Systematic Review

Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review

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Purpose: To determine (1) whether platelet-rich plasma (PRP) injection significantly improves validated patient-reported outcomes in patients with symptomatic knee osteoarthritis (OA) at 6 and 12 months postinjection, (2) differences in outcomes between PRP and corticosteroid injections or viscosupplementation or placebo injections at 6 and 12 months postinjection, and (3) similarities and differences in outcomes based on the PRP formulations used in the analyzed studies. **Methods:** PubMed, Cochrane Central Register of Controlled Trials, SCOPUS, and Sport Discus were searched for English-language, level I evidence, human in vivo studies on the treatment of symptomatic knee OA with intra-articular PRP compared with other options, with a minimum of 6 months of follow-up. A quality assessment of all articles was performed using the Modified Coleman Methodology Score (average, 83.3/100), and outcomes were analyzed using 2-proportion *z*-tests. **Results:** Six articles (739 patients, 817 knees, 39% males, mean age of 59.9 years, with 38 weeks average follow-up) were analyzed. All studies met minimal clinical important difference criteria and showed significant improvements in statistical and clinical outcomes, including pain, physical function, and stiffness, with PRP. All but one study showed significant differences in clinical outcomes between PRP and hyaluronic acid (HA) or PRP and placebo in pain and function. Average pretreatment Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were 52.36 and 52.05 for the PRP and HA groups, respectively ($P = .420$). Mean post-treatment WOMAC scores for PRP were significantly better than for HA at 3 to 6 months (28.5 and 43.4, respectively; $P = .0008$) and at 6 to 12 months (22.8 and 38.1, respectively; $P = .0062$). None of the included studies used corticosteroids. **Conclusions:** In patients with symptomatic knee OA, PRP injection results in significant clinical improvements up to 12 months postinjection. Clinical outcomes and WOMAC scores are significantly better after PRP versus HA at 3 to 12 months postinjection. There is limited evidence for comparing leukocyte-rich versus leukocyte-poor PRP or PRP versus steroids in this study. **Level of Evidence:** Level I, systematic review of Level I studies.

Osteoarthritis (OA) of the knee is a common condition associated with pain and morbidity.[1] The increasing number of patients with symptomatic OA will continue to place an increasingly large economic burden on global health care systems.[1] Knee arthroplasty is a reliable and successful surgical treatment to address end-stage OA. Unfortunately, the cost of and time delay to knee replacement is potentially prohibitive in some countries. In the United States, potential overutilization of arthroplasty is being met with increasing scrutiny of preoperative nonsurgical treatment.[2] This includes both nonpharmacological and pharmacological approaches. Intra-articular corticosteroid and viscosupplementation injections have successful, albeit short-term, benefits.

Recent American Academy of Orthopaedic Surgeons clinical practice guidelines have demonstrated inconclusive evidence to recommend for or against corticosteroid and strong evidence against hyaluronic acid (HA) viscosupplementation injections for patients with symptomatic knee OA.[3] This has led to the emergence

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Table 1. Effects of Platelet-Rich Plasma on Inflammation and Metabolism

Increases Anti-inflammatory Markers	Decreases Proinflammatory Markers	Anabolic Effects
Aggregan	Cyclooxygenases	Proteoglycan synthesis
	Metalloproteinases	Cartilage regeneration
	Disintegrins	
	Tumor necrosis factor alpha	
	Interferon gamma	
	Selectins	
	Interleukin-1	

of other injectable options for symptom relief and functional improvement in these patients.

Platelet-rich plasma (PRP) is an autologous derivative of whole blood that contains high concentrations of growth factors including transforming growth factor-β, insulin-like growth factor, platelet-derived growth factor, basic fibroblast growth factor, and vascular endothelial growth factor, as well as bioactive proteins that influence the healing of tendon, ligament, muscle, and bone.[4] As a result, it has been studied for its efficacy in management of various pathologies including but not limited to OA, lateral epicondylitis, rotator cuff disease, Achilles and patella tendinopathy, hamstring injuries, and degenerative spine disease.[5-10] Through the effects of the various growth factors, PRP has been shown to have a positive effect on chondrogenesis and mesenchymal stem cell proliferation.[4] PRP has also been shown to increase anti-inflammatory and decrease proinflammatory mediators (Table 1). Evidence has shown a reduction in the transactivation of nuclear factor-kappa B, the critical regulator of the inflammatory process.[4] PRP also decreases the expression of inflammatory enzymes cycloxygenase 2 and 4, metalloproteinases, and disintegrins.[11,12] These combined effects of PRP make it a potential injectable option for management of OA.

