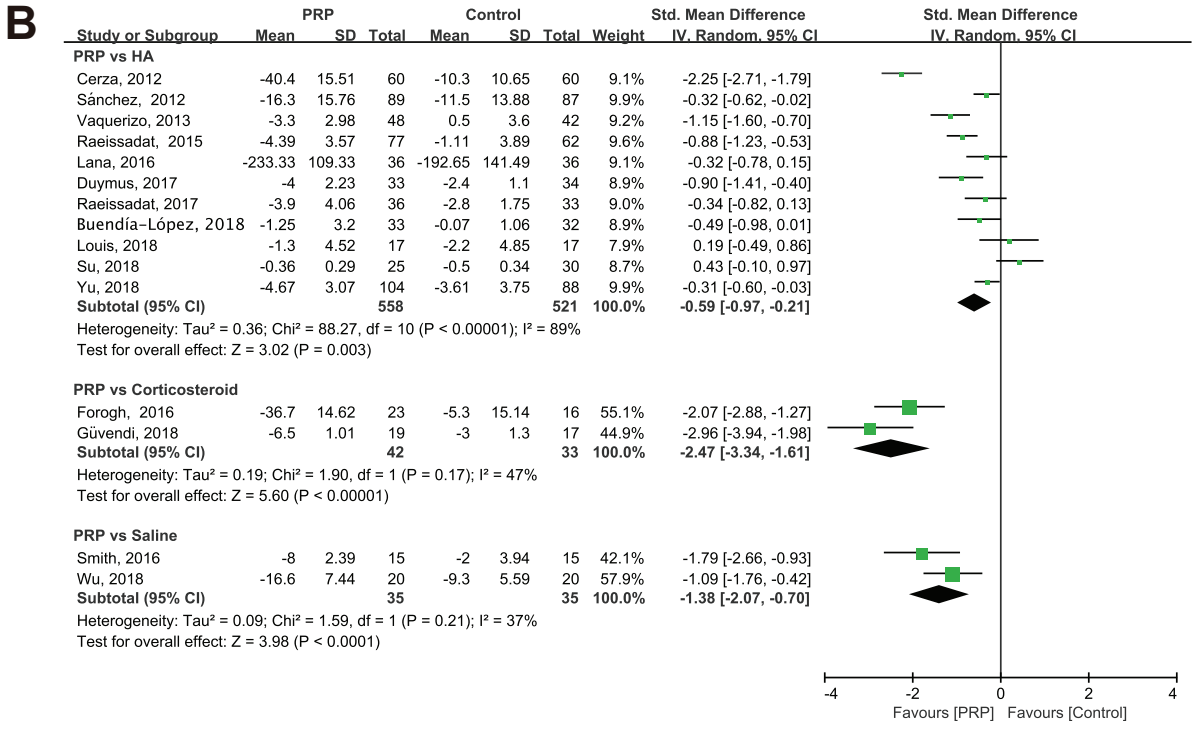


Figure 2. Forest plots for effectiveness of platelet-rich plasma (PRP) compared with different control groups for pain relief. (A) Overall effect. (B) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain overall effect.

