Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Platelet-rich plasma (PRP) and hyaluronic acid (HA) are 2 nonoperative treatment options for knee osteoarthritis (OA) that are supposed to provide symptomatic relief and help delay surgical intervention.

Purpose: To systematically review the literature to compare the efficacy and safety of PRP and HA injections for the treatment of knee OA.

Study Design: Meta-analysis of level 1 studies.

Methods: A systematic review was performed by searching PubMed, the Cochrane Library, and Embase to identify level 1 studies that compared the clinical efficacy of PRP and HA injections for knee OA. The search phrase used was *platelet-rich plasma hyaluronic acid knee osteoarthritis randomized.* Patients were assessed via the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS) for pain, and Subjective International Knee Documentation Committee (IKDC) scale. A subanalysis was also performed to isolate results from patients who received leukocyte-poor and leukocyte-rich PRP.

Results: A total of 18 studies (all level 1) met inclusion criteria, including 811 patients undergoing intra-articular injection with PRP (mean age, 57.6 years) and 797 patients with HA (mean age, 59.3 years). The mean follow-up was 11.1 months for both groups. Mean improvement was significantly higher in the PRP group (44.7%) than the HA group (12.6%) for WOMAC total scores ($P < .01$). Of 11 studies based on the VAS, 6 reported PRP patients to have significantly less pain at latest follow-up when compared with HA patients ($P < .05$). Of 6 studies based on the Subjective IKDC outcome score, 3 reported PRP patients to have significantly better scores at latest follow-up when compared with HA patients ($P < .05$). Finally, leukocyte-poor PRP was associated with significantly better Subjective IKDC scores versus leukocyte-rich PRP ($P < .05$).

Conclusion: Patients undergoing treatment for knee OA with PRP can be expected to experience improved clinical outcomes when compared with HA. Additionally, leukocyte-poor PRP may be a superior line of treatment for knee OA over leukocyte-rich PRP, although further studies are needed that directly compare leukocyte content in PRP injections for treatment of knee OA.

Keywords: platelet-rich plasma; hyaluronic acid; knee; osteoarthritis

Osteoarthritis (OA) is one of the most common articular cartilage pathologies in the United States and is a leading cause of chronic disability worldwide.[22] It has been estimated that 16.7% of people older than 45 years have symptomatic knee OA, with 27.8% showing radiographic signs of cartilage degeneration.[28] The clinical efficacy of platelet-rich plasma (PRP) versus hyaluronic acid (HA) injections has recently gained significant attention as nonoperative treatment options for knee OA in the orthopaedic sports medicine community.[15,19]

HA, a naturally occurring glycosaminoglycan found in synovial fluid, has been demonstrated as a safe and effective way to treat knee OA.[4,6] By providing increased mechanical and viscoelastic properties of the synovial fluid in the affected region and increasing overall joint lubrication, exogenous HA has been shown to induce satisfactory pain relief and facilitate functional improvements in osteoarthritic knee, hip, and ankle joints.[3,10] However, HA injections are expensive and synthetically manufactured and have shown inconsistent effects on inflammation.[12] Despite the lack of clear recommendations for PRP, encouraging outcomes reported by preliminary clinical evidence and the unfavorable qualities of HA have led many clinicians to adopt PRP as an effective form of treatment for degenerative knee OA.[5]

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PRP involves modulation of the intra-articular environment by introducing autologous blood products in the joint, which can lead to reduced inflammatory distress and promote chondrogenesis.[8,15,18] Multiple studies have shown the antinociceptive and cell-proliferative properties of PRP to be effective inhibitors of the OA process,[26,40] although the clinical indications of PRP remain unclear. The purpose of this study was to systematically review the literature to compare the efficacy and safety of PRP and HA injections for the treatment of knee OA.

METHODS

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines with a PRISMA checklist. Two independent reviewers (D.A.H., M.J.K.) searched PubMed, Embase, and the Cochrane Library up to September 5, 2019. The electronic search strategy used was as follows: *platelet-rich plasma hyaluronic acid knee osteoarthritis randomized.* A total of 210 studies were reviewed by title and/or abstract to determine study eligibility based on inclusion criteria. In cases of disagreement, a third reviewer (J.W.B.) made the final decision. Inclusion and exclusion criteria followed the PICOS strategy: participants, interventions, comparators, outcomes, and study design. Studies selected for inclusion met the following criteria:

Participants: patients with knee OA diagnosed based on radiographic evaluation with a validated scoring system
Intervention: intra-articular injections of PRP
Comparator: intra-articular injections of HA
Outcomes: clinical efficacy and adverse events
Study design: level 1 randomized controlled trials that were published in English

Exclusion criteria included level 2-5 studies that did not meet the aforementioned inclusion criteria. A total of 18 studies were determined to meet inclusion criteria (Figure 1). Data extraction from each study was performed independently and then reviewed by a second author (M.J.K.). There was no need for funding or a third party to obtain any of the collected data. Risk of bias was assessed according to the Cochrane Collaboration's risk-of-bias tool,[24] which incorporates an assessment of randomization, blinding, completeness of outcomes data, selection of outcomes reported, and other sources of bias.

Reporting Outcomes

Outcomes assessed included patient-reported outcomes (PROs). PROs included the visual analog scale (VAS) for pain, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score,[7] and the Subjective International Knee Documentation Committee (IKDC) score.[23] Eleven studies[§] used the VAS; 12 studies[‖] used the WOMAC score; and 7 studies[1,13,16,18,21,29,30] used the Subjective IKDC score. For the VAS, all scores were standardized to a 100-point scale. A meta-analysis was performed to compare differences in PROs.

Study Methodology Assessment

The Modified Coleman Methodology Score (MCMS)[14] was used to evaluate study methodology quality. The MCMS has a scaled potential score ranging from 0 to 100. Scores ranging from 85 to 100 are excellent; 70 to 84, good; 55 to 69, fair; and <55, poor. The primary outcomes assessed by the MCMS are study size and type, follow-up time, attrition rates, number of interventions per group, and proper description of study methodology.