Clinically, the comparative efficacy and effectiveness of intra-articular injections of PRP, HA, and corticosteroid in the treatment of knee OA are unclear and controversial. There are limited studies comparing these options, and there are variations in the treatment approach including subject-, knee-, and outcome-specific variables including PRP preparation techniques, platelet count, severity of OA, number of injections, and molecular weight of HA.[13-15] There have been numerous studies investigating the effects of PRP or HA in the treatment of knee OA, but most do not compare these 2 or use a control group.[13,16]

The purpose of this systematic review was (1) to determine whether PRP injection is able to significantly improve validated patient-reported outcomes in patients with OA of the knee at 6 and 12 months postinjection, (2) to determine whether there is a significant difference in outcomes between PRP and viscosupplementation or PRP and placebo injections at 6 and 12 months postinjection; and (3) to determine the similarities and differences between the variety of PRP formulations used in the analyzed studies. It was hypothesized that (1) PRP injections will significantly improve validated patient-reported outcomes in patients with OA of the knee at 6 to 12 months postinjection, (2) there will be a significant difference in outcomes between PRP and viscosupplementation or PRP and placebo at 6 and 12 months postinjection, and (3) different preparations of PRP will yield significantly different results.

Methods

A systematic review was registered on PROSPERO on August 12, 2014 (registration ID: CRD42014013032). Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.[17] English-language original research therapeutic level I evidence (based on Oxford Centre for Evidence Based Medicine) randomized comparative trials were eligible for inclusion.[18] The studies that were sought compared the use of autologous PRP with HA viscosupplementation, corticosteroid, placebo, or other intra-articular injections for the treatment of symptomatic knee OA in humans with a minimum follow-up of 6 months. Basic science ex vivo and in vitro studies, levels II, III, IV, or V evidence, letters to the editor, nonknee OA, asymptomatic OA, and PRP compared with surgical options were excluded.

Separate electronic searches of the following databases were conducted: PubMed, Cochrane Central Register of Controlled Trials, SCOPUS, and Sport Discus. The searches were performed on February 12, 2015. The search terms used including "platelet-rich plasma knee osteoarthritis", "platelet rich plasma gonarthrosis", and "platelet rich plasma knee degenerative joint disease" were entered as medical subject headings for searches in all the databases used. The search results were reviewed for duplicates and the inclusion criteria to determine articles that were included in the final analysis (Fig 1).

Two authors (C.J.M. and J.D.H.) independently reviewed all articles using the methodology recommended by Harris et al.[19] The study type and design, methods, level of evidence, and populations enrolled were first identified. Primary and secondary outcomes were analyzed. This information was used to reach a consensus based on the conclusions made by the authors of the original studies.

Because of the heterogeneity of outcome measures, a best-evidence synthesis[20] was used instead of a meta-analysis. The results of the quality assessments of the individual studies were used to classify the level of evidence.[21] This qualitative analysis was performed

