Systematic Review

The Efficacy of Platelet-Rich Plasma in the Treatment of Symptomatic Knee Osteoarthritis: A Systematic Review With Quantitative Synthesis

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Purpose: The purpose of this systematic review was to synthesize the available Level I and Level II literature on platelet-rich plasma (PRP) as a therapeutic intervention in the management of symptomatic knee osteoarthritis (OA). **Methods:** A systematic review of Medline, Embase, Cochrane Central Register of Controlled Trials, PubMed, and www.clinicaltrials.gov was performed to identify all randomized controlled trials and prospective cohort studies that evaluated the clinical efficacy of PRP versus a control injection for knee OA. A random-effects model was used to evaluate the therapeutic effect of PRP at 24 weeks by use of validated outcome measures (Western Ontario and McMaster Universities Arthritis Index, visual analog scale for pain, International Knee Documentation Committee Subjective Knee Evaluation Form, and overall patient satisfaction). **Results:** Six Level I and II studies satisfied our inclusion criteria (4 randomized controlled trials and 2 prospective nonrandomized studies). A total of 577 patients were included, with 264 patients (45.8%) in the treatment group (PRP) and 313 patients (54.2%) in the control group (hyaluronic acid [HA] or normal saline solution [NS]). The mean age of patients receiving PRP was 56.1 years (51.5% male patients) compared with 57.1 years (49.5% male patients) for the group receiving HA or NS. Pooled results using the Western Ontario and McMaster Universities Arthritis Index scale (4 studies) showed that PRP was significantly better than HA or NS injections (mean difference, −18.0 [95% confidence interval, −28.8 to −8.3]; $P < .001$). Similarly, the International Knee Documentation Committee scores (3 studies) favored PRP as a treatment modality (mean difference, 7.9 [95% confidence interval, 3.7 to 12.1]; $P < .001$). There was no difference in the pooled results for visual analog scale score or overall patient satisfaction. Adverse events occurred more frequently in patients treated with PRP than in those treated with HA/placebo (8.4% *v* 3.8%, $P = .002$). **Conclusions:** As compared with HA or NS injection, multiple sequential intra-articular PRP injections may have beneficial effects in the treatment of adult patients with mild to moderate knee OA at approximately 6 months. There appears to be an increased incidence of nonspecific adverse events among patients treated with PRP. **Level of evidence:** Level II, systematic review of Level I and II studies.

Osteoarthritis (OA) is a progressively debilitating condition that is associated with pain and morbidity.[1] This condition adversely impacts patient mobility and quality of life.[1] OA management can involve both conservative and operative approaches.[1,2] Conservative management includes physiotherapy, analgesia, nonsteroidal anti-inflammatory agents, and intra-articular injections.[3-7] Although these agents have been beneficial in the short-term, there is a lack of evidence that such interventions alter the natural history or progression of OA.[3-7] Other complementary medications, such as glucosamine and chondroitin, are also commonly used despite equivocal efficacy.[8-11] With respect to surgical options for OA, there is little

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evidence to support routine arthroscopy and debridement.[12-14] Definitive surgical options include osteotomy for unicompartmental OA, as well as partial or total joint arthroplasty.[1,15] The change in composition of synovial fluid at different stages of OA has been well reported. This degenerative process involves decreased hyaluronic acid (HA) content and fluid viscosity when compared with unaffected knees.[16,17] There has also been interest in using HA as an adjunct in cartilage repair.[18-20] HA is a mucopolysaccharide component of synovial fluid responsible for its viscoelastic properties.[18] In animal models of OA, HA has been found to inhibit degenerative changes within cartilage matrix, decrease the extent of synovial inflammation, and enhance proteoglycan content.[21] Intra-articular HA viscosupplementation has been shown to be clinically efficacious for the management of knee OA, particularly in the short term.[4,22-24] The main therapeutic action of HA is to increase the viscosity of synovial fluid and promote endogenous production of HA[10,25]; however, its molecular weight (MW) may influence the efficacy and side effect profile.[26-28] Higher-MW preparations are thought to be more clinically efficacious in the treatment of OA.[26]

More recently, platelet-rich plasma (PRP) has been used in the management of knee OA. PRP is an autologous blood product produced by the centrifugation of whole blood yielding a concentration of platelets above baseline levels.[29,30] However, despite its widespread use, multiple systematic reviews on the use of PRP injections for tissue, tendon, or cartilage healing have shown conflicting supporting evidence.[31-34]