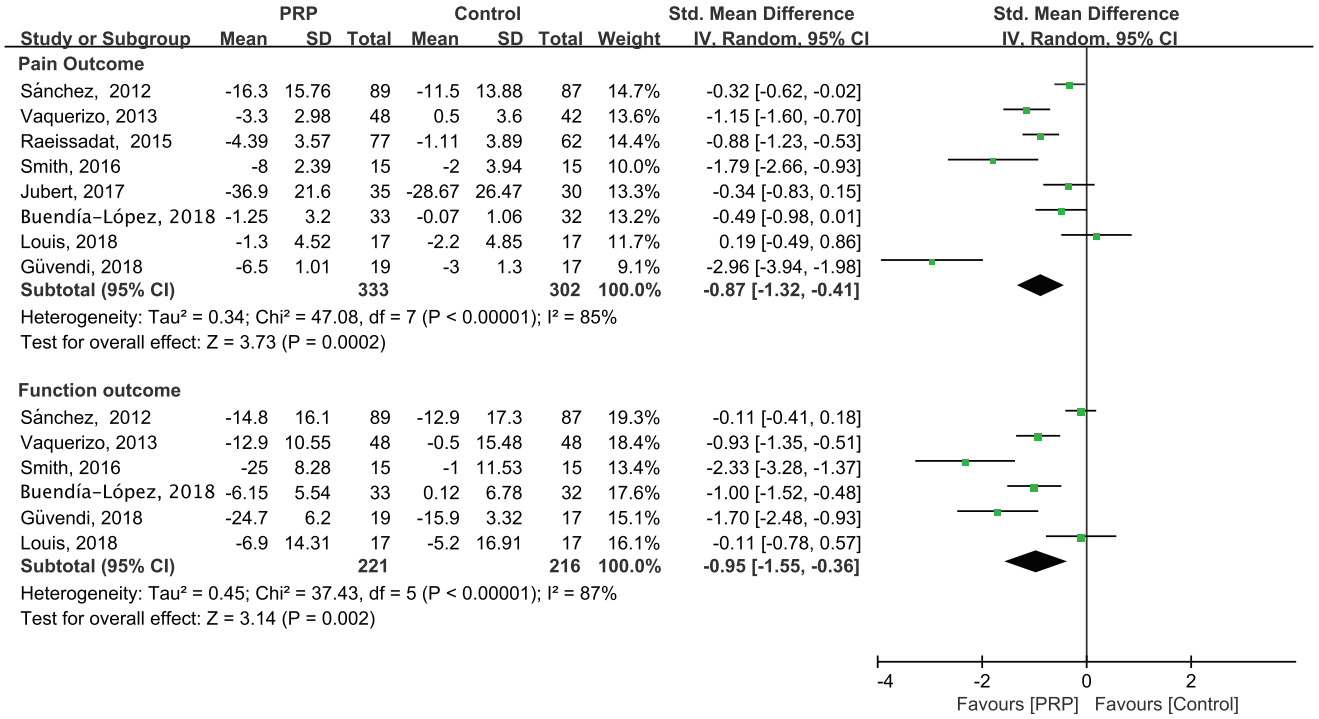


Figure 3. Results of sensitivity analysis for (A) pain relief and (B) functional improvement.