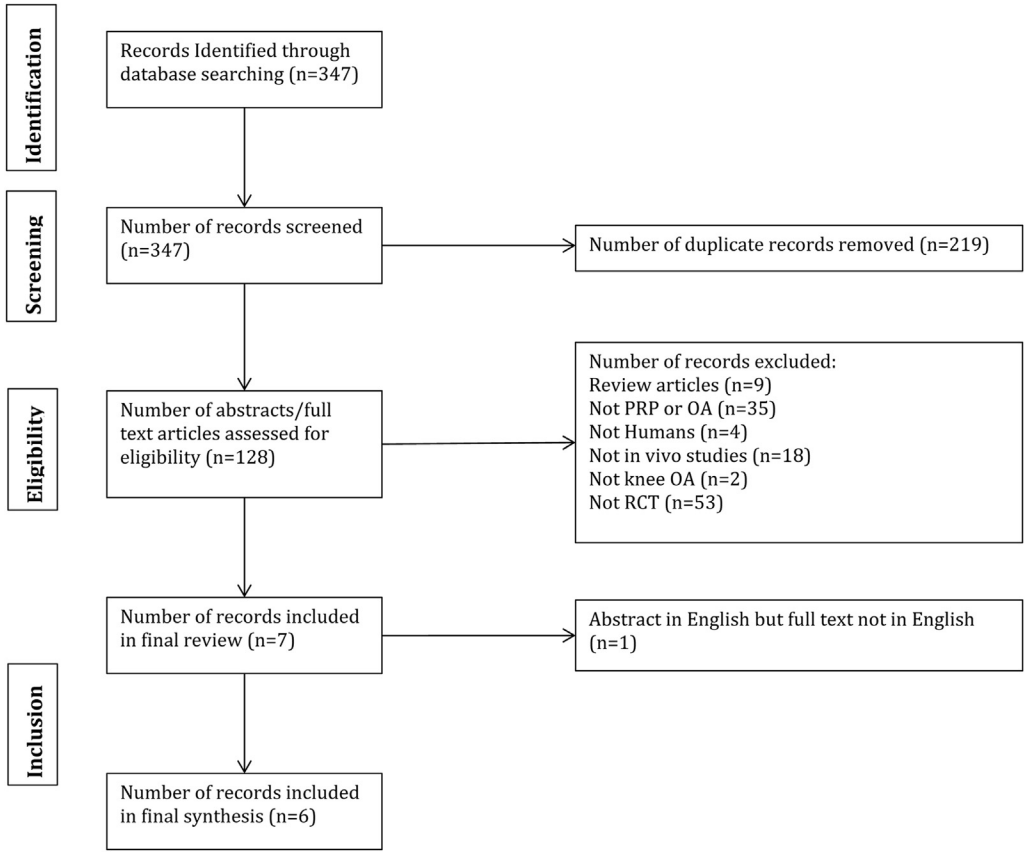

Fig 1. Flow diagram summarizing the literature search, screening, and review.

with 5 levels of evidence based on the quality and results of the included studies.[22] In addition, study methodological quality was analyzed using the Modified Coleman Methodology Score (MCMS).[23] Descriptive statistics were calculated using the mean ± standard deviation for quantitative continuous data and frequencies with percentages for qualitative categorical data. Comparisons in outcome scores at pre- and post-injection time points and between PRP and HA groups were made using the 2-proportion *z*-test calculator (http://in-silico.net/tools/statistics/ztest) using alpha 0.05 because of the difference in sample sizes between compared groups.

Results

Six articles (739 patients, 817 knees) were analyzed (Table 2). There were 39% males and 61% females with a mean age of 59.9 years per patient and 59.2 years per knee and mean follow-up of 38 weeks per patient and 37 weeks per knee. Radiographically, the Kellgren-Lawrence and Ahlback grading systems were used determine severity of knee OA. Two studies used the Ahlback classification system and showed that 58.2% were grade I, 32.4% were grade II, and 9.4% were grade III. Four studies used the Kellgren-Lawrence classification and showed that 8.7% were grade I, 40.7% were grade II, 37.9% were grade III, and 12.6% were grade IV. The Filardo et al. study only reported average Kellgren-Lawrence grades for HA and PRP groups (2.1 and 2.2, respectively) and therefore was not included in the grade-percentage stratification above. According to the MCMS, 3 articles were excellent (with scores of 85 or greater), and 3 were good (scores between 70 and 84), with a mean score of 83.3/100. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was the most frequently used outcome score (5 of 6 studies), however, one of 6 used International Knee Documentation Committee (IKDC), one of 6 used Knee Injury and Osteoarthritis Outcome Score (KOOS), one of 6 used Short Form-36, one of 8 used Tegner, 2 of 6 used the visual analog scale (VAS), and 2 of 6 used Lequesne.

PRP significantly improved validated patient-reported outcomes, according to WOMAC and IKDC scores, in patients with OA of the knee at 6 and 12 months post-injection (Table 3). PRP was also shown to be better than HA at improving patient outcomes. The outcomes evaluated included pain, physical function, and stiffness. According to 2-proportion *z*-tests, the average pretreatment WOMAC scores for PRP and HA were 52.36 and 52.05, respectively ($P = .420$), among studies that compared both treatment modalities. At 12 to 26 weeks, the average WOMAC scores for PRP and HA treatments were 28.5 and 43.4, respectively, with a significant