The clinical efficacy of PRP in the treatment of knee OA is unclear, with shortcomings in the current literature, including a lack of volume standardization and interval/frequency of administration.[34-36] In addition, the use of anticoagulants, activating agents, and separation techniques has varied considerably among studies.[35,36] Many nonrandomized studies have had small sample sizes that were reviewed retrospectively without comparisons to control groups.[35,36]

The purpose of this systematic review was to synthesize the available Level I and Level II literature on PRP as a therapeutic intervention in the management of symptomatic knee OA. We hypothesized that there would be no difference in functional outcomes or satisfaction of patients who received PRP when compared with HA and placebo.

Methods

Inclusion and Exclusion Criteria

All published randomized controlled trials (RCTs) or prospective cohort studies (PCSs) that evaluated the clinical efficacy of intra-articular PRP (or similarly defined preparations—autologous platelet concentrate, autologous conditioned plasma, or platelet-rich growth factors) against either HA or placebo (defined as normal saline solution [NS]) in the treatment of knee OA in humans were eligible for inclusion. It was decided a priori that only RCTs (deemed Level I studies) or prospective comparative studies (deemed Level II studies) would be included.[37] This would absolve any recall or selection bias with retrospective observational studies.[38] Only studies that included patients aged 18 years or older and had a minimum of 24 weeks of follow-up were included.[3] Furthermore, all severities of degenerative OA, either grade 0 to IV on the Kellgren-Lawrence grading (KLG) scale[39] or grade 1 to 3 on the Ahlbäck scale,[40] were included. Other than the patients who were excluded for receiving only one PRP injection (group A in the study of Patel et al.[36]), patients were not actively excluded. The effective follow-up rate is based on the follow-up in each of the included studies.[17,22,36,41-43]

Primary and Secondary Outcomes

The primary outcome for this systematic review (at 24 weeks of follow-up) was the Western Ontario and McMaster Universities Arthritis Index (WOMAC).[44,45] Secondary outcomes included the (1) visual analog scale (VAS) for pain,[46,47] (2) International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form,[48] (3) patient-reported procedure satisfaction (binary outcome), and (4) number of patients with adverse events (AEs) (defined later) at the time of injection (binary outcome).

Search Strategy and Study Selection

A systematic search of Medline (1946 onward to week 6 of 2013), Embase (1980 onward to week 6 of 2013), Cochrane Central Register of Controlled Trials (week 6 of 2013), PubMed (week 6 of 2013), and www.clinicaltrials.gov (for any ongoing registered randomized clinical trials) was performed independently by 2 investigators. Any discrepancies were resolved by discussion.

The bioinformatics search strategy used was a text search (within titles or keywords) for (1) "*platelet*" or "*PRP*" AND (2) "*arthritis*." The search was only limited to human studies. No language or date exclusions were applied. Two reviewers concurrently reviewed all titles and abstracts for relevance and inclusion criteria. If ambiguity or uncertainty was encountered, the study was included until full-text review could be performed. Before search initiation, we defined unpublished studies, which may have been presented only at society meetings, as ineligible because of the high probability that complete results could not be extracted and the inability to accurately grade the methodologic quality.

Full texts of all relevant studies were obtained, and 2 independent reviewers reviewed studies to ensure concordance with the a priori—defined inclusion criteria. Any discrepancies between reviewers were resolved through discussion with a third reviewer (senior author) until consensus was reached. Reviewers were not blinded to the authors or affiliated institutions of the retrieved studies. The bibliographies of included studies were manually back-referenced to ensure that no relevant studies were missed.

Data Extraction

Studies meeting the inclusion criteria had their data extracted by 2 reviewers on collection report forms. To minimize error, all data extraction was performed in duplicate by a third reviewer (J.C.). The data were inputted into RevMan version 5.1 (The Cochrane Collaboration, Oxford, England) for pooling and data analysis.

