Meta-analysis

Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Meta-analysis of Randomized Controlled Trials

Wen-Li Dai, M.Sc., Ai-Guo Zhou, M.D., Hua Zhang, M.D., and Jian Zhang, M.D.

Purpose: To use meta-analysis techniques to evaluate the efficacy and safety of platelet-rich plasma (PRP) injections for the treatment knee of osteoarthritis (OA). **Methods:** We performed a systematic literature search in PubMed, Embase, Scopus, and the Cochrane database through April 2016 to identify Level I randomized controlled trials that evaluated the clinical efficacy of PRP versus control treatments for knee OA. The primary outcomes were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores. The primary outcomes were compared with their minimum clinically important differences (MCID)—defined as the smallest difference perceived as important by the average patient. **Results:** We included 10 randomized controlled trials with a total of 1069 patients. Our analysis showed that at 6 months postinjection, PRP and hyaluronic acid (HA) had similar effects with respect to pain relief (WOMAC pain score) and functional improvement (WOMAC function score, WOMAC total score, International Knee Documentation Committee score, Lequesne score). At 12 months postinjection, however, PRP was associated with significantly better pain relief (WOMAC pain score, mean difference −2.83, 95% confidence interval [CI] −4.26 to −1.39, $P = .0001$) and functional improvement (WOMAC function score, mean difference −12.53, 95% CI −14.58 to −10.47, $P < .00001$; WOMAC total score, International Knee Documentation Committee score, Lequesne score, standardized mean difference 1.05, 95% CI 0.21-1.89, $P = .01$) than HA, and the effect sizes of WOMAC pain and function scores at 12 months exceeded the MCID (−0.79 for WOMAC pain and −2.85 for WOMAC function score). Compared with saline, PRP was more effective for pain relief (WOMAC pain score) and functional improvement (WOMAC function score) at 6 months and 12 months postinjection, and the effect sizes of WOMAC pain and function scores at 6 months and 12 months exceeded the MCID. We also found that PRP did not increase the risk of adverse events compared with HA and saline. **Conclusions:** Current evidence indicates that, compared with HA and saline, intra-articular PRP injection may have more benefit in pain relief and functional improvement in patients with symptomatic knee OA at 1 year post-injection. **Level of Evidence:** Level I, meta-analysis of Level I studies.

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Osteoarthritis (OA) of the knee is one of the most common chronic degenerative joint diseases affecting the quality of life of patients.[1,2] Pain and loss of function are the main clinical features that lead to treatment.[3,4] Although knee-replacement surgery provides an effective solution for severe knee OA,[5] for younger and middle-aged patients with earlier stages of OA, conservative nonsurgical interventions have been proposed to treat the painful joint.[6,7] Conservative nonsurgical interventions include analgesics, nonsteroid and steroid anti-inflammatory drugs, and corticosteroid and hyaluronic acid (HA) injections. Although these agents have been beneficial in the short term, there is a lack of evidence that such interventions alter the progression of OA.[6-8] More recently, platelet-rich plasma (PRP), a biological therapy, has become an intriguing treatment option to improve the status of the joint for patients with OA.[9-11]

PRP is an autologous blood product that contains high concentrations of growth factors including vascular endothelial growth factor, transforming growth factor-β, epidermal growth factor, fibroblast growth factor,

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The authors report that they have no conflicts of interest in the authorship and publication of this article.

Received May 31, 2016; accepted September 22, 2016.

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0749-8063/16453/$36.00
http://dx.doi.org/10.1016/j.arthro.2016.09.024

and platelet-derived growth factor. These growth factors serve to promote local angiogenesis, modulate inflammation, inhibit catabolic enzymes and cytokines, recruit local stem cells and fibroblasts to sites of damage or injury, and induce healthy nearby cells to manufacture greater numbers of growth factors.[12-14] Thus, the local use of PRP directly at the site of cartilage injury is thought to stimulate a natural healing cascade and accelerate the formation of cartilage repair tissue.[10,15,16]

Despite the promising preclinical findings and wide clinical applications, benefits and possible risks associated with PRP injection for knee OA remain a pertinent issue. To date, PRP-preparation techniques, platelet count, number of injections, the use of anticoagulants, activating agents, and severity of OA have varied considerably among studies. Studies reporting the effect of PRP injection in patients with knee OA convey conflicting results.[17-19] In addition, because of small sample sizes, these studies were not powered adequately to detect the effect of PRP for patients with knee OA.

The purpose of this study was to use meta-analysis techniques to evaluate the efficacy and safety of PRP injections for knee OA treatment. We hypothesized that PRP injections would be more efficacious in pain relief and functional improvement in the treatment of patients with knee OA compared with HA and saline at 6 and 12 months postinjection.

Methods

We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[20] to carry out the study, and we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[21] to report our meta-analysis. There was no registered protocol.

Search Strategy

We conducted a systematic literature search in PubMed (1946 to April 30, 2016), Embase (1974 to April 30, 2016), Scopus (1966 to April 30, 2016), and the Cochrane database (issue 4, 2016) to identify relevant studies published in English. Electronic searches were performed with the use of Medical Subject Headings (MeSH) terms and corresponding keywords. The search terms used were (MeSH "Platelet-Rich Plasma" and keywords "platelet-rich plasma," "PRP"), and (MeSH "Arthritis" and keywords "arthritis," "osteoarthritis," "gonarthrosis"). We also searched ClinicalTrial.gov and manually checked the bibliographies of identified articles, including relevant reviews and meta-analyses to identify additional eligible studies.

Selection Criteria

Two reviewers independently carried out the initial search, removed duplicate records, screened the titles and abstracts for relevance, and identified as included, excluded, or uncertain. In case of uncertainty, the full-text article was reviewed to identify eligibility. Discrepancies were resolved through discussion.

We included Level I RCTs in this study based on the following criteria: (1) population: patients diagnosed with knee OA based on the criteria described by the American College of Rheumatology[22]; (2) intervention: intra-articular injection with PRP; (3) comparison: intra-articular HA, saline, corticosteroid, exercise or no treatment; and (4) 1 or more of the following outcomes: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score, WOMAC subscores (WOMAC pain, function scores),[23] International Knee Documentation Committee (IKDC) Subjective Score,[24] Lequesne score,[25] and adverse events. Adverse events were defined as local and systemic reactions such as pain, stiffness, dizziness, headache, nausea, or infection.

Data Extraction

Data were extracted by 2 reviewers and confirmed by a third reviewer using a standardized electronic form. Disagreements were resolved through discussion before the analyses were performed. The following data were extracted: first author, year of publication, country, number of participants, affected knees, age, sex, body mass index, severity of OA, intervention, method of administration, and outcomes data. Predefined primary outcomes were WOMAC pain and function scores. Secondary outcomes included WOMAC total score, IKDC score, Lequesne score, and adverse events. When the same patients were reported in several publications, we retained only the largest study to avoid duplication of information. We also sought supplementary appendices of included studies or contacted corresponding authors to verify extracted data or request missing data.