Table 2. Demographics and Methods of the Various Clinical Trials

Publication year	Cerza et al.[27] 2012	Filardo et al.[28] 2012	Patel et al.[29] 2013	Sanchez et al.[30] 2012	Vaquerizo et al.[31] 2013	Raeissadat et al.[32] 2014
Subject enrollment date	September 2009-September 2010	Not recorded	Not recorded	January 2008-November 2009	Not recorded	Not recorded
Country, Continent	Italy, Europe	Italy, Europe	India, Asia	Spain, Europe	Spain, Europe	Iran, Asia
Conflict of interest	None	None	Not mentioned	None	Not mentioned	None
No. of subject (knees)	120 (120)	109 (109)	78 (156)	176 (176)	96 (96)	160 (160)
Gender: male, female	53, 67	68, 41	22, 53	85, 91	38, 58	23, 116
Mean age	66.4	56.5	52.8	59.8	63.6	58.8
Bilateral *v* unilateral knee injections	Unilateral	Unilateral	Bilateral	Unilateral	Unilateral	Unilateral
Right *v* left	91 right, 29 left	Not recorded	78 left, 78 right	Not recorded	Not recorded	Not recorded
Study Group 1	60 patients received 4 weekly intra-articular injections of PRP	54 patients received 3 weekly intra-articular injections of PRP	26 patients (52 knees) received a single injection of PRP and 25 patients (50 knees) received 2 injections of PRP 3 weeks apart	87 patients received 3 weekly intra-articular PRGF-Endoret	48 patients received 3 biweekly intra-articular PRGF-Endoret	87 patients received 2 intra-articular injections of PRP 4 weeks apart
Study Group 2	60 patients received 4 weekly intra-articular injections of HA	55 patients received 3 weekly intra-articular injections of HA	23 patients (46 knees) received a single injection of normal saline (8 mL)	89 patients received 3 weekly intra-articular HA	48 patients who received 1 intra-articular HA	73 patients received 3 weekly intra-articular HA
Radiographic classification	Kellgren-Lawrence Grade I: 25 Grade II: 22 Grade III: 13	Kellgren-Lawrence Average of Grade 2.2 for PRP group and Grade 2.1 for HA group	Ahlback Grade I: 98 Grade II: 39 Grade III: 7	Ahlback Grade I: 87 Grade II: 64 Grade III: 23	Kellgren-Lawrence Grade II: 32 Grade III: 47 Grade IV: 17	Kellgren-Lawrence Grade I: 6 Grade II: 91 Grade III: 75 Grade IV: 28
Length of follow up	24 weeks	12 months	6 months	24 weeks	48 weeks	52 weeks
Outcome scores used	WOMAC	IKDC, TEGNER, KOOS, EQ-VAS	WOMAC, VAS	WOMAC, Lequesne	WOMAC, Lequesne, OMERACT-OARSI	WOMAC, SF-36
Prior surgeries	No	63 subjects	No	Not recorded	Not recorded	Not recorded
Prior Injections	No	Not recorded	none in prior 3 months	none in prior 3 months	none in prior 6 months	None in prior 2 weeks
Prior physical therapy	Yes	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded
Post injection treatments	None	None	None	None	None	Physical therapy
Use of NSAIDs (few days pre injection and immediate post-injection)	No	No	Not recorded	No	None	None
Use of cryotherapy post-injection	No	Yes	No	No	Not recorded	No
Injection approach	Superolateral	Not recorded	Superolateral	Not recorded	Superolateral	Anteromedial or Lateral midpatellar

(continued)

Table 2. Continued

Publication year	Cerza et al.[27] 2012	Filardo et al.[28] 2012	Patel et al.[29] 2013	Sanchez et al.[30] 2012	Vaquerizo et al.[31] 2013	Raeissadat et al.[32] 2014
Control group injection	HA 20 mg/2 mL; Hyalgan; Fidia, Abano Terme, Italy	HA >150 Kda, Hyalubrix; Fidia, Abano Terme, Italy	Normal saline	HA, Euflexxa; Copenhagen, Denmark	Durolane (Non-animal stabilized HA); Q-MED AB, Uppsala, Sweden	Hyalgan (High molecular weight HA; 500 Kda - 730 Kda); Fifia Farmaceutici S.p.A, Abano Terme, Italy
Primary and secondary outcomes	WOMAC score before the infiltration and at 4, 12, and 24 weeks after the first injection	IKDC, EQ-VAS, TEGNER, and KOOS scores, range of motion and knee circumference changes were evaluated at 2, 6 and 12 months	WOMAC at 6 weeks, 3 months, and 6 months	WOMAC scores at 1, 2, and 6 months	WOMAC and Lequesne scores at 24 and 48 weeks	WOMAC and SF-36 scores at 52 weeks

NOTE. Patel et al.[29] had 78 patients with bilateral knee osteoarthritis, all of which were included in the study, and this study had 3 separate treatment groups (2 with PRP, one with HA). The level of evidence for all trials was level I. Knee range of motion was not recorded for any trial.