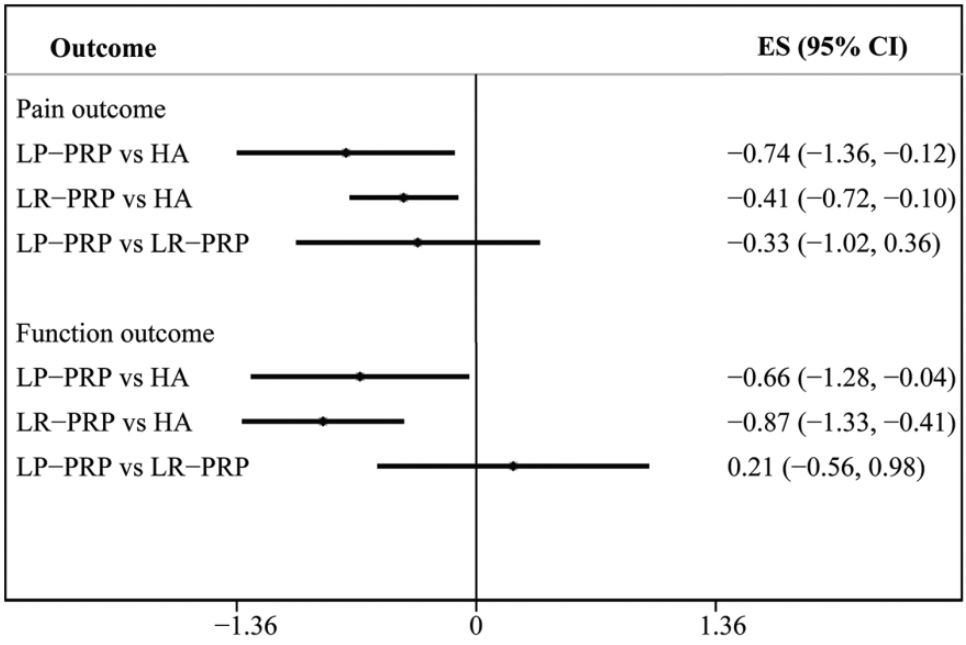


Figure 4. Indirect comparison of the effect of LP-PRP versus LR-PRP. ES, effect size; HA, hyaluronic acid; LP, leukocyte-poor; LR, leukocyte-rich; PRP, platelet-rich plasma.

clinical improvement was observed in trials that directly compared PRP with placebo or corticosteroid, with satisfactory evidence synthesis (acceptable heterogeneity). As such, it could be inferred that PRP was superior to saline and corticosteroid in relieving pain and improving self-reported function. LP-PRP and LR-PRP have similar effect profiles, although both induce more transient reactions than does HA.

Our results are not in accordance with the conclusions of 2 recent meta-analyses.[46,50] When integrating all available high-quality randomized data on the effectiveness of PRP to treat knee OA, 1 meta-analysis[46] inferred that PRP was not

superior to HA (SMD = –0.09 [95% CI, –0.30 to 0.11]; I^2 = 0%). However, the authors of that meta-analysis excluded trials that were not blinded and thus considered only 2 trials to be scientifically high-quality studies.[13,38] Another meta-analysis[50] found that PRP injections reduced pain more effectively than HA injections at 6 and 12 months of follow-up when evaluated by the WOMAC Pain score, but pain reduction was not significant when evaluated by the VAS score. Because WOMAC is the most widely used and thoroughly validated instrument,[27] the conclusion that the intra-articular injection of PRP was not significantly superior to HA in knee OA needs to be re-evaluated. Most meta-analyses did not take into account the statistical heterogeneity and concluded that PRP tends to be more effective than HA administration,[6,8,21,22,25,37,39] but a systematic review regarding the efficacy of PRP treatment remained inconclusive.[23] In our analysis, we also found that PRP was more effective than HA when considering the collective effect size of all the trials and even when restricted to high-quality RCTs, but with the existing high heterogeneity, more RCTs are needed to confirm this conclusion. Because intra-articular injections of corticosteroid are more efficacious in improving the symptoms of knee OA,[3] the clinical importance of PRP is self-evident. Relevant policies and regulations should rapidly promote the clinical application of PRP and ensure standardization among PRP protocols.[19]

We performed an indirect comparison using ITC software to merge the pooled effect sizes of all trials comparing PRP with HA in terms of pain relief and functional improvement. The conclusion was in accordance with that of Riboh et al.[36] LP-PRP and LR-PRP displayed similar profiles, although both induce more transient reactions than does HA. Which preparation, LP-PRP or LR-PRP, to use for treatment is an interesting point of debate. Two laboratory comparative studies directly investigated the effects of LP-PRP and LR-PRP, finding that LR-PRP caused a significantly greater acute inflammatory response and that LP-PRP could improve tendon healing, which is a preferable option for the clinical treatment of tendinopathy.[10,47] Thus, future research should be focused on the direct comparison of LP-PRP and LR-PRP in the treatment of knee OA.

The AAOS guideline mentions, "We are unable to recommend for or against growth factor injections and/or platelet-rich plasma for patients with symptomatic osteoarthritis of the knee"[18] as evidence from a single low-quality study or conflicting findings. Our meta-analysis found that PRP was superior in relieving pain and improving self-reported function when compared with saline and corticosteroid, with low heterogeneity. Our evidence may provide some decision support for the development of future guidelines.