Pertinent data (for pooled odds ratios [ORs] or mean differences [MDs]) that were not reported in paper or E-publication manuscripts of studies were retrieved through email correspondence with study authors. Personal correspondence was attempted for 3 studies.[36,41,49] One study failed to mention the standard deviation values for WOMAC scores at 6 months, and this was successfully retrieved through email correspondence; in addition, this study failed to report the OA severity of 2 patients.[36] A second study failed to report the percent patient satisfaction in the control arm at 6 months.[41] Unfortunately, email correspondence was not successful with the authors of the study.[41] Similarly, no correspondence was successfully made with the authors of a third study that failed to report absolute (non-normalized) WOMAC scores for both the experimental and control arms of the study, and it could not be included in the pooled analysis.[49] One study included 2 control groups: low—molecular weight (LMW) HA and high—molecular weight (HMW) HA.[22] For the latter study, HMW HA data were used and a separate sensitivity analysis was also performed using the LMW HA data.

Quality Assessment

Only Level I or Level II studies were included.[37] As has been previously performed, studies were assessed for methodologic quality using the Detsky Scale for RCT evaluation or the Newcastle-Ottawa Scale (NOS) for PCS evaluation.[50,51] The Detsky Scale uses a 21-point scale (or 22-point scale for negative trials) to evaluate RCTs and their methodologic rigor on several domains. These domains include randomization, blinding, outcome measures, inclusion/exclusion criteria, description of treatment, and statistical analysis.[35,50,52] Higher Detsky Scale scores are representative of higher methodologic quality.[50] As has been previously reported, percent converted Detsky scores of 75% or greater are considered high-quality RCT studies,[35] and as such, only RCTs satisfying this requirement were included. Similarly, the NOS has been used to evaluate both case-control studies and PCSs.[50] The NOS uses a 9-point scale.[51] A score of 7 or greater is representative of a high-quality PCS, and PCSs meeting this threshold were included.[35,51] The domains evaluated by the NOS include comparability, selection, and outcome/exposure.[51,52] It should be noted that the NOS has not yet been published in a peer-reviewed journal to date (available through Web link) and has not been validated fully. Two reviewers independently evaluated all included studies, and as defined a priori, only high-quality studies satisfying either a Detsky score of 75% or greater or an NOS score of 7 or greater were included. A consensus agreement was reached between reviewers, and if discrepancies were encountered, they were resolved through discussion with the senior author.

Data Analysis

For continuous outcomes, 95% confidence intervals (CIs) and weighted MDs were calculated. For categorical outcomes, pooled risk ratios were calculated and all tests of significance (2 tailed) were performed with an α value of .05. The random-effects model was used to pool results and weighed accordingly based on the sample size and standard error of the study.[53] The I^2 statistic was used to test for heterogeneity, and the Cochran λ^2 test was used to evaluate for homogeneity.[52,54] As previously defined, an I^2 statistic value of less than 25% was indicative of low heterogeneity whereas an I^2 value greater than 75% was indicative of high heterogeneity.[53,54] Furthermore, a sensitivity analysis was performed (through the sequential removal of included studies one by one) to assess the robustness of the observed results.[52]

Results

Baseline Demographics

The results of our literature search are depicted in the study selection log (Fig 1). After the search, review, and assessment, 4 Level I randomized trials[17,36,41,42] and 2 Level II PCSs with comparative control groups[22,43] were included. All studies were published in peer-reviewed journals. Of the 6 studies, 5 were written in English[17,22,36,41,43] and one required translation (Chinese to English) by a bilingual Chinese-English orthopaedic researcher.[42] Two studies included patients with previous operative treatments for knee OA; however, these procedures were performed more than 1 year before study enrollment.[22,41]

A total of 653 patients were included (727 knees) in the 6 trials; however, only 577 patients (625 knees) were included in this systematic review, on the basis of