EQ-VAS, EuroQol visual analog scale; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; PRGF-Endoret, platelet-rich growth factor-Endoret; PRP, platelet-rich plasma; SF-36, Short Form-36; TEGNER, Tegner activity score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

difference ($P = .0008$) favoring PRP over HA. At 26 to 52 weeks, the average WOMAC scores for PRP and HA treatments were 22.8 and 38.1, respectively, with a significant difference ($P = .0062$) favoring PRP over HA. There was a significant difference between pre-PRP and 4 to 6 weeks ($P = .047$), 6 to 12 weeks ($P = .006$), 12 to 26 weeks ($P < .001$), and 26 to 52 weeks ($P < .001$). There was no significant difference between 4 to 6 weeks and 6 to 12 weeks ($P = .52$); 6 to 12 weeks and 12 to 26 weeks ($P = .26$); and 12 to 26 weeks and 26 to 52 weeks ($P = .21$). WOMAC was most frequently used outcome score (5/6 studies). All post-PRP time points up to 12 months were significantly better than preinjection in WOMAC score. The distribution-based method using the standard error of measurement was used to determine the minimal clinical important difference (MCID). A difference in WOMAC and IKDC scores of at least one standard error of measurement was considered the criterion for achieving MCID.[24] The WOMAC and IKDC scores analyzed in this review revealed true MCID in outcomes.

All studies showed significant clinical and statistical improvements in outcomes at 3 to 12 months of follow-up, including pain, physical function, and stiffness, with the use of PRP in treating knee OA according to WOMAC and IKDC scores. All but one study showed significant differences between PRP and HA or PRP and placebo in clinical outcomes of improvement of pain and function for at least 6 to 12 months. One study compared PRP to saline (placebo), and no studies compared PRP to corticosteroid injection.

No study compared leukocyte-poor PRP to leukocyte-rich PRP. However, all studies except Filardo et al. used leukocyte-poor PRP, and all studies except Filardo et al. showed significant clinical and statistical improvements on WOMAC scores between HA and PRP or HA and placebo groups. The studies used different PRP preparations with 3 of 6 using calcium chloride activator, one of 6 used leukocyte-rich PRP, 4 of 6 using the single spin approach, and 2 of 6 using the double spin approach (Table 4). The different PRP systems used were also classified using the PAW classification system, a classification system for PRP that looks at platelet concentration, activation method, and white blood cell (WBC) count.[25]

Owing to the fact that the only outcomes that were able to be compared were those of WOMAC scores as indicated above, the best-evidence synthesis is moderate and the summary of recommendation taxonomy is "B" for this review.[22,26]

Discussion

It was determined that intra-articular PRP injections significantly improve the clinical outcomes in symptomatic knee OA. PRP was also shown to be significantly better than HA or placebo for the treatment of symptomatic knee OA. Treating OA nonoperatively has

Table 3. Summary of Results Including WOMAC, VAS, Tegner, Lequesne, IKDC, and SF-36 Scores from the Various Studies