Statistical Analysis

A weighted average was calculated for numerical demographics (age, follow-up). In the 1 case where standard deviations were not provided,[13] a quarter of the mean was used as the standard deviation, as previously described.[44] When data from ≥3 studies were available, the outcomes were summarized in a forest plot. Continuous outcome data of these studies were stratified by follow-up time, and mean differences (MDs) with 95% CIs were calculated through random effects models and included in the forest plot. A random effects model was utilized because these models incorporate between-study heterogeneity into the overall summary measures. When there is no between-study heterogeneity, a random effects model equals a fixed effects model.[25] To quantify the degree of heterogeneity attributed to between-study characteristics, I^2 statistics were used to calculate heterogeneity. To indirectly compare the effects of leukocyte-poor PRP

[§]References 1, 13, 16-18, 21, 27, 31-33, 39.
[‖]References 11, 13, 17, 27, 29, 30, 33, 34, 37, 39, 42, 43.

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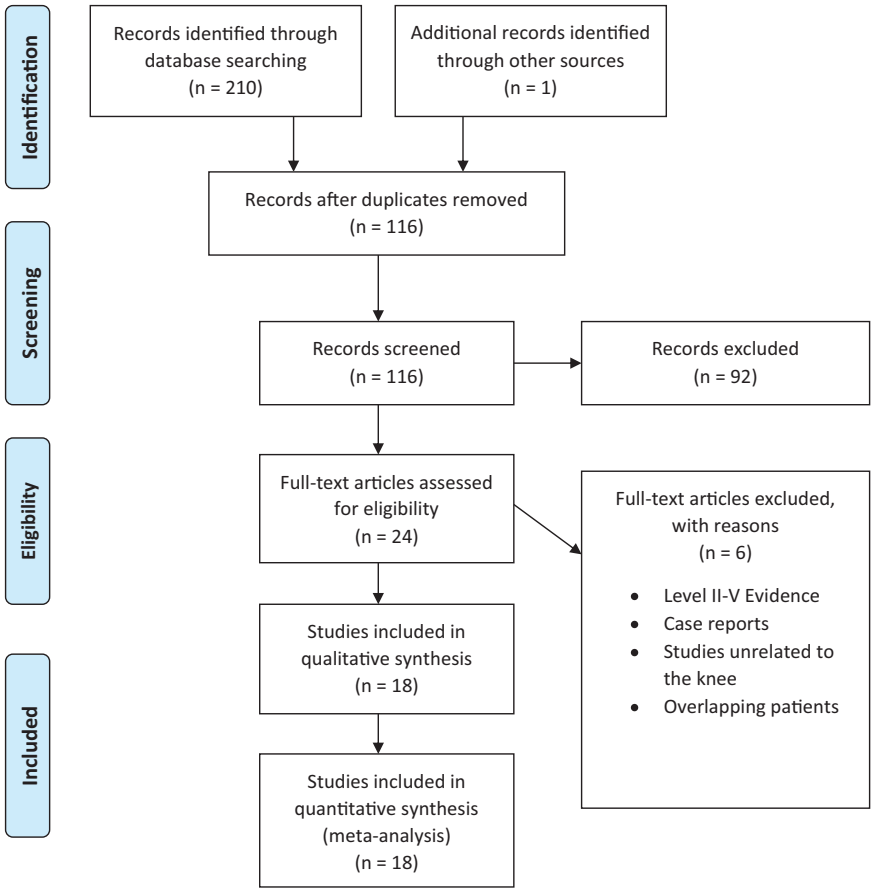

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

(LP-PRP) and leukocyte-rich PRP (LR-PRP), a network meta-analysis was performed with a random effects model for each continuous outcome variable.[36] Meta-analysis statistics, generation of forest plots, and risk-of-bias figures were performed with a combination of RevMan (v 5.3; Cochrane Collaboration) and R (v 3.6.1; R Foundation for Statistical Computing).

RESULTS

In total, 18 studies met inclusion and exclusion criteria (Figure 1), including a total of 1608 patients (PRP, n = 811; HA, n = 797). The mean patient age at the time of injection was 57.6 and 59.3 years in the PRP and HA groups, respectively, and the mean follow-up time was 11.1 months for each group (Table 1). The percentage of males was 40.9% and 40.6% in the PRP and HA groups.

PRP/HA Preparation and Treatment Method

All patients underwent harvest of peripheral venous blood from the antecubital vein, which was then centrifuged to isolate the red blood cells from the upper plasma layer. The upper plasma layer was carefully collected with a serological pipette and placed into a new centrifuge tube. In 13 studies[¶] (72.2%), the remaining erythrocyte layer was then centrifuged again to separate the platelet-poor plasma layer from the PRP layer. PRP was then activated by adding calcium chloride through low-level ultraviolet irradiation and used for intra-articular injection. In 7 studies,[16-18,21,29,31,33] platelet concentration was between 1.8- and 9.8-times baseline values. Eleven studies[#] did not report on platelet concentration. Systems used for PRP preparation were highly variable and largely unreported. Nine studies[**] (50.0%) described the use of a superolateral approach. Under ultrasound guidance, the suprapatellar pouch was localized, and the needle was inserted laterally between the iliotibial band and the vastus lateralis muscle. Two studies[29,32] (11.1%) described an anteromedial approach. One study[42] (5.5%) reported administering the injection through a superomedial approach. For HA, patients were treated with high molecular weight HA preparation (>1.5 million Da) in 13 studies[††] and low molecular weight HA (0.5-1.5 million Da) in 3 studies.[11,33,39] Two studies[30,32] did not specify HA composition. HA and PRP injection procedures were identical in all studies. All patients were

[¶]References 13, 16-18, 21, 27, 29, 31-34, 37, 39.
[#]References 1, 11, 13, 27, 30, 32, 34, 37, 39, 42, 43.
[**]References 11, 17, 21, 27, 30, 33, 34, 39, 43.
[††]References 1, 13, 16-18, 21, 27, 29, 31, 34, 37, 42, 43.