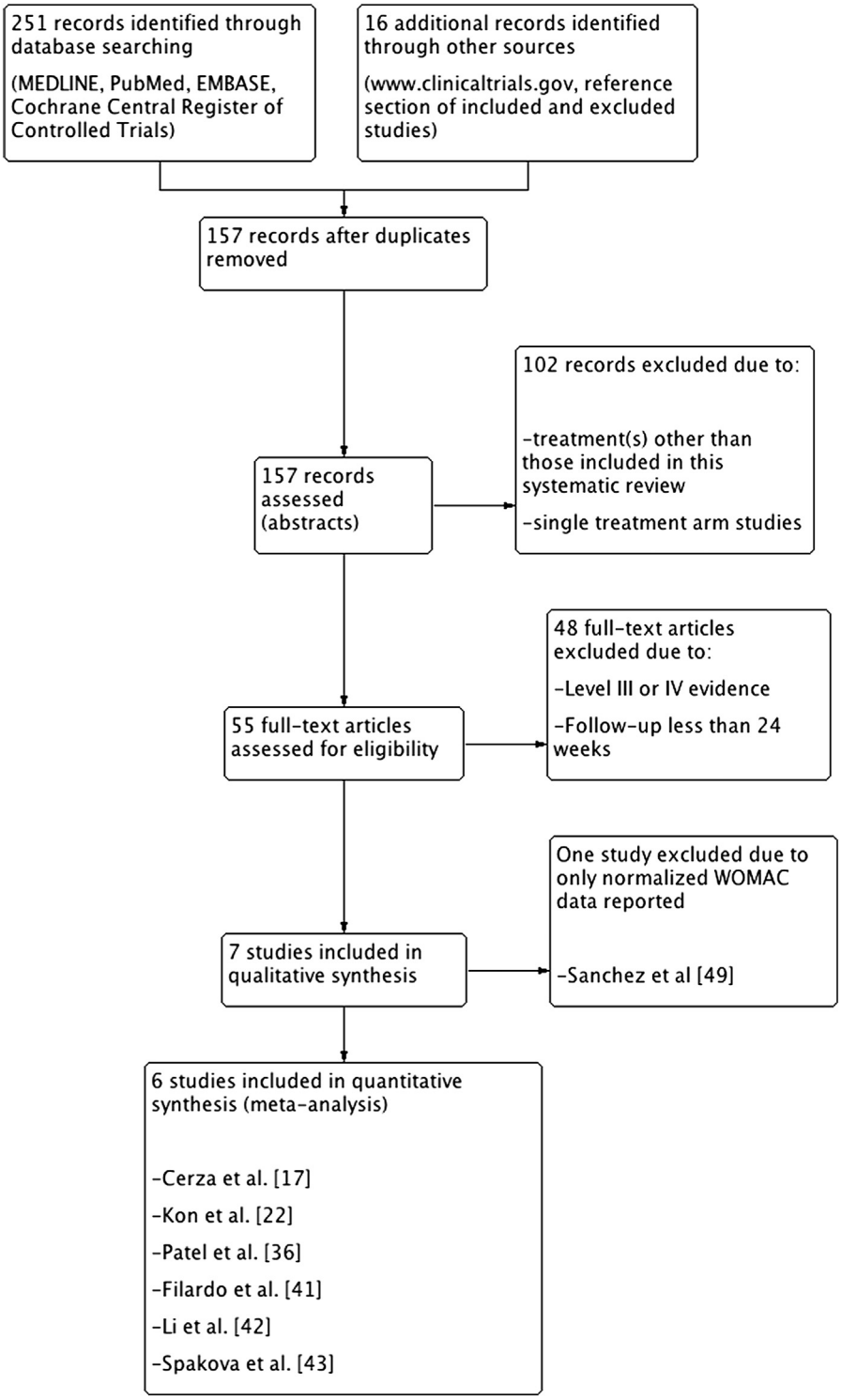

Fig 1. Search strategy results.

the one study that had 2 HA control cohorts and one PRP cohort.[22] Excluded patients included those who only received one injection of PRP (27 patients, 54 knees).[36] The mean age of included patients who received PRP injections was 56.1 years, and 51.5% were male patients. The mean age of the control patients (HA or NS) was 57.1 years, and 49.5% were male patients. Complete baseline characteristics for each study are shown in Table 1.

OA Severity

Among the 6 studies, 2 different radiographic grading scales were used to determine OA severity: the KLG scale[39] and the Ahlbäck grading scale.[40] Five studies

Table 1. Baseline Patient Demographics

	Demographic Variable							
	Sample Size (No. of Patients)		Male Gender		Female Gender		Age (yr)	
Study	PRP	Control	PRP	Control	PRP	Control	PRP	Control
Cerza et al.[17]	60	60	25	28	35	32	66.5 ± 11.3	66.2 ± 10.6
Filardo et al.[41]	54	55	37	31	17	24	55*	58*
Kon et al.[22]	50	50	30	25	20	25	50.6 ± 13.8	54.9 ± 12.6
Kon et al.[22]†		50		27		23		53.2 ± 13.0
Spakova et al.[43]	60	60	33	31	27	29	52.8 ± 12.4	53.2 ± 14.5
Patel et al.[36]	25	23‡	5	6‡	20	17‡	51.6 ± 9.2	53.7 ± 8.2‡
Li et al.[42]	15	15	6	7	9	8	57.6*	58.2*
Total	264	313	136	155	128	158	56.1	57.1
%	45.8	54.2	51.5	49.5	48.5	50.5		