Articles	Pretreatment	Early (4-6 Weeks)	Mid (6-12 Weeks)	Late (12-26 Weeks)	Extended (26-52 Weeks)
Cerza et al.[27]	ACP: WOMAC 76.9 ± 9.5 HA: WOMAC 75.4 ± 10.7	ACP: WOMAC 49.6 ± 17.7 HA: WOMAC 55.2 ± 12.3 ($P < .001$) between groups	ACP: WOMAC 39.1 ± 17.8 HA: WOMAC 57 ± 11.7 ($P < .001$) between groups	ACP: WOMAC 36.5 ± 17.9 HA: WOMAC 65.1 ± 10.6 ($P < .001$) between groups	DNC
Filardo et al.[28]	PRP: IKDC score 50.2 ± 15.7 Tegner score 2.9 ± 1.4 HA: IKDC score 47.4 ± 15.7 Tegner score 2.6 ± 1.2	DNC	PRP: IKDC score 62.8 ± 17.6 HA: IKDC score 61.4 ± 16.2	PRP: IKDC score 64.3 ± 16.4 HA: IKDC score 61.0 ± 18.2	PRP: IKDC score 64.9 ± 16.8 Tegner score 3.8 ± 1.3 HA: IKDC score 61.7 ± 19.0 Tegner score 3.4 ± 1.6 *P* values not recorded
Patel et al.[29]	PRP1: WOMAC 49.86 ± 17.83 VAS 4.56 ± 0.61 PRP2: WOMAC 53.20 ± 16.18 VAS 4.64 ± 0.56 Saline: WOMAC 45.54 ± 17.29 VAS 4.57 ± 0.62	PRP1: WOMAC 25.36 PRP2: WOMAC 24.96 Saline: WOMAC 46.78	PRP1: WOMAC 22.48 PRP2: WOMAC 25.70 Saline: WOMAC 50.70	PRP1: WOMAC 27.18 VAS 2.16 ± 1.543 PRP2: WOMAC 30.48 VAS 2.54 ± 1.717 Saline: WOMAC 53.09 VAS 4.61 ± 0.745 WOMAC: percentage benefit from baseline at each follow up was greater in PRP1 and PRP2 than Saline ($P < .001$) with no difference between PRP1 and PRP2. VAS pain reduction benefit for the PRP1 and PRP 2 groups ($P = .001$) with no significant benefit between the groups ($P = .410$). No VAS pain reduction benefit for saline group ($P = .598$)	DNC
Sanchez et al.[30]	PRGF: WOMAC 121.8 ± 44.4 Lequesne 9.5 ± 3.0 HA: WOMAC 115.6 ± 45.1 Lequesne 9.1 ± 3.2	DNR	DNR	PRGF: WOMAC 74.0 ± 42.7 38.2% of patients had 50% decrease in WOMAC pain score 57.3% of patients had 20% decrease in WOMAC pain scoreLequesne 5.2 ± 3.4 HA: WOMAC 78.3 ± 48.1 24.1% of patients had 50% decrease in WOMAC pain	DNC

(continued)

Table 3. Continued

Articles	Pretreatment	Early (4-6 Weeks)	Mid (6-12 Weeks)	Late (12-26 Weeks)	Extended (26-52 Weeks)
				score. 52.9% of patients had 20% decrease in WOMAC pain score. Lequesne 5.4 ± 3.3 Differences between PRGF and HA for 50% decrease in WOMAC pain score ($P = .044$), for 20% decrease ($P = .555$), for total WOMAC score ($P = .561$), and for Lequesne score ($P = .714$)	
Vaquerizo et al.[31]	PRGF: WOMAC 45.9 ± 12.7 Lequesne 12.8 ± 3.8 HA: WOMAC 50.8 ± 18.4 Lequesne 13.1 ± 38	DNC	DNC	For patients with 30% decrease in: WOMAC summed score: rate of response of PRGF was 66, 43, and 23 percentage points higher than that of HA for pain, physical function and stiffness, respectively ($P < .001$, $P < .001$, $P = .02$, respectively). Lequesne score: PRGF group is 56 percentage points higher than HA group ($P < .001$) For patients with 50% decrease in: WOMAC summed score: rate of response of PRGF was 43, 29, and 19 percentage points higher than that of HA for pain, physical function and stiffness, respectively ($P < .001$, $P = .001$, $P = .035$, respectively). Lequesne score: PRGF group is 25 percentage points higher than HA group ($P = .002$)	For patients with 30% decrease in: WOMAC summed score: rate of response of PRGF was 46, 37, and 40 percentage points higher than that of HA for pain, physical function and stiffness, respectively ($P < .001$, $P < .001$, $P < .001$, respectively). Lequesne score: PRGF group 46 percentage points higher than HA group ($P < .001$) For patients with 50% decrease in: WOMAC summed score: rate of response of PRGF was 29-, 31-, and 28 percentage points higher than that of HA for pain, physical function and stiffness, respectively ($P < .001$, $P < .001$, $P = .001$, respectively). Lequesne score: 19 and 2 percentage points in the PRGF and HA groups, respectively
Raeissadat et al.[32]	PRP: WOMAC 39.5 ± 17.06 SF-36 (PCS) 178.14 ± 81.0 SF-36 (MCS) 229.22 ± 95.62 HA: WOMAC 28.69 ± 16.69 SF-36 (PCS) 180.4 ± 68.52 SF-36 (MCS) 226.43 ± 97.39	DNC	DNC	DNC	PRP: WOMAC 18.44 ± 14.35 ($P < .001$)SF-36 (PCS) 255.96 ± 77.59 ($P < .001$)SF-36 (MCS) 269.92 ± 91.48 ($P < .001$) HA: WOMAC 27.46 ± 16.36 ($P = .009$)SF-36 (PCS) 189.39 ± 103.73 ($P = .37$) SF-36 (MCS) 216.91 ± 100.9 ($P = .74$)