Risk of Bias Assessment

Two reviewers used the Cochrane Risk of Bias tool[20] to assess the risk of bias in the RCTs. Each study was reviewed and scored as high, low, or unclear risk of bias according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We calculated interobserver agreement for reviewer's assessments of risk of bias with the Cohen κ statistic.[26] Discrepancies between the reviewers were resolved by discussion until consensus was achieved.

Statistical Analysis

In each study and for the outcome measures (WOMAC total, pain and function scores, IKDC score, Lequesne score), we calculated the treatment effect from the difference between the preintervention and postintervention changes in the treatment and control groups. For dichotomous outcome data (adverse events), we calculated relative risks (RRs) with 95% confidence intervals (CIs). For continuous outcome data, we calculated mean differences (MDs) with 95% CIs for the primary outcomes (WOMAC pain and function scores) and standardized mean differences (SMDs) with 95% CIs for the secondary outcomes (WOMAC total score, IKDC score, Lequesne score). For the primary outcomes (WOMAC pain and function scores), the pooled effect sizes were compared with their minimum clinically important differences (MCID)—defined as the smallest difference perceived as important by the average patient.[27] When the magnitude of the treatment effect equals or exceeds the MCID, the management of a patient should be changed, unless there are adverse side-effects or excessive costs.[28]

Based on previous work, the MCID for changes in WOMAC pain and function scores was set at 20%.[29-31] Heterogeneity across studies was tested by using the I^2 statistic. I^2 values of 25%, 50%, and 75% were considered to indicate low, moderate, and high heterogeneity, respectively.[32] If $I^2 < 50\%$, a fixed-effects model was used; otherwise, a random-effects model was used. To check the effect of various factors on the primary outcomes, we performed subgroup analyses according to number of PRP injections (1 or $\geq$2), PRP spinning approach (single or double), mean platelet concentration (platelet $<5 \times$ baseline or $>5 \times$ baseline) leukocyte-poor (LP) or leukocyte-rich (LR) PRP, risk of bias (low or unclear/high), and whether an activator was used. We assessed publication bias by using the Begg and Egger tests.[33,34] All statistical analyses were performed by RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata 13.1 (StataCorp LP, College Station, TX). The results were considered statistically significant at 2-sided P values $< .05$.

Results

Literature Search

In the initial search, we identified 1259 records. After examination of the titles and abstracts, there were 16 potentially eligible studies assessed for inclusion. After we reviewed the full text, 10 RCTs[35-44] were included in the meta-analysis. The study flow diagram, including the reasons for exclusion of studies, is shown in Figure 1.

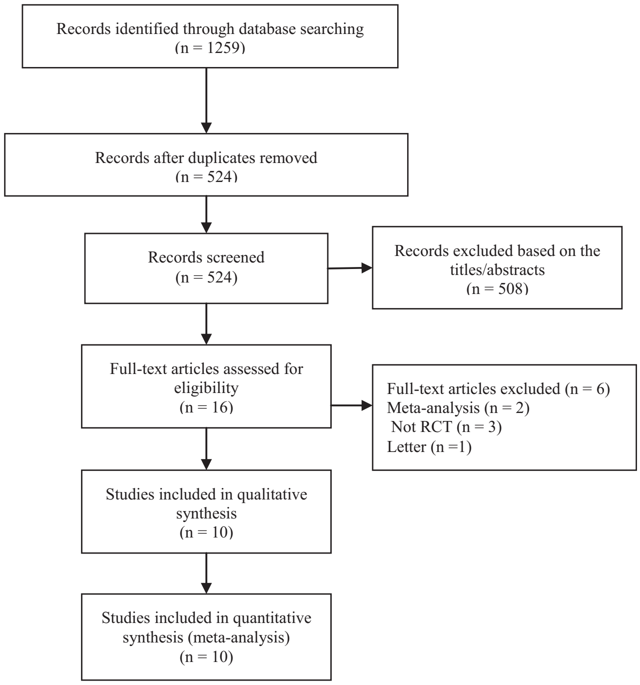

Fig 1. Flowchart illustrating the literature search. (RCT, randomized controlled trial.)

Study Characteristics

The study characteristics are presented in Table 1. These studies were published between 2011 and 2016. Eight studies[35-38,40-42,44] included comparisons of PRP with HA, whereas 3 studies[38,39,43] included comparisons of PRP with saline. The sample size of the studies ranged from 21 to 183, with a total of 1069 patients (1142 knees) comprising 562 (612 knees) in the PRP group, 429 (429 knees) in the HA group, and 78 (101 knees) in the saline group. Five of the studies had a total follow-up of 12 months,[36,37,41,43,44] 4 studies had a follow-up of 6 months,[35,38,39,42] and 1 had a total follow-up of 3 months.[40] The severity of OA was classified by the Kellgren and Lawrence grading scale in 8 studies[35-38,40,41,43,44] and the Ahlbäck grading scale in 2 studies.[39,42] The distribution of OA severity among the studies is shown in Table 1. The preparation and administration of PRP varied among studies.

Appendix Table 1 (available at www.arthroscopyjournal.org) shows the PRP preparation and administration protocols specific to each study, including PRP spinning approach, mean platelet concentration, LR or LP PRP, PRP activator, PRP volume per injection, and number of injections. Among the 10 studies, 1 study[39] included 2 PRP groups: 1 PRP injection group and 2 PRP injections group. For this study, data of the 2 PRP injections were used and a separate sensitivity analysis also was performed by using the data of the 1 PRP injection. Similarly, another study[38] included 2 PRP groups: 1 PRP injection group and 3 PRP injections group. For this study, data of the 3 PRP injections were used and a separate sensitivity analysis also was performed by using the data of the 1 PRP injection.