*Studies failed to mention standard deviation for age.
†Second control cohort (LMW HA).
‡NS control injection.

used the former,[17,22,41-43] whereas one used the latter.[36] The distribution of OA severity among the 6 studies is listed in Table 2. One study grouped grading scales,[22] and although the distributions of OA severity between case and control patients were similar, data from this study were not included in the pooling of mean OA grade. According to studies that used the KLG scale, the mean OA grades for knees receiving PRP and HA injections were 2.14 and 2.08, respectively. The one study that used the Ahlbäck grading scale determined the mean OA grade of knees receiving PRP and NS injections to be 1.29 and 1.52, respectively.

PRP Preparation

PRP preparation techniques varied among studies. Table 3 shows the PRP preparation protocols specific to each study, including PRP system, number of centrifugations, platelet and white blood cell concentrations, and use of an activator (calcium chloride or thrombin).

Table 2. OA Grade

		Radiographic OA Grading Scale							
		KLG					Ahlbäck		
Study	Intervention	0	I	II	III	IV	1	2	3
Cerza et al.[17]	PRP	0	21	24	15	0			
	Control	0	25	22	13	0			
Filardo et al.[41]	PRP	Mean, 2.2							
	Control	Mean, 2.1							
Kon et al.[22]	PRP	22	20			8			
	Control	21	19			10			
	Control*	19	22			9			
Spakova et al.[43]	PRP	0	2	39	19	0			
	Control	0	2	37	21	0			
Patel et al.[36]	PRP†						36	10	2
	Control‡						25	18	3
Li et al.[42]	PRP	0	6	2	4	3			
	Control	0	6	3	3	3			
Mean grade	PRP	2.14					1.29		
	Control	2.08					1.52‡		

*Second control cohort (LMW HA).
†Two knees not reported.
‡NS control cohort.

Injection Protocol

Platelet-Rich Plasma. In all 6 studies, PRP treatment included multiple injections. The total number of PRP intra-articular knee injections each patient received varied: 2 injections,[36] 3 injections,[22,41-43] or 4 injections.[17] The volume, injection interval (weeks between injections), and location of injection varied (Table 4).

Control. In 5 of the 6 studies, the control injection was HA,[17,22,41-43] whereas one study used NS.[36] Among those studies using HA injections, each used a unique formulation and the MW varied (Table 5). Similar to PRP, the total number of injections, injection interval, volume per injection, and location of injection varied (Table 4).

Follow-Up

Follow-up intervals and length were variable among studies (Table 6). All studies, however, reported functional outcomes at 24 weeks (6 months). In 5 of the 6 studies, no patients were lost to follow-up or refused treatment.[17,22,41-43] In one study, 3 patients in the control cohort (NS injections) refused treatment, and these patients were excluded before follow-up.[36] Moreover, one additional patient (PRP group) underwent a total knee replacement before final follow-up,[36] and this patient was excluded in the pooling of results.

Patient-Reported Outcomes

Western Ontario and McMaster Universities Arthritis Index. At 24 weeks, the MD in overall WOMAC score between the treatment (PRP) and control (HA and NS) groups favored PRP (4 studies [318 patients]; MD, −18.03 [95% CI, −27.75 to −8.30]; $P < .001$) (Fig 2A). There was significant heterogeneity in the data ($I^2 = 89\%$, $P < .001$), and as such, a random-effects

Table 3. PRP Preparation Protocol

Study	PRP System	No. of Centrifugations	Mean Concentration (per mL)		Activator
			Platelet	WBC	
Cerza et al.[17]	ACP	Single	3-5 (10^8)	NR	NR
Filardo et al.[41]	Custom	Double	5× WB	1.2× WB	NR
Kon et al.[22]	Custom	Double	>6 (10^7)	NR	Yes
Spakova et al.[43]	Custom	Double	6.8 (10^8)	2.3 (10^7)	NR
Patel et al.[36]	Custom	Single	3.1 (10^8)	0	Yes
Li et al.[42]	NR	NR	NR	NR	NR

NOTE. All reported activators were calcium chloride.