TABLE 1
Studies Included[a]

		Patient Age, Mean ± SD, y		Minimum Follow-up, mo		
	No. (PRP, HA)	PRP	HA	PRP	HA	Male, % (PRP, HA)
Ahmad (2018)[1]	45, 44	56.2 ± 6.8	56.8 ± 7.4	6.0	6.0	31.1, 31.2
Cerza (2012)[11]	60, 60	66.5 ± 11.3	66.2 ± 10.6	6.0	6.0	41.6, 46.7
Cole (2017)[13]	49, 50	55.9 ± 10.4	56.8 ± 10.5	12.0	12.0	57.1, 40.0
Di Martino (2019)[16]	85, 82	52.7 ± 13.2	57.5 ± 11.7	24.0	24.0	62.5, 57.3
Duymus (2017)[17]	33, 34	60.4 ± 5.1	60.3 ± 9.1	12.0	12.0	3.0, 2.9
Filardo (2015)[18]	94, 89	53.3 ± 13.2	57.6 ± 11.8	12.0	12.0	63.8, 58.4
Görmeli (2017)[21]	39, 39	53.8 ± 13.4	53.5 ± 14.0	6.0	6.0	42.2, 43.5
Lana (2016)[27]	36, 36	60.9 ± 7.0	60.0 ± 6.6	12.0	12.0	19.4, 8.3
Lin (2019)[29]	31, 29	61.2 ± 13.1	62.5 ± 9.9	12.0	12.0	29.0, 34.5
Lisi (2018)[30]	25, 22	53.5 ± 15.1	57.1 ± 10.0	6.0	6.0	67.0, 57.0
Montanez-Heredia (2016)[31]	27, 26	66.3 ± 8.3	61.5 ± 8.6	6.0	6.0	44.4, 34.6
Paterson (2016)[32]	10, 9	49.9 ± 13.7	52.7 ± 10.3	3.0	3.0	72.7, 70.0
Raeissadat (2015)[34]	77, 62	56.9 ± 9.1	61.1 ± 7.5	12.0	12.0	10.4, 24.2
Raeissadat (2017)[33]	36, 33	57.0 ± 7.2	59.5 ± 7.5	6.0	6.0	18.2, 19.4
Sánchez (2012)[37]	79, 74	60.5 ± 7.9	58.9 ± 8.2	6.0	6.0	48.0, 48.0
Su (2018)[39]	27, 30	50.7 ± 8.7	53.1 ± 6.4	18.0	18.0	37.0, 40.0
Vaquerizo (2013)[42]	48, 48	62.4 ± 6.6	64.8 ± 7.7	11.0	11.0	33.3, 45.8
Vasavilbaso (2017)[43]	10, 30	60.3 ± 9.5	64.8 ± 10.4	18.0	18.0	40.0, 56.7
Total, weighted average	811, 797	57.6	59.3	11.1	11.1	40.9, 40.6

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

monitored for 10 to 15 minutes to ensure that there were no adverse reactions. Six studies[1,13,16,18,31,37] (27.8%) did not describe the method of injection.

PRP Leukocyte Content

Eight studies[1,16-18,27,32,34,39] utilized LR-PRP, and 7 studies[11,13,29,31,33,37,42] utilized LP-PRP. Three studies[21,30,43] did not report whether they used LR- or LP-PRP. In studies that did report leukocyte content, leukocyte concentration was largely unreported.

PRP/HA Administration Strategy

One study[11] administered either 4 PRP or HA injections at 1-week intervals. Eight studies[13,16,18,21,29,32,37,42] administered 3 injections at 1-week intervals. Four studies[1,17,27,31] administered 3 injections at 2-week intervals; 1 study[39] administered 2 injections at 2-week intervals; and 1 study[30] administered 3 injections at 4-week intervals. Two studies[33,34] administered 2 injections at 3-week intervals. One study[43] administered only 1 injection. Five studies[21,33,34,39,42] had nonidentical administration strategies between PRP and HA groups. Two studies[21,42] administered 3 injections at 1-week intervals for PRP patients and only 1 injection for HA patients. One study[39] administered 2 injections at 2-week intervals for PRP patients and 5 injections at 1-week intervals for HA patients. Two studies[33,34] administered 2 injections at 3-week intervals for PRP patients and 3 injections at 1-week intervals for HA patients.

TABLE 2
Modified Coleman Methodology Scores

Study	Score, Mean ± SD
Ahmad (2018)[1]	82
Cerza (2012)[11]	92
Cole (2017)[13]	82
Di Martino (2019)[16]	89
Duymus (2017)[17]	83
Filardo (2015)[18]	86
Görmeli (2017)[21]	90
Lana (2016)[27]	84
Lin (2019)[29]	84
Lisi (2018)[30]	80
Montanez-Heredia (2016)[31]	82
Paterson (2016)[32]	85
Raeissadat (2015)[34]	93
Raeissadat (2017)[33]	89
Sánchez (2012)[37]	90
Su (2018)[39]	81
Vaquerizo (2013)[42]	82
Vasavilbaso (2017)[43]	85
Total	85.5 ± 4.0

Modified Coleman Methodology Score

Table 2 shows the MCMSs from the 18 included studies. Nine studies[11,16,18,21,32-34,37,43] received excellent scores, and 9 studies[1,13,17,27,29-31,39,42] received good scores.

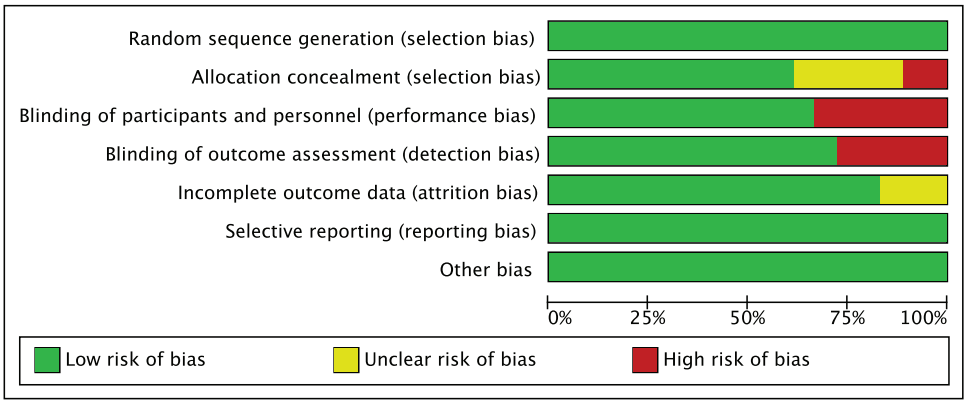

Figure 2. Risk-of-bias graph. Risk of bias is presented as a percentage across all included studies.