Risk of Bias

Among the 10 studies, 2 studies[39,43] were judged to be at low risk of bias, whereas 8 studies[35-38,40-42,44] were found to have a high risk of bias (Fig 2). Adequate randomized sequence was generated in 9 studies.[36-44] appropriate allocation concealment was reported in 7 studies,[37-40,42-44] blinding of participants

Table 1. Characteristics of Included Studies

		No. of Patients			Age, yr			Sex (Male: Female), n			BMI				Radiographic Classification								
															K-L					Ahlbäck			
Authors	Country	PRP	HA	Saline	PRP	HA	Saline	PRP	HA	Saline	PRP	HA	Saline	Follow-up, mo	0	I	II	III	IV	1	2	3	Level of Evidence
Cerza et al.[35]	Italy	60	60	—	66.5	66.2	—	25:35	28:32	—	NR	NR	—	6	0[*]	21[*]	24[*]	15[*]	0[*]	—	—	—	I
(2012)															0[†]	25[†]	22[†]	13[†]	0[†]	—	—	—	
Duymus et al.[36]	Turkey	33	34	—	60.4	60.3	—	1:32	1:33	—	27.6	28.4	—	12	0[*]	0[*]	22[*]	11[*]	0[*]	—	—	—	I
(2016)															0[†]	0[†]	24[†]	10[†]	0[†]	—	—	—	
Filardo et al.[37]	Italy	94	89	—	53.3	57.6	—	60:34	52:37	—	27.6	26.9	—	12			2.0 (mean score)[*]			—	—	—	I
(2015)																	2.0 (mean score)[†]			—	—	—	
Gormeli et al.[38]	Turkey	39[‡]	39	40	53.7	53.5	52.8	16:23	17:22	20:20	28.7	29.7	29.5	6	0[‡]		26 (I-III)[‡]		13[‡]	—	—	—	I
															0[§]		30 (I-III)[§]		14[§]	—	—	—	
(2015)		44[§]			53.8			19:25			28.4				0[†]		25 (I-III)[†]		14[†]	—	—	—	
															0[‖]		27 (I-III)[‖]		13[‖]	—	—	—	
Patel et al.[39]	India	25[¶]	—	23	51.6	—	53.7	5:20	—	6:17	25.8	—	26.2	6	—	—	—	—	—	36[¶]	10[¶]	2[¶]	I
(2013)															—	—	—	—	—	37[§]	11[§]	2[§]	
		27[§]			53.1			11:16			26.3				—	—	—	—	—	25[‖]	18[‖]	3[‖]	
Paterson et al.[40]	Australia	11	10	—	49.9	52.7	—	8:3	7:3	—	27.9	30.9	—	3	0[*]	0[*]	11 (II-III)[*]		0[*]	—	—	—	I
(2016)															0[†]	0[†]	10 (II-III)[†]		0[†]	—	—	—	
Raeissadat et al.[41]	Iran	77	62	—	56.9	61.1	—	8:69	15:47	—	28.2	27.0	—	12	0[*]	5[*]	34[*]	29[*]	9[*]	—	—	—	I
(2015)															0[†]	0[†]	29[†]	23[†]	10[†]	—	—	—	
Sanchez et al.[42]	Spain	89	87	—	60.5	58.9	—	43:46	42:45	—	27.9	28.2	—	6	—	—	—	—	—	45[*]	32[*]	12[*]	I
(2012)															—	—	—	—	—	43[†]	33[†]	11[†]	
Smith et al.[43]	USA	15	—	15	53.5	—	46.6	5:10	—	6:9	29.5	—	27.5	12	0[*]	0[*]	8[*]	7[*]	0[*]	—	—	—	I
(2016)															0[‖]	0[‖]	10[‖]	5[‖]	0[‖]	—	—	—	
Vaquerizo et al.[44]	Spain	48	48	—	62.4	64.8	—	16:32	22:26	—	30.7	31.0	—	12			2.6 (mean score)[*]			—	—	—	I
(2013)																	2.8 (mean score)[†]			—	—	—	

BMI, body mass index; HA, hyaluronic acid; K-L, Kellgren and Lawrence grading scale; PRP, platelet-rich plasma; NR, not reported.
*PRP group.
†HA group.
‡3 doses of PRP group.
§1 dose of PRP group.
‖Saline group.
¶2 doses of PRP group.

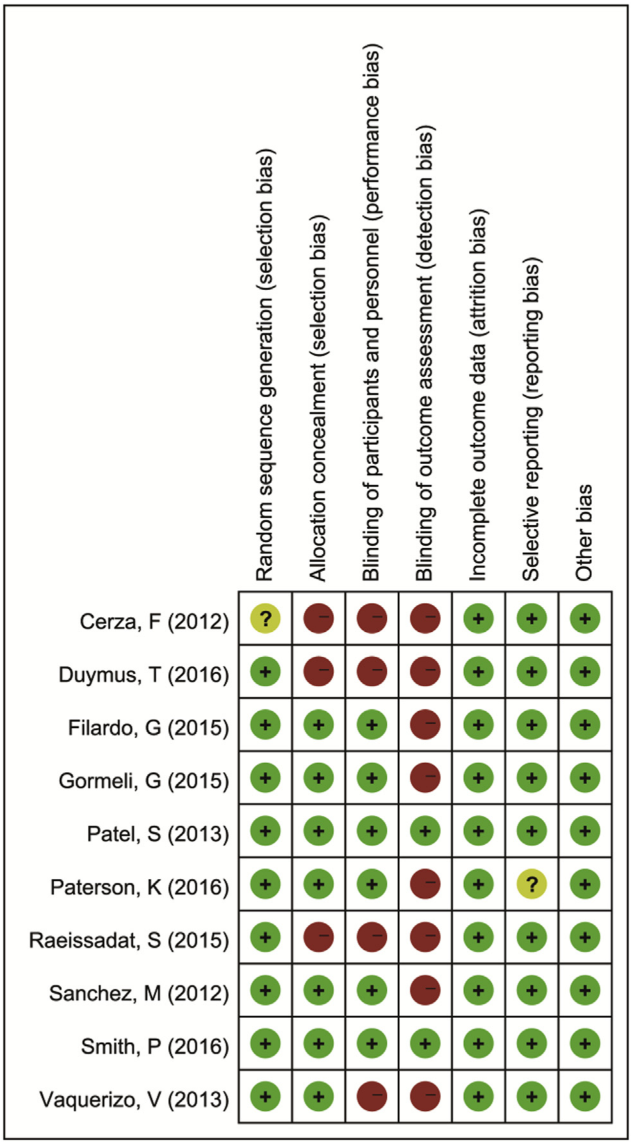

Fig 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (+, low risk of bias; −, high risk of bias; ?, unclear risk of bias.)

was clear in 6 studies,[37-40,42,43] and blinding of outcome assessors was reported only in 2 studies.[39,43] The Cohen κ statistic for agreement on risk of bias was 0.86.

PRP Versus HA

Among the studies comparing PRP with HA, the WOMAC pain score was reported in 4 studies,[36,41,42,44] WOMAC function score in 4 studies,[36,41,42,44] WOMAC total score in 5 studies,[35,36,41,42,44] IKDC score in 2 studies,[37,38] Lequesne score in 2 studies,[42,44] and adverse events in 4 studies.[37,40,42,44]

WOMAC Pain Score (PRP vs HA)

At 6 months, a total of 3 studies[36,42,44] (339 participants) provided relevant data on the WOMAC pain score. The pooled analysis showed that there was no significant difference between the PRP and HA groups (MD −1.54, 95% CI −4.27 to 1.20, $P = .27$, Fig 3). Heterogeneity was significant in the pooled result ($I^2 = 96\%$).