The strength of this meta-analysis lies in its compliance with the PRISMA statement and registration of the protocol with PROSPERO, and we conducted an in-depth analysis to investigate the effect of PRP on treatment of OA. One potential limitation of our review is the unexplained heterogeneity in comparisons with HA (which may come from the heterogeneity of OA patients or varied PRP preparation protocols). Even though we used meta-regression to explore the source of heterogeneity, the results are limited. To some extent, this affected the accuracy of our results.

CONCLUSION

We found that the benefit of intra-articular PRP in the treatment of knee OA was clinically important when compared with intra-articular saline or corticosteroid solution injections. In addition, we found that LP-PRP and LR-PRP had similar effect profiles. Larger randomized studies of good quality are needed to test whether PRP injections should be a routine treatment for patients with knee OA and to compare the curative effects of LP-PRP and LR-PRP.

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APPENDIX

TABLE A1
Search Strategy for Each Database[a]

	Search Strategy	Results
PubMed		
1	"Osteoarthritis"[Mesh]	57,671
2	osteoarthr*[Title/Abstract] OR "degenerative arthritis"[Title/Abstract] OR arthrosis[Title/Abstract]	70,876
3	#1 OR #2	88,094
4	Platelet-Rich Plasma[MeSH] OR Blood Platelets[MeSH] OR Platelet-Derived Growth Factor[MeSH] OR Platelet Activation[MeSH]	115,144
5	"platelet rich plasma"[Title/Abstract] OR "platelet rich therapy"[Title/Abstract] OR "platelet rich therapies"[Title/Abstract] OR "platelet rich fibrin"[Title/Abstract] OR "platelet-derived growth factor"[Title/Abstract] OR "platelet plasma" [Title/Abstract] OR "platelet gel" [Title/Abstract] OR "platelet concentrate" [Title/Abstract] OR "buffy layer" [Title/Abstract] OR PRP[Title/Abstract] OR PRF[Title/Abstract] OR PDGF[Title/Abstract]	46,433
6	#4 OR #5	142,358
7	("Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh: NoExp] OR randomized[Title/Abstract] OR placebo [Title/Abstract] OR randomly[Title/Abstract] OR trial[Title]) NOT ("Animals"[Mesh] NOT ("Humans"[Mesh]) AND "Animals"[Mesh]))	1,500,389
8	#3 AND #6 AND #7	197
Cochrane Library		
1	MeSH descriptor: [Osteoarthritis] explode all trees	6131
2	(osteoarthr*): ti, ab, kw OR ("degenerative arthritis"): ti, ab, kw OR (arthrosis): ti, ab, kw	12,178
3	#1 OR #2	12,178
4	MeSH descriptor: [Platelet-Rich Plasma] explode all trees	346
5	MeSH descriptor: [Blood Platelets] explode all trees	1911
6	MeSH descriptor: [Platelet-Derived Growth Factor] explode all trees	139
7	MeSH descriptor: [Platelet Activation] explode all trees	2159
8	("platelet-rich plasma"): ti, ab, kw OR ("platelet rich therapy"): ti, ab, kw OR ("platelet rich therapies"): ti, ab, kw OR ("platelet rich fibrin"): ti, ab, kw OR ("platelet-derived growth factor"): ti, ab, kw OR ("platelet plasma"): ti, ab, kw OR ("platelet gel"): ti, ab, kw OR ("platelet concentrate"): ti, ab, kw OR ("buffy layer"): ti, ab, kw OR (PRP): ti, ab, kw OR (PRF): ti, ab, kw OR (PDGF): ti, ab, kw	2786
9	#4 OR #5 OR #6 OR #7 OR #8	5981
10	#3 AND #9	197
EMBASE		
1	'osteoarthritis'/exp	119,965
2	'osteoarthr*': ab, ti OR 'degenerative arthritis': ab, ti OR 'arthrosis': ab, ti	97,646
3	#1 OR #2	142,236
4	'thrombocyte rich plasma'/exp OR 'thrombocyte'/exp OR 'platelet derived growth factor'/exp OR 'thrombocyte activation'/exp	156,755
5	'platelet-rich plasma': ab, ti OR 'platelet rich therapy': ab, ti OR 'platelet rich therapies': ab, ti OR 'platelet rich fibrin': ab, ti OR 'platelet-derived growth factor': ab, ti OR 'platelet plasma': ab, ti OR 'platelet gel': ab, ti OR 'platelet concentrate': ab, ti OR 'buffy layer': ab, ti OR 'prp': ab, ti OR 'prf': ab, ti OR 'pdgf': ab, ti	59,927
6	#4 OR #5	190,498
7	'crossover procedure': de OR 'double-blind procedure': de OR 'randomized controlled trial': de OR 'single-blind procedure': de OR random*: de, ab, ti OR factorial*: de, ab, ti OR crossover*: de, ab, ti OR ((cross NEXT/1 over*): de, ab, ti) OR placebo*: de, ab, ti OR ((doubl* NEAR/1 blind*): de, ab, ti) OR ((singl* NEAR/1 blind*): de, ab, ti) OR assign*: de, ab, ti OR allocat*: de, ab, ti OR volunteer*: de, ab, ti	2,358,887
8	#3 AND #6 AND #7	373
9	#8 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	175