Patient Characteristics

Three studies[16,18,34] reported a significant difference in age between the PRP and HA groups, in which the HA patients were significantly older ($P < .05$). One study[34] reported a significant difference in sex between groups, in which the PRP group had a significantly higher proportion of female patients. Seventeen studies[‡‡] reported no differences in sex; 15 studies[§§] reported no differences in age; and 15 studies[‖‖] reported no differences in body mass index (BMI) between groups. Lin et al[29] reported a significant difference in BMI between groups, in which HA patients had a significantly higher BMI ($P = .01$). Fourteen studies[¶¶] included patients with mild to moderate OA based on a grade I-III Kellgren-Lawrence or Ahlbäck rating. Three studies[21,34,42] included patients with advanced OA based on a grade IV Kellgren-Lawrence rating. Görmeli et al[21] reported 33.3% and 35.8% of PRP and HA patients, respectively, to have grade IV OA; Raeissadat et al,[34] 12.0% and 16.0%; and Vaquerizo et al,[42] 16.7% and 18.8%. One study[30] did not report on preinjection OA grades with conventional scales. No studies found a significant difference in preinjection OA grades between groups.

Methodologic Quality Assessment

Figure 2 presents the results of the methodologic quality assessment of included studies based on the Cochrane Collaboration's risk-of-bias tool. Sequence generation and allocation were adequately reported by most studies, except in 7 studies where the concealment of allocation from the investigators was unclear (unclear risk of bias) [1,13,16,34,39] or not concealed (high risk of bias).[11,17] All studies were deemed to be at low risk for detection bias because of the blinding of the outcome assessor, except in 5 studies[1,11,17,34,39] in which the outcome assessor was not blinded (high risk of bias). Patients in most studies were blinded to their intervention group (low risk of bias), except in 6 studies[11,17,33,34,39,43] in which patients were aware of their treatment group (high risk of bias). Three studies[17,27,39] reported a minor loss of follow-up, between 10% and 20%, without proper explanation (unclear risk of bias), while no other studies reported significant loss of follow-up (low risk of bias).

Patient-Reported Outcomes

Nine studies[##] reported results of the WOMAC total score (Table 3). Eight studies[11,17,29,33,34,39,42,43] reported P values on pre- to posttreatment scores within each group, 7 of which[11,17,33,34,39,42,43] found PRP patients to improve significantly ($P < .05$) from pretreatment to latest follow-up and 3 of which[11,33,43] found HA patients to improve significantly ($P < .05$) from pretreatment to latest follow-up. Six studies[11,17,29,34,39,42] found PRP patients to report significantly better WOMAC scores ($P < .05$) at latest follow-up, while no studies found HA patients to report better scores. The 1 study[29] not included in Table 3 defined improved WOMAC outcomes as an increased score when compared with baseline, while all other studies reported improved WOMAC outcomes as a decreased score versus baseline. This study[29] found PRP patients to report significantly better WOMAC scores ($P < .05$) at latest follow-up with no difference in preinjection scores between groups.

Three studies[13,27,37] reported results of the WOMAC pain subscale score. Two of these studies[13,37] found the PRP and HA groups to improve significantly ($P < .05$) from preinjection to latest follow-up. None of these studies found significant differences in reported scores between groups at latest-follow-up.

Pooled analysis from 5 studies with a mean follow-up of at least 12 months demonstrated that the PRP group had significantly better WOMAC scores as compared with the HA group (MD, −13.6 [95% CI, −18.2 to −9.1]; $P < .0001$) (Figure 3). The I^2 statistic for WOMAC scores was 81%,

[‡‡]References 1, 11, 13, 16-18, 21, 27, 29-33, 37, 39, 42, 43.
[§§]References 1, 11, 13, 17, 21, 27, 29-33, 37, 39, 42, 43.
[‖‖]References 1, 13, 16-18, 21, 27, 31-34, 37, 39, 42, 43.
[¶¶]References 1, 11, 13, 16-18, 27, 29, 31-33, 37, 39, 43.

[##]References 11, 17, 29, 30, 33, 34, 39, 42, 43.

TABLE 3
WOMAC Total Scores[a]

Study	WOMAC Preinjection			WOMAC Postinjection		
	PRP	HA	*P* Value[b]	PRP	HA	*P* Value[b]
Cerza (2012)[11]	79.6 ± 9.5	75.4 ± 10.7		36.5 ± 17.9	65.1 ± 10.6	.001
Duymus (2017)[17]	76.1 ± 9.4	77.0 ± 2.5		54.9 ± 10.8	69.3 ± 4.3	<.001
Lisi (2018)[30]	37.0 ± 3.3	28.5 ± 2.2		NR	NR	
Raeissadat (2015)[34]	39.5 ± 17.1	28.7 ± 16.7	<.001	18.4 ± 14.4	27.5 ± 16.4	.0001
Raeissadat (2017)[33]	42.9 ± 13.5	38.8 ± 12.6		24.4 ± 16.5	27.4 ± 11.4	
Su (2018)[39]	50.2 ± 1.1	49.9 ± 1.5		36.4 ± 1.7	46.9 ± 3.8	<.05
Vaquerizo (2013)[42]	45.9 ± 12.7	50.8 ± 18.4		30.8 ± 15.5	54.2 ± 19.2	<.001
Vasavilbaso (2017)[43]	54.8 ± 11.3	58.7 ± 15.6		27.0 ± 36.8	29.6 ± 10.4	
Weighted improvement,[c] %				44.7	12.6	<.01

[a]Scores are reported as a mean ± SD at latest follow-up. HA, hyaluronic acid; NR, not reported; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]Blank cells indicate *not significant*.
[c]Reported as a percentage improvement from the preinjection score. Studies that did not provide all data were not included in the weighted improvement calculations.