At 12 months, a total of 3 studies[36,41,44] (302 participants) provided relevant data on the WOMAC pain score. The pooled analysis showed that PRP was significantly more efficacious in pain relief compared with HA (MD −2.83, 95% CI −4.26 to −1.39, $P = .0001$, Fig 4), with significant heterogeneity ($I^2 = 79\%$).

For the WOMAC pain score at 6 and 12 months, the overall effect sizes exceeded the MCID (−0.83 for WOMAC pain score at 6 months and −0.79 at 12 months). CI values suggest that the smallest treatment effect exceeded the MCID for the WOMAC pain score at 12 months, whereas for WOMAC pain score at 6 months the CI values encompassed the MCID.

WOMAC Function Score (PRP vs HA)

At 6 months, a total of 3 studies[24,30,32] (339 participants) provided relevant data on the WOMAC function score. The pooled analysis showed that there was no significant difference between PRP and HA groups (MD −4.39, 95% CI −10.51 to 1.74, $P = .16$, Fig 5). Heterogeneity was significant in the pooled result ($I^2 = 87\%$).

At 12 months, a total of 3 studies[24,29,32] (302 participants) provided relevant data on the WOMAC function score. The pooled analysis showed that PRP was significantly more efficacious in functional improvement compared with HA (MD: −12.53, 95% CI: −14.58 to −10.47, $P < .00001$, Fig 6), with moderate heterogeneity ($I^2 = 31\%$).

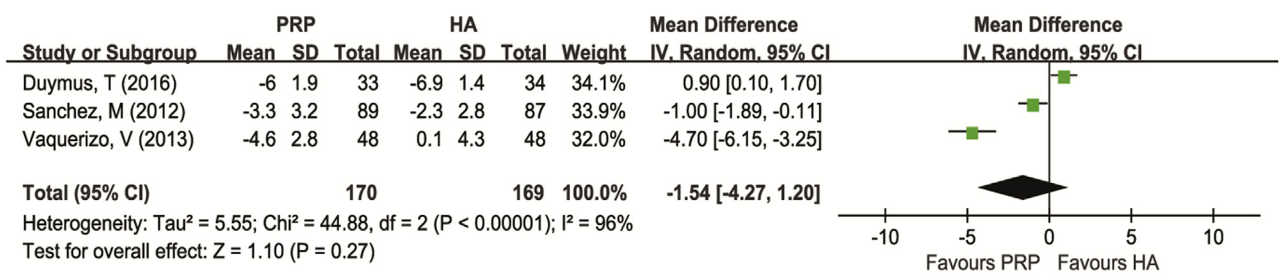

Fig 3. Forest plot of comparison: PRP versus HA; outcome: WOMAC pain score at 6 months. (CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

Study or Subgroup	PRP Mean	PRP SD	PRP Total	HA Mean	HA SD	HA Total	Weight	Mean Difference IV, Random, 95% CI
Duymus, T (2016)	-4	2.2	33	-2.4	1.1	34	37.0%	-1.60 [-2.44, -0.76]
Raeissadat, S (2015)	-4.4	3.6	77	-1.1	3.9	62	31.9%	-3.30 [-4.56, -2.04]
Vaquerizo, V (2013)	-3.3	3	48	0.5	3.6	48	31.1%	-3.80 [-5.13, -2.47]
Total (95% CI)			**158**			**144**	**100.0%**	**-2.83 [-4.26, -1.39]**

Heterogeneity: Tau² = 1.27; Chi² = 9.68, df = 2 (P = 0.008); I² = 79%
Test for overall effect: Z = 3.86 (P = 0.0001)

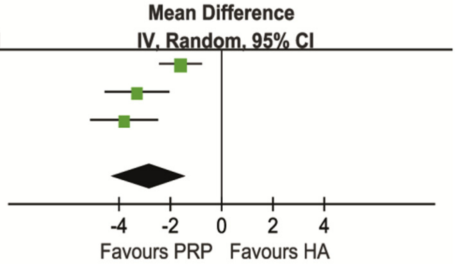

Fig 4. Forest plot of comparison: PRP versus HA; outcome: WOMAC pain score at 12 months. (CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

For the WOMAC function score at 6 and 12 months, the overall effect sizes exceeded the MCID (−2.74 for WOMAC function score at 6 months and −2.85 at 12 months). CI values suggest that the smallest treatment effect exceeded the MCID for the WOMAC function score at 12 months, whereas for WOMAC function score at 6 months the CI values encompassed the MCID.

WOMAC Total Score, IKDC Score, and Lequesne Score (PRP vs HA)

At 6 months, 4 studies[35,36,42,44] (459 participants) provided relevant data on the WOMAC total score, 2 studies[37,38] (261 participants) provided relevant data on the IKDC score, and 2 studies[42,44] (272 participants) provided relevant data on the Lequesne score. The pooled analysis showed that there was no significant difference between PRP and HA group (SMD 0.68, 95% CI −0.04 to 1.41, $P = .06$). Heterogeneity was significant in the pooled result ($I^2 = 95\%$). A separate analysis using data with 1 PRP injection in the study by Gormeli et al[38] did not result in a change in the observed results (SMD 0.43, 95% CI −0.18 to 1.04, $P = .17$).

At 12 months, 3 studies[36,41,44] (302 participants) provided relevant data on the WOMAC total score, 1 study[37] (183 participants) provided relevant data on the IKDC score, and 1 study[44] (96 participants) provided relevant data on the Lequesne score. The pooled analysis showed that PRP was associated with significantly better outcome compared with HA (SMD 1.05, 95% CI 0.21-1.89, $P = .01$). Again, heterogeneity was significant in the pooled result ($I^2 = 94\%$).

Adverse Events (PRP vs HA)

Among the 10 studies, 4 studies[37,40,42,44] compared the risk of adverse events in PRP versus HA. The pooled analysis showed that there was no significant difference between PRP and HA group (RR 0.63, 95% CI 0.20-1.98, $P = .43$, Fig 7). Heterogeneity was significant in the pooled result ($I^2 = 66\%$).

PRP Versus Saline

Among the studies comparing PRP with saline, the WOMAC pain and function scores were reported in 1 study[43] and adverse events in 2 studies.[39,43]

WOMAC Pain Score (PRP vs Saline)

Smith et al[43] found a statistically significant difference in the WOMAC pain score in favor of PRP compared with saline at 6 months (MD −5.00, 95% CI −6.98 to −3.02, $P < .00001$) and 12 months (MD −6.00, 95% CI −8.32 to −3.68, $P < .00001$) postinjection.