(continued)

Table 3. Continued

Articles	Pretreatment	Early (4-6 Weeks)	Mid (6-12 Weeks)	Late (12-26 Weeks)	Extended (26-52 Weeks)
Average WOMAC scores across studies	PRP: 52.36 HA: 52.05 No significant difference ($P = .420$) between PRP and HA groups			PRP: 28.5 HA: 43.4 Significant difference ($P = .0008$) favoring PRP over HA	PRP: 22.8 HA: 38.1 Significant difference ($P = .0062$) favoring PRP over HA

NOTE. To assess the severity of gonarthrosis, the sum of all points is determined, with a minimum score of 0 and a maximum of 24, where 0 indicates no severity; 1-4, mild; 5-7, moderate; 8-10, severe; 11-13, very severe; and 14 or greater, extremely severe. Average WOMAC scores for the studies that compared PRP versus HA with follow-up of at least 12-26 weeks with *P*-values determined by 2-proportion *z*-tests were included.

ACP, autologous conditioned plasma; DNC, study did not collect data during this time period; DNR, study collected data but did not report the numbers on the manuscript; IKDC, International Knee Documentation Committee; MCS, mental component of SF-36; PCS, physician component of SF-36; PRGF-Endoret (platelet-rich growth factor-Endoret); SF-36, Persian form of short form 36; TEGNER, Tegner activity score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; Lequesne score is an index of severity for osteoarthritis of the knee that includes 3 subscales (pain or discomfort, maximum distance walked, and activities of daily living).

been ongoing for several decades. Multiple studies have reported the use of HA, PRP, and corticosteroids, among other agents, in the nonoperative treatment of OA. While there are a good amount of studies documenting the use of HA in the treatment of knee OA, there are limited studies documenting the use of PRP for the same purpose. More importantly, there are very limited studies comparing the use of PRP with that of HA or PRP with placebo in the treatment of knee OA.[27-32] This study's aim was to determine whether PRP injection is able to significantly improve validated patient-reported outcomes in patients with OA of the knee, determine whether there is a significant difference in outcomes between PRP and viscosupplementation or PRP and placebo injections, and evaluate the similarities and differences between the variety of PRP formulations used in the analyzed studies. The hypotheses that (1) PRP injections will significantly improve validated patient-reported outcomes in patients with OA of the knee and (2) that there will be significant differences in outcomes between PRP and viscosupplementation or PRP and placebo were confirmed; the third hypothesis that different preparations of PRP will yield significantly different results was inconclusive. Clinicians should use PRP in patients with symptomatic knee OA with Ahlback grades I to III or Kellgren-Lawrence grades I to III. PRP injections can be administered in 2 to 4 sessions, 2 to 4 weeks apart. This recommendation is based on ranges used in the studies included in this review.

Multiple studies have shown improved patient outcomes with the use of PRP for the treatment of knee OA. Gobbi et al. tried to determine the effectiveness of intra-articular PRP injections in active patients with knee OA and to evaluate clinical outcomes in patients with and without previous surgical treatment for cartilage lesions.[33] The PRP treatment showed positive effects in patients with knee OA. Operated and non-operated patients showed significant improvement by means of pain reduction and improved symptoms and quality of life.

Autologous PRP injections have shown more and longer efficacy than HA injections in reducing pain and function and recovering articular function.[15] Three homogenous groups of patients were treated with 3 injections of PRP, low molecular weight HA, and high molecular weight HA. The results showed better performance for PRP group at 6 months of follow-up. This study also showed that younger and more active patients achieved better results with a low degree of cartilage degeneration.

There are many PRP systems, some of which have higher concentrations of WBCs, with others having higher concentrations of growth factors but not the additional concentration of WBCs. Since neutrophils are the most abundant type of WBCs, excessive neutrophil infiltration has been associated with chronic

Table 4. Platelet-Rich Plasma (PRP) Preparation and Characteristics and Use of Ultrasound Guidance for Verification of Injection in Knee Joint