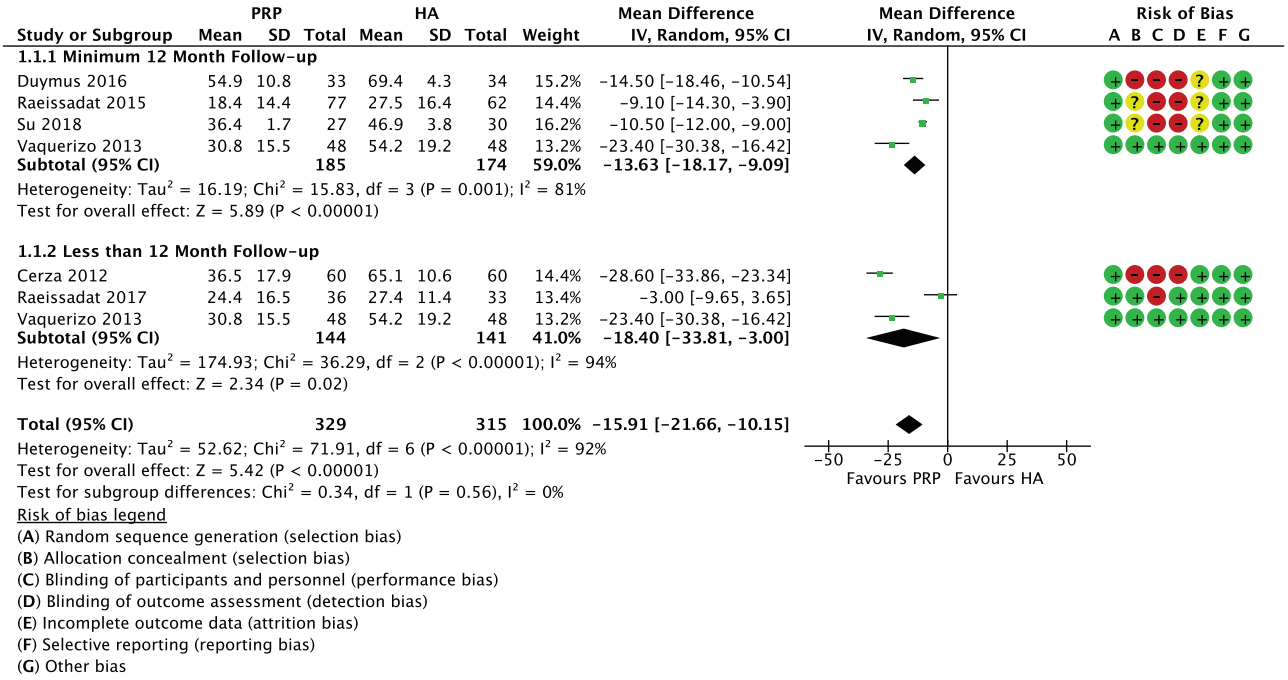

Figure 3. Forest plot of WOMAC scores. HA, hyaluronic acid; IV, inverse variance; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

suggesting that moderate to high heterogeneity may be present. However, these statistics are greatly underpowered, making it difficult to draw strong inferences. Pooled analysis from 3 studies[11,33,42] with a mean follow-up <12 months demonstrated that the PRP group had significantly better WOMAC scores than the HA group (MD, –18.4 [95% CI, −33.8 to −3.00]; $P < .0001$) (Figure 3). The I^2 statistic for WOMAC scores was 94%, suggesting that significant heterogeneity may be present.

Eleven studies[a] reported results of the VAS score (Table 4). Four studies[1,16,33,39] found PRP patients to improve significantly ($P < .05$) from preinjection to latest follow-up, and 1 study[33] found HA patients to improve significantly ($P < .05$) from preinjection to latest follow-up. Five studies[1,13,17,21,39] found PRP patients to report significantly less pain ($P < .05$) at latest follow-up when compared with HA patients, while no studies found HA patients to report significantly less pain than PRP patients. Two studies[21,27] that reported VAS scores are

[a]References 1, 13, 16, 17, 18, 21, 27, 30, 32, 33, 39.

TABLE 4
VAS Scores for Pain Severity[a]

Study	VAS Preinjection			VAS Postinjection		
	PRP	HA	*P* Value[b]	PRP	HA	*P* Value[b]
Ahmad (2018)[1]	58.0 ± 1.90	61.0 ± 17.0		41.0 ± 14.0	60.0 ± 15.0	.01
Cole (2017)[13]	57.2 ± 14.3	62.9 ± 15.7		34.6 ± 3.2	48.6 ± 3.7	.01
Di Martino (2019)[16]	72.7 ± 12.3	71.2 ± 13.3		71.9 ± 13.6	66.6 ± 14.2	
Duymus (2017)[17]	74.0 ± 10.0	83.0 ± 4.0	<.001	51.0 ± 13.0	68.0 ± 1.0	<.001
Filardo (2015)[18]	73.2 ± 12.0	71.6 ± 13.4		77.6 ± 11.1	73.4 ± 15.2	
Lisi (2018)[30]	63.0 ± 6.0	54.0 ± 4.0		NR	NR	
Paterson (2016)[32]	48.1 ± 23.8	39.7 ± 21.9		36.9 ± 25.4	14.1 ± 9.3	
Raeissadat (2017)[33]	76.0 ± 18.0	74.0 ± 15.0		46.0 ± 28.0	48.0 ± 24.0	
Su (2018)[39]	71.0 ± 3.0	70.0 ± 3.0		38.0 ± 3.0	65.0 ± 3.0	<.05
Weighted improvement,[c] %				15.5	11.4	.85

[a]Scores are reported as a mean ± SD at latest follow-up. HA, hyaluronic acid; NR, not reported; PRP, platelet-rich plasma; VAS, visual analog scale.
[b]Blank cells indicate *not significant.*
[c]Reported as a percentage improvement from the preinjection score. Studies that did not provide all data were not included in the weighted improvement calculations.