For the WOMAC pain score at 6 and 12 months, the overall effect sizes exceeded the MCID (−1.4 for WOMAC pain score at 6 months and −1.6 at 12 months). CI values suggest that the smallest treatment effect exceeded the MCID for the WOMAC pain score at 6 and12 months.

Study or Subgroup	PRP Mean	PRP SD	PRP Total	HA Mean	HA SD	HA Total	Weight	Mean Difference IV, Random, 95% CI
Duymus, T (2016)	-24.9	6.3	33	-24.2	5	34	36.1%	-0.70 [-3.43, 2.03]
Sanchez, M (2012)	-10	11	89	-8.8	14.2	87	33.9%	-1.20 [-4.96, 2.56]
Vaquerizo, V (2013)	-12.9	10.6	48	-0.5	15.5	48	30.1%	-12.40 [-17.71, -7.09]
Total (95% CI)			**170**			**169**	**100.0%**	**-4.39 [-10.51, 1.74]**

Heterogeneity: Tau² = 25.14; Chi² = 15.47, df = 2 (P = 0.0004); I² = 87%
Test for overall effect: Z = 1.40 (P = 0.16)

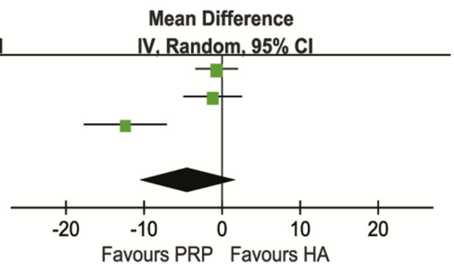

Fig 5. Forest plot of comparison: PRP versus HA; outcome: WOMAC function score at 6 months. (CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

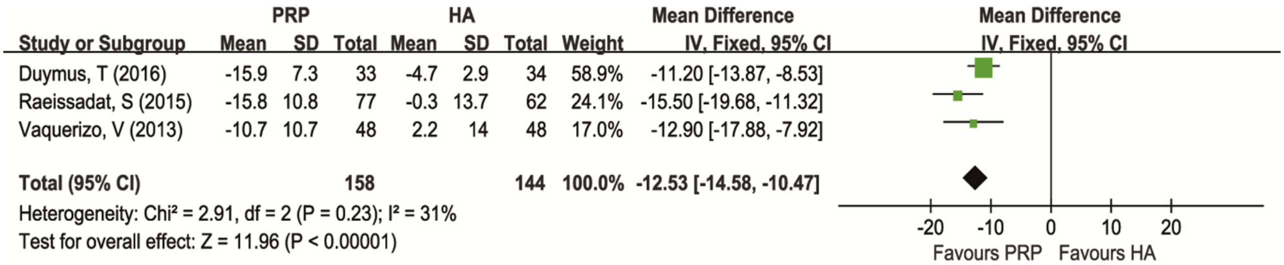

Fig 6. Forest plot of comparison: PRP versus HA; outcome: WOMAC function score at 12 months. (CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

WOMAC Function Score (PRP vs Saline)

Smith et al[43] found a statistically significant difference in the WOMAC function score in favor of PRP compared with saline at 6 months (MD −24.00, 95% CI −31.30 to −16.70, $P < .00001$) and 12 months (MD −24.00, 95% CI −30.01 to −17.99, $P < .00001$) postinjection.

For the WOMAC function score at 6 and 12 months, the overall effect sizes exceeded the MCID (−4.8 for WOMAC function score at 6 months and −5 at 12 months). CI values suggest that the smallest treatment effect exceeded the MCID for the WOMAC function score at 6 and12 months.

Adverse Events (PRP vs Saline)

There were 2 studies[39,43] that compared the risk of adverse events in PRP versus saline, the pooled analysis showed that there was no significant difference between PRP and saline group (RR 2.63, 95% CI 0.04 to 158.93, $P = .64$), with significant heterogeneity ($I^2 = 73\%$).

Subgroup Analysis

The results of subgroup analyses are presented in Table 2. The subgroup analysis based on number of PRP injections (1 or ≥2), PRP spinning approach (single or double), mean platelet concentration (platelet <5 × baseline or >5 × baseline), LP or LR PRP, risk of bias (low or unclear/high), and whether an activator was performed for WOMAC pain and function scores. The findings of WOMAC pain and function scores at 6 and 12 months were consistent in all subgroup analyses except for the platelet >5 × baseline, LR PRP, using an activator subgroups. In the subgroups of platelet >5 × baseline, LR PRP and using an activator, we found that HA was associated with significantly better pain relief than PRP at 6 month.

Publication Bias

The Egger and Begg tests were performed to investigate publication bias. The Egger test indicated no evidence of publication bias ($P = .47$). Similarly, in the Begg test, there was no evidence of substantial publication bias ($P > .99$).

Discussion

The principal findings of this study show that at 6 months postinjection, PRP and HA had similar effects with respect to pain relief (WOMAC pain score) and functional improvement (WOMAC function score, WOMAC total score, IKDC score, Lequesne score). At 12 months postinjection, however, PRP was associated with significantly better pain relief (WOMAC pain score) and functional improvement (WOMAC function score, WOMAC total score, IKDC score, Lequesne

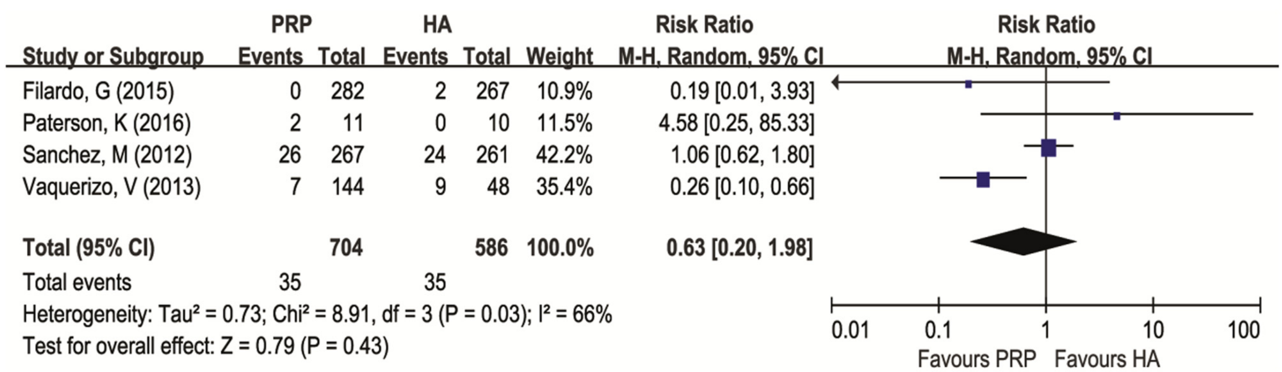

Fig 7. Forest plot of comparison: PRP versus HA; outcome: adverse events. (CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma.)