[a]Search performed on March 13, 2019.

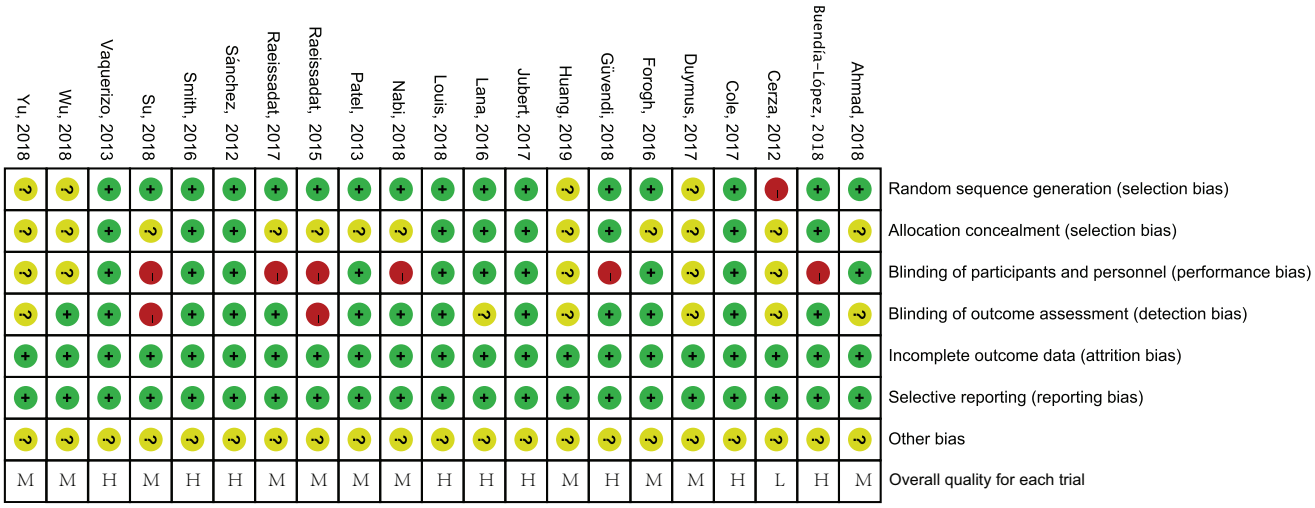

FIGURE A1. Risk of bias of included trials. According to the Cochrane Collaboration tool,[16] each item was graded as low risk (+), high risk (-), or unclear risk (?). The included trials were then graded as low quality (L), high quality (H), or moderate quality (M) based on the criteria as described by Zhao et al.[49]

TABLE A2
Meta-regression *P* Values[a]

	Outcome	
Characteristic	Pain	Function
PRP category	.629	.547
Spinning approach	.075	.153
Activator	.549	.098
No. of injections	.565	.249
Randomization confirmed	.642	.795
Allocation concealment confirmed	.832	.818
Sufficient blinding	.394	.407
Control group	.033; .147[b]	.217
Outcome measure instrument	.921	NA
Follow-up duration	.058	.228

[a]NA, not applicable; PRP, platelet-rich plasma.
[b]*P* value for meta-analysis restricted to high-quality trials.