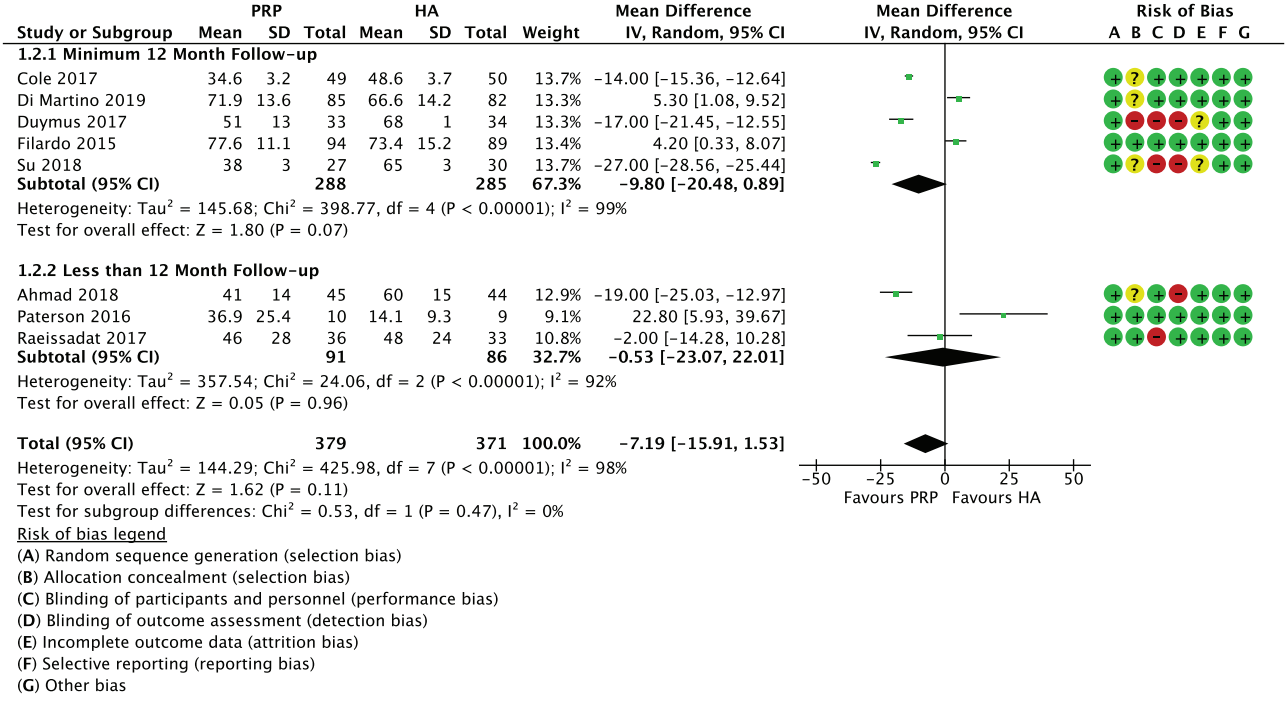

Figure 4. Forest plot of VAS scores. HA, hyaluronic acid; IV, inverse variance; PRP, platelet-rich plasma; VAS, visual analog scale.

not included in Table 4. One of these studies[27] reported medians, in which preinjection VAS scores between groups were not significantly different. At the 12-month follow-up, PRP patients demonstrated significantly lower VAS scores than the HA group ($P < .01$). The other study[21] defined improved VAS outcomes as an increased score versus baseline, while all other studies reported improved VAS outcomes as a decreased score versus baseline. This study[21] found PRP patients to report significantly better VAS scores ($P < .05$) at latest follow-up, with no difference in preinjection scores between groups.

Pooled analysis from 5 studies with a mean latest follow-up of at least 12 months demonstrated no significant differences in VAS pain scores between the groups (MD, –9.8 [95% CI, –20.5 to 0.89]; $P = .07$) (Figure 4). The I^2 statistic for VAS pain scores was 99%, suggesting that high heterogeneity may be present. However, these statistics are greatly underpowered, making it difficult to draw

TABLE 5
Subjective IKDC Scores[a]

Study	IKDC Preinjection			IKDC Postinjection		
	PRP	HA	*P* Value[b]	PRP	HA	*P* Value[b]
Ahmad (2018)[1]	49.2 ± 14.9	47.2 ± 16.2		75.7 ± 15.1	65.6 ± 16.9	.004
Cole (2017)[13]	NR	NR		65.5 ± 3.6	55.8 ± 3.8	.01
Di Martino (2019)[16]	53.3 ± 14.3	50.3 ± 13.2		72.5 ± 19.0	68.6 ± 18.8	
Filardo (2015)[18]	52.4 ± 14.1	49.7 ± 13.0		66.2 ± 16.7	64.2 ± 18.0	
Görmeli (2017)[21]	40.4 ± 5.0	40.6 ± 4.5		60.8 ± 9.8	48.4 ± 6.2	<.05
Lin (2019)[29]	35.7 ± 13.8	35.9 ± 12.7		49.9 ± 17.7	38.6 ± 16.1	
Weighted improvement,[c] %				38.0	29.2	.11

[a]Scores are reported as a mean ± SD at latest follow-up. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; NR, not reported; PRP, platelet-rich plasma.
[b]Blank cells indicate *not significant*.
[c]Reported as a percentage improvement from the preinjection score. Studies that did not provide all data were not included in the weighted improvement calculations.

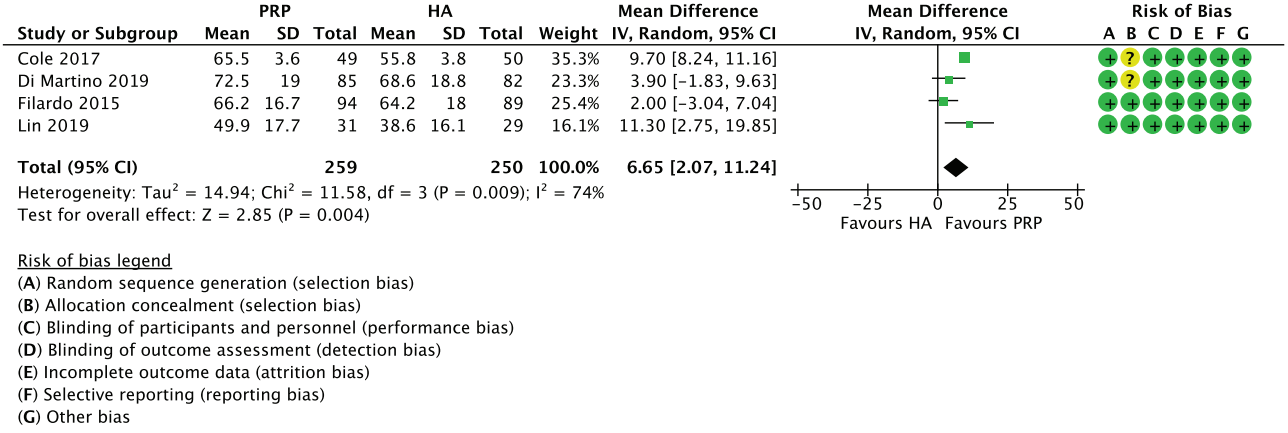

Figure 5. Forest plot of Subjective IKDC scores. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; IV, inverse variance; PRP, platelet-rich plasma.

strong inferences. Pooled analysis from 3 studies[1,32,33] with a mean follow-up <12 months demonstrated no significant differences in VAS pain scores between the groups (MD, –0.5 [95% CI, –23.1 to 22.0]; $P = .96$) (Figure 4). The I^2 statistic for VAS pain scores was 92%, suggesting that high heterogeneity may be present.

Six studies[1,13,16,18,21,29] reported results of the Subjective IKDC score (Table 5). Four studies[13,16,18,29] found PRP patients to improve significantly ($P < .05$) from preinjection to latest follow-up, and 2 studies[16,18] found HA patients to improve significantly ($P < .05$) from preinjection to latest follow-up. Three studies[1,13,21] found PRP patients to report significantly better Subjective IKDC scores ($P < .05$) at latest follow-up when compared with HA patients, while no studies found HA patients to report better scores than the PRP group.