Table 2. Subgroup Analyses of PRP Compared With HA

	WOMAC Pain, 6 mo				WOMAC Function, 6 mo				WOMAC Pain, 12 mo				WOMAC Function, 12 mo			
Factors	Trials	MD (95% CI)	*P*	I^2, %	Trials	MD (95% CI)	*P*	I^2, %	Trials	MD (95% CI)	*P*	I^2, %	Trials	MD (95% CI)	*P*	I^2, %
Total	3	−1.54 (−4.27, 1.20)	.27	96	3	−4.39 (−10.51, 1.74)	.16	87	3	−2.83 (−4.26, −1.39)	.0001	79	3	−12.80 (−15.43, −10.17)	<.00001	31
Number of PRP injections																
1	0	NA	NA	NA	0	NA	NA	NA	0	NA	NA	NA	0	NA	NA	NA
≥2	3	−1.54 (−4.27, 1.20)	.27	96	3	−4.39 (−10.51, 1.74)	.16	87	3	−2.83 (−4.26, −1.39)	.0001	79	3	−12.80 (−15.43, −10.17)	<.00001	31
PRP spinning approach																
Single	3	−1.54 (−4.27, 1.20)	.27	96	3	−4.39 (−10.51, 1.74)	.16	87	2	−2.64 (−4.79, −0.48)	.02	87	2	−11.58 (−13.94, −9.22)	<.00001	0
Double	0	NA	NA	NA	0	NA	NA	NA	1	−3.30 (−4.56, −2.04)	<.00001	NA	1	−15.50 (−19.68, −11.32)	<.00001	NA
Mean platelet concentration																
Platelet <5 × baseline	2	−2.80 (−6.43, 0.82)	.13	94	2	−6.64 (−17.61, 4.33)	.24	91	1	−3.80 (−5.13, −2.47)	<.00001	NA	1	−12.90 (−17.88, −7.92)	<.00001	NA
Platelet >5 × baseline	1	0.90 (0.10, 1.70)	.03	NA	1	−0.70 (−3.43, 2.03)	.62	NA	2	−2.38 (−4.04, −0.72)	.005	79	2	−13.04 (−17.21, −8.87)	<.00001	65
LP or LR																
LP	2	−2.80 (−6.43, 0.82)	.13	94	2	−6.64 (−17.61, 4.33)	.24	91	1	−3.80 (−5.13, −2.47)	<.00001	NA	1	−12.90 (−17.88, −7.92)	<.00001	NA
LR	1	0.90 (0.10, 1.70)	.03	NA	1	−0.70 (−3.43, 2.03)	.62	NA	2	−2.38 (−4.04, −0.72)	.005	79	2	−13.04 (−17.21, −8.87)	<.00001	65
Activator used																
Yes	2	−2.80 (−6.43, 0.82)	.13	94	2	−6.64 (−17.61, 4.33)	.24	91	1	−3.80 (−5.13, −2.47)	<.00001	NA	1	−12.90 (−17.88, −7.92)	<.00001	NA
No	1	0.90 (0.10, 1.70)	.03	NA	1	−0.70 (−3.43, 2.03)	.62	NA	2	−2.38 (−4.04, −0.72)	.005	79	2	−13.04 (−17.21, −8.87)	<.00001	65
Risk of bias																
Low	0	NA	NA	NA	0	NA	NA	NA	0	NA	NA	NA	0	NA	NA	NA
Unclear/high	3	−1.54 (−4.27, 1.20)	.27	96	3	−4.39 (−10.51, 1.74)	.16	87	3	−2.83 (−4.26, −1.39)	.0001	79	3	−12.80 (−15.43, −10.17)	<.00001	31

HA, hyaluronic acid; LP, leukocyte-poor PRP; LR, leukocyte-rich PRP; NA, not applicable; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

score) than HA. Compared with saline, PRP was associated with significantly better pain relief (WOMAC pain score) and functional improvement (WOMAC function score) at 6 months and 12 months post-injection. We also found PRP did not increase the risk of adverse events compared with HA and saline.

In the past few years, the use of PRP has been extended to the treatment of several musculoskeletal injuries.[45-48] The application of PRP in patients with OA was developed because of the physiological roles of several bioactive proteins and growth factors expressed in platelets, which lead to tissue regeneration.[49-51] Despite technique and formulation discrepancies, intra-articular PRP injection was reported to be effective in degenerative knees in several studies.[39,52,53] Furthermore, a study that explored the mechanism of PRP found that in synovium and cartilage harvested from patients undergoing total knee arthroplasty, PRP could stimulate HA production, reduce cartilage catabolism, and increase cartilage synthetic activity.[10] With better improvements in both pain and function than saline at 6 and12 months and HA at 12 months, this meta-analysis reinforces the idea that PRP has the potential to be an option for patients with knee OA.

Theoretically, LR PRP may be detrimental to tissues because of the proinflammatory substances that they release[54,55]; however, in the subgroup analysis, the results of WOMAC pain at 12 months, function at 6 and 12 months remained unchanged in LP and LR PRP. Similarly, most of these results were also consistent in different PRP spinning approaches (single or double) and platelet concentration (platelet $<5 \times$ baseline or $>5 \times$ baseline) groups, which suggested that these factors may have little influence on the efficacy of PRP. Given the small numbers of studies and patients involved in subgroup analyses, however, these findings require further confirmation.

During the last 25 years, the concept of an MCID has emerged in the outcomes literature. A clinically important difference is defined as a change or difference in the outcome measure that would be perceived as important and beneficial by the clinician or the patient.[50,51] An MCID is therefore a threshold value for such change. It can be estimated with an anchor-based approach (which correlates the score of interest with a known measure of clinical change) or a distribution-based approach (which suggests that one-half of an standard deviation of a continuous outcome score constitutes a clinically meaningful difference).[56] In Outcome Measures in Rheumatology (OMERACT) meetings 5 to 7, the anchor-based method was recommended as the method of choice.[57,58] The MICD aids clinicians a tool in evaluating therapeutic options and determining whether significant outcomes will have clinically meaningful implications.[59] In our study, the effect sizes of primary outcomes (WOMAC pain and function scores) were compared with their MCID. Our meta-analysis shows that at 12 months, PRP was associated with better pain relief and function improvement compared with HA, because the smallest treatment effect was greater than the MCID (ie, the lower limit of the CI of WOMAC pain and function scores was greater than the MCID). However, at 6 months, the clinical importance of PRP injection is not clear because the CI of the effect size encompassed the MCID for WOMAC pain and function scores.