ACP, autologous conditioned plasma (Biocore; Arthrex, Karlsfeld, Germany); NR, not reported; WB, whole blood concentrations per injection; WBC, white blood cell.

model was used. A comparison of PRP versus HA only did not change the direction or significance of the results. In a sensitivity analysis, when the results from Patel et al.[36] were removed, PRP continued to show improved WOMAC scores at 24 weeks compared with control treatment (MD, −16.65 [95% CI, −28.90 to −4.40]; $P = .008$).

IKDC Score. At 24 weeks, the MD in overall IKDC score between the treatment (PRP) and control (HA) groups favored PRP (3 studies [289 patients]; MD, 7.90 [95% CI, 3.72 to 12.08]; $P = .004$) (Fig 2B). There was no significant statistical heterogeneity in the aforementioned analysis ($I^2 = 44\%$, $P = .17$). A separate analysis using data with LMW HA (as opposed to HMW HA) in the study by Kon et al.[22] did not result in a change in the observed results (MD, 8.40 [95% CI, 2.72 to 14.07]; $P = .004$).

Visual Analog Scale (Pain). At 24 weeks, there was no statistical difference in VAS scores between the treatment (PRP) and control (HA and NS) groups (2 studies [198 patients]; MD, 0.46 [95% CI, −0.52 to 1.43]; $P = .36$) (Fig 2C). A random-effects model was used because the data were found to be significantly heterogeneous ($I^2 = 88\%$, $P = .004$). A separate analysis using data with LMW HA (as opposed to HMW HA) in the study by Kon et al.[22] did not result in a change in the observed results (MD, 0.47 [95% CI, −0.53 to 1.48]; $P = .36$).

Patient Satisfaction. At 24 weeks, there was no difference in patient satisfaction between PRP treatment and the control (HA and NS) groups (2 studies [198 patients]; OR, 8.97 [95% CI 0.54 to 149.25]; $P = .13$) (Fig 2D). Again, there was considerable heterogeneity in the data ($I^2 = 90\%$, $P = .002$), and a random-effects model was used. A separate analysis using data with LMW HA (as opposed to HMW HA) in the study by Kon et al.[22] did not result in a change in the observed results (OR, 9.35 [95% CI, 0.62 to 142.1]; $P = .11$).

Adverse Events. No AEs related to treatment injections were observed in 2 studies[17,22] (Table 7). One study reported 19 AEs over the course of PRP treatment.[36] Nonspecific AEs reported were pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia, and all complications were self-limited.[36] Another study reported 31 AEs in the PRP group and 30 AEs in the control group.[42] In this study AEs reported were post-injection pain, swelling of the injection site, and activity limitations.[42] All AEs reported resolved in all patients within 4 days.[42]

One study was not included in the pooled study for AE rates because the number of patients with AEs was not reported.[41] In this study a higher post-injection length of pain in the PRP group versus the control group (16.7 days *v* 9.2 days, $P = .039$) was reported. This pain reaction was self-limited in all patients.[41] Similarly, another study reported that 6 patients had worsening of pain after PRP treatment, which resolved in all patients within 2 days.[43] With respect to AEs, PRP treatment had a higher incidence of AEs when compared with control treatments (8.4% *v* 3.8%, $P = .002$).

Discussion

The main findings of this systematic review were that multiple sequential intra-articular PRP knee injections

Table 4. PRP Injection Protocol

Study	No. of Injections	Injection Interval (wk)	Volume per Injection (mL)	Ultrasonography Guided	Injection Location
Cerza et al.[17]	4	1	5.5	No	Superolateral
Filardo et al.[41]	3	1	5	No	Not reported
Kon et al.[22]	3	2	5	No	Lateral
Spakova et al.[43]	3	1	3	No	Lateral
Patel et al.[36]	2	3	8	No	Superolateral
Li et al.[42]	3	1	3.5	No	Parapatellar

Table 5. Control Injection Protocol

Study	Type	MW*	No. of Injections	Injection Interval (wk)	Volume per Injection	Injection Technique
Cerza et al.[17]	HA	LMW	4	1	2 mL, 20 mg	Superolateral
Filardo et al.[41]	HA	IMW	3	1	2 mL, 30 mg	NR
Kon et al.[22]	HA	IMW-HMW	3	2	2 mL, 30 mg	Lateral
	HA	LMW	3	2	2 mL, 20 mg	Lateral
Spakova et al.[43]	HA	NR	3	1	2 mL, 24 mg	Lateral
Patel et al.[36]	NS		1	NA	8 mL	Superolateral
Li et al.[42]	HA	NR	3	1	NR	Parapatellar

IMW, intermediate molecular weight; NA, not applicable; NR, not reported.
*LMW is 500 to 730 kDa, IMW is 800 to 2,000 kDa, and HMW is 6,000 kDa or greater.