Pooled analysis from 4 studies with a mean latest follow-up of at least 12 months demonstrated that the PRP group had significantly better Subjective IKDC scores than the HA group (MD, 6.7 [95% CI, 2.1-11.2]; $P = .004$) (Figure 5). The I^2 statistic for VAS pain scores was 74%, suggesting that moderate to high heterogeneity may be present. However, these statistics are greatly underpowered, making it difficult to draw strong inferences.

Subanalysis on Studies Utilizing LP-PRP

Of the 7 studies[11,13,29,31,33,37,42] that utilized LP-PRP, 4 reported WOMAC scores[11,29,33,42]; 2 reported VAS scores[13,33]; and 2 reported Subjective IKDC scores[13,29] (Table 6). All 4 studies[11,29,33,42] reporting on WOMAC scores, 1 of 2 studies[33] reporting on VAS, and both studies[13,29] reporting on Subjective IKDC scores found PRP patients to improve significantly ($P < .05$) from preinjection to latest follow-up. The 1 study[29] not included in Table 3 in the WOMAC section defined improved outcomes as an increased score when compared with baseline, while all other studies reported improved WOMAC outcomes as a decreased score versus baseline. This study[29] found

TABLE 6
Patient-Reported Outcomes in Studies of Leukocyte-Poor PRP[a]

	Preinjection			Postinjection		
Study	PRP	HA	*P* Value[b]	PRP	HA	*P* Value[b]
WOMAC						
Cerza (2012)[11]	79.6 ± 9.5	75.4 ± 10.7		36.5 ± 17.9	65.1 ± 10.6	.001
Raeissadat (2017)[33]	42.9 ± 13.5	38.8 ± 12.6		24.4 ± 16.5	27.4 ± 11.4	
Vaquerizo (2013)[42]	45.9 ± 12.7	50.8 ± 18.4		30.8 ± 15.5	54.2 ± 19.2	<.001
VAS						
Cole (2017)[13]	57.2 ± 14.3	62.9 ± 15.7		34.6 ± 3.2	48.6 ± 3.7	.01
Raeissadat (2017)[33]	76.0 ± 18.0	74.0 ± 15.0		46.0 ± 28.0	48.0 ± 24.0	
Subjective IKDC						
Cole (2017)[13]	NR	NR		65.5 ± 3.6	55.8 ± 3.8	.01
Lin (2019)[29]	35.7 ± 13.8	35.9 ± 12.7		49.9 ± 17.7	38.6 ± 16.1	

[a]Scores are reported as a mean ± SD at latest follow-up. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; NR, not reported; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]Blank cells indicate *not significant.*

PRP patients to report significantly better WOMAC scores ($P < .05$) at latest follow-up, with no difference in preinjection scores between groups. Overall, when comparing LP-PRP and HA patients at latest follow-up, 5 of the possible 8 outcome scores (62.5%) demonstrated significant improvement in patients undergoing treatment with PRP, while none (0%) demonstrated superiority with HA.

Subanalysis on Studies Utilizing LR-PRP

Of the 8 studies[1,16-18,27,32,34,39] that utilized LR-PRP, 2 reported WOMAC scores[17,39]; 5 reported VAS scores[1,16,18,32,39]; and 3 reported Subjective IKDC scores[1,16,18] (Table 7). Both studies[17,39] reporting on WOMAC score, 3 of the 5 studies reporting on VAS,[1,16,39] and all 3 studies[1,16,18] reporting on Subjective IKDC scores found PRP patients to improve significantly ($P < .05$) from preinjection to latest follow-up. When comparing LR-PRP and HA patients at latest follow-up, 5 of the possible 10 outcome scores (50%) demonstrated significant improvement in patients undergoing treatment with PRP when compared with HA, while none (0%) demonstrated superiority with HA.

LP-PRP vs LR-PRP

Pooled analysis of studies that compared LR-PRP and LP-PRP found no significant differences in the efficacy of either on WOMAC or VAS scores but indicated that LP-PRP resulted in greater improvements in Subjective IKDC scores.

Analysis of the effects of LR-PRP versus LP-PRP on WOMAC scores was performed among 4 studies[11,29,33,42] comparing LP-PRP and HA and 2 studies[17,39] comparing LR-PRP and HA. Pooled analysis found no evidence of a statistically significant difference in the effects of LP-PRP versus LR-PRP on WOMAC scores (Table 8).

Analysis of the effects of LR-PRP versus LP-PRP on VAS scores was performed between 2 studies[13,33] comparing LP-PRP and HA and 5 studies[1,16,18,32,39] comparing LR-PRP and HA. Pooled analysis found no evidence of a statistically significant difference in the effects of LP-PRP versus LR-PRP on VAS scores (Table 8).

Finally, analysis of the effects of LR-PRP versus LP-PRP on Subjective IKDC scores was performed between 2 studies[13,29] comparing LP-PRP and HA and 3 studies[1,16,18] comparing LR-PRP and HA. Pooled analysis found that LP-PRP resulted in greater improvements in Subjective IKDC scores. Results from the indirect effects analysis estimated that LP-PRP resulted in a mean 5.1-unit-greater improvement in Subjective IKDC scores versus LR-PRP (95% CI, −10.1 to −0.2) (Table 8).

Outcomes by OA Grade

Because 15 of the 18 included studies (83.3%) did not analyze postinjection outcomes based on OA grades, we could not perform a subanalysis on OA grade. Two studies[11,13] that included only patients with Kellgren-Lawrence grade I-III OA analyzed outcomes based on preinjection OA grade. Cerza et al[11] found no significant differences in any outcome at latest follow-up among patients with grade I, II, or III OA. Cole et al[13] found that the PRP and HA groups with grade I OA experienced significantly improved Subjective IKDC scores compared with patients with grade III OA ($P = .005$). However, there were no significant differences in outcomes between patients with grade I and II or between patients with grade II and III. No differences were found in WOMAC or VAS scores among patients with grade I, II, or III OA. Only 1 study[21] that included patients with grade IV OA analyzed results based on preinjection OA grades. Görmeli et al[21] found that patients with grade I-III OA experienced significantly better VAS and Subjective IKDC scores at latest follow-up than patients with grade IV OA ($P < .005$).