Differences between the current meta-analysis and previous meta-analyses should be noted. In a previous meta-analysis of 6 studies comparing PRP and control (HA and saline) in patients with knee OA, Khoshbin et al[60] found that intra-articular PRP injections have beneficial effects based on the WOMAC total score and IKDC score in the treatment of patients with knee OA compared with HA and saline at 6 months; however, 2 observational studies accounted for 32.8%, 41.8%, 51.0%, and 51.0% of the total weight in the primary analysis of the WOMAC total score, IKDC score, VAS for pain and patient satisfaction, respectively. Furthermore, the authors pooled the HA and saline together as a control group to be compared against PRP group. Therefore, their results may not be considered as definitive.

Similarly, in another meta-analysis comprising 6 RCTs and 4 observational studies, Laudy et al[61] also concluded that PRP reduced pain and improved function more effectively than HA in patients with knee OA based on WOMAC pain (MD -0.53, 95% CI -0.77 to -0.28, $P < .0001$) and function (MD -0.41, 95% CI -0.65 to -0.17, $P = .001$) scores at 6 months. However, the results were based on an improper model of fixed effects model of Mantel-Haenszel due to significant heterogeneity ($I^2 = 94\%$ both for WOMAC pain and function scores). If adopting appropriate random effects model, no significant association was detected between PRP and HA in patients with knee OA on WOMAC pain (MD -0.73, 95% CI -1.83 to 0.37, $P = .20$) and function (MD -0.60, 95% CI -1.66 to -0.47, $P = .27$) scores. In the their updated meta-analysis[62] comprising 6 RCT and 11 observational studies, similar results were found that PRP reduced pain and improved function more effectively than HA in patients with knee OA at 6 months. In another meta-analysis comprising 4 observational studies, 3 quasi-experimental studies, and 5 RCTs, Chang et al[63] concluded that PRP injections in patients with degenerative knee pathology showed continual efficacy for 12 months; however, this conclusion was only based on the function scores, they did not extract the data reflecting the pain relief and analyze them. Compared with the previous meta-analyses, our updated meta-analysis included 10 studies and the data were all from RCTs.

The results of the present meta-analysis were based on change from preinjection to postinjection scores, which was different from the previous meta-analyses that only used postinjection scores. In contrast to the previous meta-analyses, the present meta-analysis suggested that PRP and HA had similar effects with respect to pain relief (WOMAC pain score) and functional improvement (WOMAC function score, WOMAC total score, IKDC score, Lequesne index) at 6 months postinjection. Besides, we found that at 12 months postinjection, PRP was more effective in pain relief (WOMAC pain score) and functional improvement (WOMAC function score, WOMAC total score, Lequesne score) than HA. Moreover, we further compared the effect size of WOMAC pain and function scores with its MCID and found PRP was associated with better pain relief and function improvement compared with HA at 12 months, because the magnitude of the improvement was greater than the MCID.

Limitations

Some limitations of our study need to be mentioned. First, the studies included were heterogeneous in terms of PRP preparation (use of the single- vs double-spinning technique, speed, length of centrifugation, whether used an activator), PRP and HA administration (frequency of PRP and HA injections, injection volume), HA types, and preparation. These factors may lead to potentially differing biological activity of PRP and HA that can result in different physiological responses in patients. There is also substantial heterogeneity among the patients included in the meta-analyses, including patient age, sex, body mass index, activity level, or OA grade. Second, although 10 studies representing 1069 patients were included, the majority of the conclusions are based on 2-3 studies and, at times, 1 study alone; thus, the type II statistical error due to an underpowered analysis might be occurred. In addition, the studies included in the analysis suffered from important methodologic limitations. The potential risk of bias that those studies poses has weakened our inference of the treatment effects. Finally, we only included studies published in English, which might lead to a language or cultural bias.

Conclusions

Current evidence indicates that compared with HA and saline, intra-articular PRP injection may have more benefit in pain relief and functional improvement in patients with symptomatic knee OA at 1 year postinjection.

Acknowledgment

The authors thank information specialist Xiao Han from Chongqing Medical University, Chongqing, China, for assistance in the literature search.

References

1. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: Estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1323-1330.
2. Haywood L, Mcwilliams DF, Pearson CI, et al. Inflammation and angiogenesis in osteoarthritis. *Arthritis Rheum* 2003;48:2173-2177.
3. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005;365:965-973.
4. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol* 2014;28:5-15.
5. Carr AJ, Robertsson O, Graves S, et al. Knee replacement. *Lancet* 2012;379:1331-1340.
6. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: An update with relevance for clinical practice. *Lancet* 2011;377:2115-2126.
7. Richmond J, Hunter D, Irrgang J, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis (OA) of the knee. *J Bone Joint Surg Am* 2010;92:990-993.
8. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:363-388.
9. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: A milieu of bioactive factors. *Arthroscopy* 2012;28:429-439.
10. Sundman EA, Cole BJ, Karas V, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. *Am J Sports Med* 2014;42:35-41.
11. Cugat R, Cusco X, Seijas R, et al. Biologic enhancement of cartilage repair: The role of platelet-rich plasma and other commercially available growth factors. *Arthroscopy* 2015;31:777-783.
12. Spreafico A, Chellini F, Frediani B, et al. Biochemical investigation of the effects of human platelet releasates on human articular chondrocytes. *J Cell Biochem* 2009;108:1153-1165.
13. Anitua E, Sanchez M, Orive G, Andia I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. *Biomaterials* 2007;28:4551-4560.
14. Pettersson S, Wettero J, Tengvall P, Kratz G. Human articular chondrocytes on macroporous gelatin microcarriers form structurally stable constructs with blood-derived biological glues in vitro. *J Tissue Eng Regen Med* 2009;3:450-460.
15. Kon E, Filardo G, Di Martino A, Marcacci M. Platelet-rich plasma (PRP) to treat sports injuries: Evidence to support its use. *Knee Surg Sports Traumatol Arthrosc* 2011;19:516-527.
16. Milano G, Deriu L, Sanna Passino E, et al. Repeated platelet concentrate injections enhance reparative response of microfractures in the treatment of chondral