Article	PRP Spinning Approach	Duration of Spin (Minutes)	Company	PRP Activator	PRP Volume Injected (mL)/No. of Injections	Platelet Concentration	White Blood Cell Count	PAW Classification
Cerza et al.[27]	Single	NR	Biocore, Arthrex Inc, Karlsfeld, Germany	None	5.5/4	>5× baseline	Low	P4-B
Filardo et al.[28]	Double	6 and 15[a]	NR	NR	8/3	5× baseline	1.2× baseline	P4-A
Patel et al.[29]	Single	15	PGIMER	$CaCl_2$	8/1 and 2[b]	<5× baseline	0	P2-B/P3-B
Sanchez et al.[30]	Single	8	BTI, Biotechnology Institute, Vitoria, Spain	$CaCl_2$	8/3	<5× baseline	Low	P2-B/P3-B
Vaquerizo et al.[33]	Single	8	BTI, Biotechnology Institute, Vitoria, Spain	$CaCl_2$	8/3	<5× baseline	Low	P2-B/P3-B
Raeissadat et al.[32]	Double	15 and 7[a]	Arya Mabna Tashkis Corp.	None	4-6/2	5.2× and 4.8× baseline[c]	780 and 808 cells/μL	P4-B

NOTE. No ultrasound guidance was used in any study.
NR, not recorded; PAW classification, classification system for PRP that looks at platelet concentration, activation method, and white blood cell count[25]; PGIMER, Department of transfusion Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India.
[a]Represents times for first and second centrifugation.
[b]One group received one injection, and the other group received 2 injections.
[c]Averages for first and second injections, respectively.

inflammation and delayed wound healing. Through phagocytosis, macrophages are known to clear up the particulate debris that accumulates after neutrophil activation and release of proteolytic enzymes.[34] Several studies have investigated the effects of leukocyte-poor versus leukocyte-rich PRP in tissue healing. PRP rich in leukocytes have been shown to cause a significantly greater acute inflammatory response and increased synoviocyte cell death.[35,36] Despite having similar safety profiles, leukocyte-rich PRP and leukocyte-poor PRP were shown to both induce more transient reactions than does HA.[37] Of the studies included in this review, the Filardo et al. study used leukocyte-rich PRP, which showed improved outcomes in the parameters measured but no significant differences when compared to HA. All other studies included in this review used leukocyte-poor PRP and all showed improved outcomes in the parameters measured as well as significant differences when compared to HA or placebo. Given that none of the studies included in this review directly compared leukocyte-rich PRP versus leukocyte-poor PRP, a conclusion comparing the effects of these formulations on treatment of symptomatic knee OA cannot be made, and it will be an area of focus for future research.

Limitations

There were some limitations and biases noted among the studies included in this review. With the exception of Sanchez et al.,[30] none of the reviews used a double-blinded approach. Even though Patel et al.[29] reported that their study was double-blinded, it is noted that 2 out of the 3 study groups received one injection while the other received 2 injections. This variation in intervention makes it difficult to blind the participants, and it remains unclear whether performance bias is present. Also, Cerza et al.[27] and Patel et al.[29] did not report their randomization procedures. The results reported by these studies could be affected by the randomization and blinding approaches. The studies included reported follow-ups of up to 12 months in 3 papers and 6 months in 3 papers. Longer-term follow-ups will provide a better sense of the long-term effects of the interventions. Radiographic data were not collected at follow-up visits in any of the studies, and this information would have been useful in providing additional objective data for analysis. Given data from the MCMS, future studies can improve on looking at longer-term follow-ups of at least 2 years, including postinjection rehabilitation protocols, and providing adequate and consistent description of injection techniques used.

All but one study used WOMAC scores, with the outlier using IKDC scores together with KOOS and Tegner. WOMAC and IKDC both meet MCID and MDC criteria and have better test-retest reliability and

internal consistency compared with KOOS and Tegner.[24] Thus WOMAC and IKDC are the best outcome scores for knee OA studies. Future studies can improve with using both WOMAC and IKDC tools simultaneously.

There are several limitations of this review. The number of studies (n = 6) included in this review is small. Also, one of the 6 studies included compared PRP to placebo, while the others compared PRP to HA. Another possible limitation of this review is that other relevant studies on this topic could have been excluded, despite conducting a systematic search. Given that we found many duplicate studies among several databases, we do not feel that many studies, if any at all, were omitted.

Conclusions

In patients with symptomatic knee OA, PRP injection results in significant clinical improvements up to 12 months postinjection. Clinical outcomes and WOMAC scores are significantly better after leukocyte-poor PRP versus HA at 3 to 12 months postinjection. There is limited evidence for comparing leukocyte-rich versus leukocyte-poor PRP in this study.

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