TABLE 7
Patient-Reported Outcomes in Studies of Leukocyte-Rich PRP[a]

	Preinjection			Postinjection		
Study	PRP	HA	*P* Value[b]	PRP	HA	*P* Value[b]
WOMAC						
Duymus (2017)[17]	76.1 ± 9.4	77.0 ± 2.5		54.9 ± 10.8	69.3 ± 4.3	<.001
Su (2018)[39]	50.2 ± 1.1	49.9 ± 1.5		36.4 ± 1.7	46.9 ± 3.8	<.05
VAS						
Ahmad (2018)[1]	58.0 ± 1.90	61.0 ± 17.0		41.0 ± 14.0	60.0 ± 15.0	.01
Di Martino (2019)[16]	72.7 ± 12.3	71.2 ± 13.3		71.9 ± 13.6	66.6 ± 14.2	
Filardo (2015)[18]	73.2 ± 12.0	71.6 ±13.4		77.6 ± 11.1	73.4 ± 15.2	
Paterson (2016)[32]	48.1 ± 23.8	39.7 ± 21.9		36.9 ± 25.4	14.1 ± 9.3	
Su (2018)[39]	71.0 ± 3.0	70.0 ± 3.0		38.0 ± 3.0	65.0 ± 3.0	<.05
Subjective IKDC						
Ahmad (2018)[1]	49.2 ± 14.9	47.2 ± 16.2		75.7 ± 15.1	65.6 ± 16.9	.004
Di Martino (2019)[16]	53.3 ± 14.3	50.3 ± 13.2		72.5 ± 19.0	68.6 ± 18.8	
Filardo (2015)[18]	52.4 ± 14.1	49.7 ± 13.0		66.2 ± 16.7	64.2 ± 18.0	

[a]Scores are reported as a mean ± SD at latest follow-up. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]Blank cells indicate *not significant.*

TABLE 8
Effects of Leukocyte-Poor vs Leukocyte-Rich PRP[a]

Outcome	Mean Difference	95% CI
WOMAC	−5.7	−20.7 to 9.3
VAS	−4.7	−37.6 to 28.1
Subjective IKDC	−5.1[b]	−10.1 to −0.2

[a]Negative values indicate better efficacy of leukocyte-poor vs leukocyte-rich PRP. IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]$P < .05$.

DISCUSSION

The prevalence of knee OA has increased significantly because of the rising life expectancy and physical activity of the population.[2,9] As a result, intra-articular injections such as PRP and HA have gained significant interest as viable nonsurgical treatment options for OA. The superiority of one injection over the other remains a topic of controversy, however. Multiple studies have attributed the improved outcomes with PRP to its autologous makeup and high concentration of growth factors,[1,17,29,30,39] although many studies demonstrate HA to be just as effective.[13,18,33,43] Therefore, we hypothesized that there would be no difference in clinical outcomes between patients receiving PRP and HA injections for the treatment of knee OA.

The results of this systematic review suggest that patients undergoing treatment for knee OA with PRP injections can be expected to experience improved clinical outcomes at short-term follow-up when compared with patients receiving HA injections. Of all clinical outcomes assessed in this systematic review, none demonstrated superiority with HA injections, while 15 of the 29 possible outcomes (51.7%) showed greater improvement among PRP patients. These results may in part be explained by the biological contents introduced into the cartilage that stimulate proliferation of various growth factors, such as transforming growth factor β, insulin-like growth factor, and vascular endothelial growth factor,[26] as well as migration and autocrine release of hepatocytic growth factors and HA.[37] Mechanical stress and growth factors play a pivotal role in modulating the expression of chondrocytes, and the abundancy of these cells obtained from PRP has been shown to decrease nuclear factor κβ activation, which is a major contributor to the inflamed and catabolic joint environment characterized by OA.[41] In addition, the autologous proteins found in the supernatant of PRP samples inhibit the generation of tumor necrosis factor α–stimulated chondrocytes and matrix metalloproteinase enzymes, both of which have been demonstrated to promote inflammation and early-onset OA.[45] Consequently, PRP may have several important biological advantages over HA that should be considered when providing treatment for knee OA.

When each group was evaluated independently, PRP still demonstrated much improved results over HA. Out of the 21 cases where studies reported on pre- to postinjection scores, 17 (81.0%) found PRP patients to improve significantly from preinjection to the latest follow-up, as opposed to only 8 (38.1%) HA patients.

Previous studies have demonstrated that LP-PRP serves as a superior line of treatment for OA in comparison with LR-PRP.[20,35] Despite these results, other studies do not show improved clinical outcomes of LP-PRP; thus, the ideal PRP composition for the treatment of knee OA remains controversial.[1,11,13,16,17,29] Because of the decreased deleterious effects of proteases and reactive

oxygen species released from white blood cells[20] and their ability to decrease the effects of IL-1β, LP-PRP appears to be more of an anti-inflammatory treatment than LR-PRP. Conversely, LR-PRP is proinflammatory but contains a higher concentration of growth factors.[46] LP-PRP may be better suited for treatment of knee OA, as it may increase extracellular matrix repair, reduce inflammation, and slow cartilage degeneration.[38] In studies utilizing LP-PRP, 62.5% of possible outcome scores resulted in PRP patients experiencing significantly improved postinjection results versus HA patients, as opposed to only 50.0% of outcome scores in studies utilizing LR-PRP. While it is clear from the results of this study that PRP, regardless of leukocyte content, is a more effective treatment for OA than HA, further studies are necessary to directly compare the effects of PRP leukocyte content on outcomes in patients with knee OA.

The strengths of this study include a comprehensive systematic review of level 1 studies performed by 2 independent reviewers. The limitations of this study should also be noted. In particular, none of the included studies reported on knee survivorship—that is, the number of patients who ultimately failed injection therapy and went on to require a total knee arthroplasty. Moderate to high heterogeneity may be present, although these statistics are greatly underpowered. PRP and HA administration techniques and strategies were not identical across all studies; not all studies utilized the same PRP composition; and not all studies used the same PROs. Postinjection radiographic knee OA was not consistently reported in the included studies. In addition, follow-up times were short term and highly variable, ranging from 3 to 24 months.

CONCLUSION

Patients undergoing treatment for knee OA with PRP can be expected to experience improved clinical outcomes when compared with HA patients. Additionally, LP-PRP may be a superior line of treatment for knee OA over LR-PRP, although further studies are needed that directly compare leukocyte content in PRP injections for treatment of knee OA.

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