defects of the knee: An experimental study in an animal model. *Arthroscopy* 2012;28:688-701.
17. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. *Arthroscopy* 2011;27:1490-1501.
18. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord* 2012;13:229.
19. Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil* 2012;91:411-417.
20. Higgins J. Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. 2011. http://handbook.cochrane.org/. Accessed April 30, 2016.
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* 2009;339:b2535.
22. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;29:1039-1049.
23. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. *Arthritis Rheum* 2001;45:453-461.
24. Higgins LD, Taylor MK, Park D, et al. Reliability and validity of the International Knee Documentation Committee (IKDC) Subjective Knee Form. *Joint Bone Spine* 2007;74:594-599.
25. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation—value in comparison with other assessment tests. *Scand J Rheumatol Suppl* 1987;65:85-89.
26. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.
27. Doganay Erdogan B, Leung YY, Pohl C, Tennant A, Conaghan PG. Minimal clinically important difference as applied in rheumatology: An OMERACT Rasch Working Group systematic review and critique. *J Rheumatol* 2016;43:194-202.
28. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10:407-415.
29. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. *Arthritis Rheum* 2001;45:384-391.
30. Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. *Arthritis Care Res (Hoboken)* 2012;64:1699-1707.
31. Hmamouchi I, Allali F, Tahiri L, et al. Clinically important improvement in the WOMAC and predictor factors for response to non-specific non-steroidal anti-inflammatory drugs in osteoarthritic patients: a prospective study. *BMC Res Notes* 2012;5:58.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634.
34. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-1101.
35. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 2012;40:2822-2827.
36. Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN. Choice of intra-articular injection in treatment of knee osteoarthritis: Platelet-rich plasma, hyaluronic acid or ozone options [published online April 7, 2016]. *Knee Surg Sports Traumatol Arthrosc*. doi:10.1007/s00167-016-4110-5 .
37. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med* 2015;43:1575-1582.
38. Gormeli G, Gormeli CA, Ataoglu B, Colak C, Aslanturk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: A randomized, double-blind, placebo-controlled trial [published online August 2, 2015]. *Knee Surg Sports Traumatol Arthrosc*. doi:10.1007/s00167-015-3705-6.
39. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial. *Am J Sports Med* 2013;41:356-364.
40. Paterson KL, Nicholls M, Bennell KL, Bates D. Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: A double-blind, randomized controlled pilot study. *BMC Musculoskelet Disord* 2016;17:67.
41. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: Platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord* 2015;8:1-8.
42. Sanchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070-1078.
43. Smith PA. 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* 2016;44:884-891.

44. Vaquerizo V, Plasencia MA, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: A randomized controlled trial. *Arthroscopy* 2013;29: 1635-1643.
45. Lopez-Vidriero E, Goulding KA, Simon DA, Sanchez M, Johnson DH. The use of platelet-rich plasma in arthroscopy and sports medicine: Optimizing the healing environment. *Arthroscopy* 2010;26:269-278.
46. Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. *Am J Sports Med* 2012;40:534-541.
47. Warth RJ, Dornan GJ, James EW, Horan MP, Millett PJ. Clinical and structural outcomes after arthroscopic repair of full-thickness rotator cuff tears with and without platelet-rich product supplementation: A meta-analysis and meta-regression. *Arthroscopy* 2015;31:306-320.
48. Figueroa D, Figueroa F, Calvo R, Vaisman A, Ahumada X, Arellano S. Platelet-rich plasma use in anterior cruciate ligament surgery: Systematic review of the literature. *Arthroscopy* 2015;31:981-988.
49. Ornetti P, Nourissat G, Berenbaum F, Sellam J, Richette P, Chevalier X. Does platelet-rich plasma have a role in the treatment of osteoarthritis? *Joint Bone Spine* 2016;83:31-36.
50. Petrera M, De Croos JN, Iu J, Hurtig M, Kandel RA, Theodoropoulos JS. Supplementation with platelet-rich plasma improves the in vitro formation of tissue-engineered cartilage with enhanced mechanical properties. *Arthroscopy* 2013;29:1685-1692.
51. Kreuz PC, Kruger JP, Metzlaff S, et al. Platelet-rich plasma preparation types show impact on chondrogenic differentiation, migration, and proliferation of human subchondral mesenchymal progenitor cells. *Arthroscopy* 2015;31:1951-1961.
52. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2011;19:528-535.
53. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: A systematic review. *Arthroscopy* 2016;32:495-505.
54. Martin P, Leibovich SJ. Inflammatory cells during wound repair: The good, the bad and the ugly. *Trends Cell Biol* 2005;15:599-607.
55. Scott A, Khan KM, Roberts CR, Cook JL, Duronio V. What do we mean by the term “inflammation”? A contemporary basic science update for sports medicine. *Br J Sports Med* 2004;38:372-380.
56. Wells G, Beaton D, Shea B, et al. Minimal clinically important differences: Review of methods. *J Rheumatol* 2001;28:406-412.
57. Wells G, Anderson J, Beaton D, et al. Minimal clinically important difference module: Summary, recommendations, and research agenda. *J Rheumatol* 2001;28:452-454.
58. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003;56:395-407.
59. Zlowodzki M, Bhandari M. Outcome measures and implications for sample-size calculations. *J Bone Joint Surg Am* 2009;91:35-40 (suppl 3).
60. Khoshbin A, Leroux T, Wasserstein D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: A systematic review with quantitative synthesis. *Arthroscopy* 2013;29:2037-2048.
61. Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: A systematic review and meta-analysis. *Br J Sports Med* 2015;49:657-672.
62. Moen M, Weir A, Bakker E, Rekers M, Laudy G. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: An updated systematic review and meta-analysis. *Osteoarthritis Cartilage* 2016;24:S520-S521.
63. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: A systematic review and meta-analysis. *Arch Phys Med Rehabil* 2014;95:562-575.

Appendix Table 1. PRP Preparation and Administration Protocols

Authors	No. Injections	PRP Volume per Injection, mL	PRP Spinning Approach	Mean Platelet Concentration	LP or LR	PRP Activator
Cerza et al.[35] (2012)	4 (q 1 wk)	5.5	Single	>5 × baseline	LP	None
Duymus et al.[36] (2016)	2 (q 1 mo)	5	Single	>5 × baseline	LR	None
Filardo et al.[37] (2015)	3 (q 1 wk)	5	Double	(4.6 ± 1.4) × baseline	LR	$CaCl_2$
Gormeli et al.[38] (2016)	3 (q 1 wk)	5	Double	>5 × baseline	LR	$CaCl_2$
	1					
Patel et al.[39] (2013)	2 (q 3 wk)	8	Single	<5 × baseline	LP	$CaCl_2$
	1					
Paterson et al.[40] (2016)	NR	3	Double	NR	LR	Ultraviolet light
Raeissadat et al.[41] (2015)	2 (q 4 wk)	4-6	Double	>5 × baseline	LR	None
Sanchez et al.[42] (2012)	3 (q 1 wk)	8	Single	<5 × baseline	LP	$CaCl_2$
Smith et al.[43] (2016)	3 (q 1 wk)	3-8	Single	<5 × baseline	LP	None
Vaquerizo et al.[44] (2013)	3 (q 2 wk)	8	Single	<5 × baseline	LP	$CaCl_2$

LP, leukocyte-poor PRP; LR, leukocyte-rich PRP; NR, not reported; PRP, platelet-rich plasma; q, every.