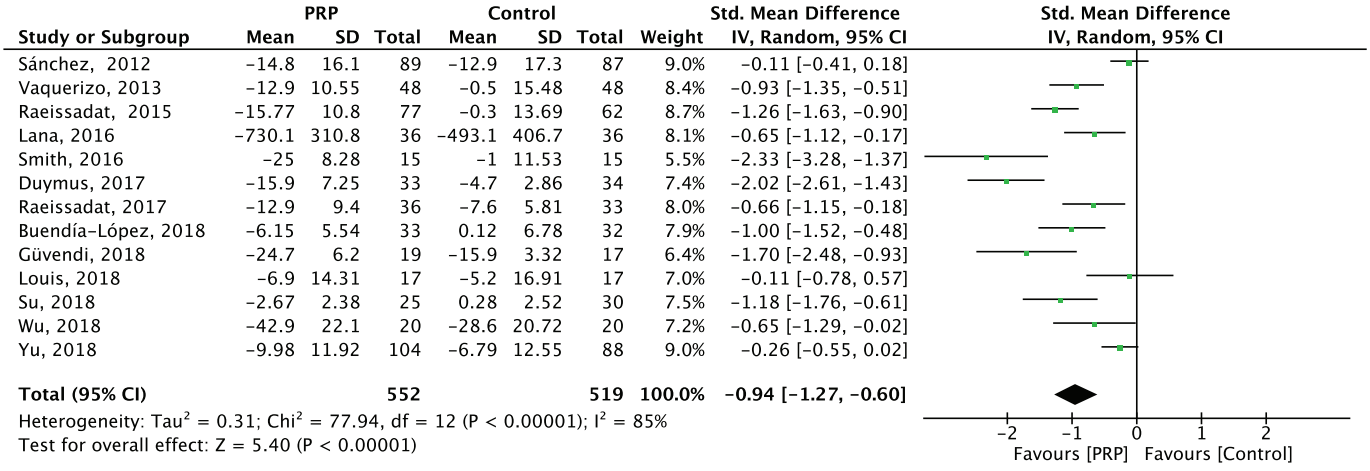

Figure A2. Forest plot for effectiveness of platelet-rich plasma (PRP) compared with controls for functional improvement. IV, inverse variance.

TABLE A3
Adverse Events

	No. of Adverse Events	
Lead Author (Year)	PRP Group	Control
Sánchez (2012)[38]	26	24
Vaquerizo (2013)[44]	7	9
Lana (2016)[24]	0	0
Smith (2016)[40]	0	1
Joshi Jubert (2017)[20]	0	0
Ahmad (2018)[1]	7	2
Buendía-López (2018)[4]	0	2
Louis (2018)[26]	1	2
Nabi (2018)[31]	0	0
Su (2018)[42]	8	5
Wu (2018)[45]	0	0
Yu (2018)[48]	28	30
Huang (2019)[17]	5	HA 2; CS 3

[a]CS, corticosteroid; HA, hyaluronic acid; PRP, platelet-rich plasma.

TABLE A4
Publication Bias *P* Values[a]

	Outcome	
Group	Pain	Function
HA	.893	
Corticosteroid	—	
Saline	—	
Overall	.100	.016

[a]Dashes indicate that <10 trials were included; thus, the publication bias was not assessed. Blank cells indicate analysis was not performed in this article. HA, hyaluronic acid.