(range of 2 to 4 injections) improved functional outcome scores (WOMAC and IKDC) at a minimum of 24 weeks. However, no benefit of PRP over control treatment was found for other pain measures (VAS) or overall patient satisfaction scores. Pooled comparisons using other common outcomes measures (e.g., Tegner scale,[41] Knee Injury and Osteoarthritis Outcome Score,[41] and an 11-point pain intensity numeric rating scale[43]) were not possible given the heterogeneity in reported outcome measures. When unpooled 6-month data from the Knee Injury and Osteoarthritis Outcome Score or Tegner scale were reviewed, there was only a favorable trend for PRP over HA treatment for lower KLG (≤2) radiographic knee OA.[41] Two recent systematic reviews have commented on the variance and importance of outcome tool selection of patient-reported knee function scores that are commonly used.[55,56] It should be noted that no studies exist that compare the superiority of any one knee-specific functional outcome over another.[55,56]

Despite technique and formulation discrepancies, there is biological plausibility for the use of PRP as a therapeutic modality in OA.[34] In vitro studies of PRP have shown increases in chondrocyte viability,[57,58] proliferation,[57-63] and synthetic capability[57,59,62-64] and that it has an inhibitory effect on the inflammatory cascade.[58,65,66] In vivo studies have shown that PRP improves both cartilage stiffness[67,68] and the histologic appearance of the articular cartilage repair tissue,[67-71] specifically increased proteoglycan[69-71] and type II collagen content.[71-73]

PRP contains a host of growth factors such as platelet-derived growth factor, transforming growth factor β (TGF-β), vascular endothelial growth factor, basic fibroblast growth factor, insulin-like growth factor, hepatocyte growth factor, and endothelial growth factor.[74,75] These growth factors are found in the α-granules[76] and released upon platelet activation.[77] It is believed that the mitogenic effects of these growth factors[78] help PRP to promote mesenchymal stem cell proliferation,[73,78-83] as well as chondrogenic[60,61,63,73,80,84] and osteogenic[79-82,85,86] differentiation both in vitro and in vivo. The TGF-β family plays a major role in bone and cartilage development. TGF-β is expressed in the growth plate and is an important regulator of chondrocyte proliferation and differentiation.[87] Platelet-derived growth factor, another one of the growth factors found in PRP, helps chondrocytes to maintain hyaline-like chondrogenic phenotype and induce proliferation and proteoglycan synthesis, and it is a potent chemotactic factor for cells of mesenchymal origin.[88] Overall, although the exact mechanisms and pathways that explain the efficacy of PRP are unknown,[34,89] we believe that the observed results may be due to its anti-inflammatory properties, anabolic effects, and alterations in the local milieu of the knee joint.

Table 6. Follow-up Assessments

Study	Follow-up Interval (wk)
Cerza et al.[17]	4, 12, 24
Filardo et al.[41]	8, 24, 48
Kon et al.[22]	8, 24
Spakova et al.[43]	0, 12, 24
Patel et al.[36]	6, 12, 24
Li et al.[42]	24

The ability to safely inject PRP in an office setting with rare AEs, such as mild injection-site pain or effusion,[34,42,89] is attractive to clinicians. In our review only 2 studies reported any AEs at the time of PRP injection.[36,42] Our results suggest that PRP injection for knee OA is efficacious up to 6 months; however, both the long-term disease-modifying potential and the potential for symptomatic relief longer than 6 months are still unknown. Furthermore, we present only mild cumulative evidence that PRP is better than HA injection, and whether this difference justifies any appreciable cost of treatment is still value-laden at the current state of knowledge. Finally, there are no comparative studies of PRP and ultrasound-guided PRP administration or noninvasive measures such as physiotherapy or weight loss.

Going forward, studies should address the shortcomings in the current body of literature, which are outlined later. To date, there have been no large-scale multicenter RCTs.[34] There is no consensus on the optimal treatment protocol for PRP use or its ideal

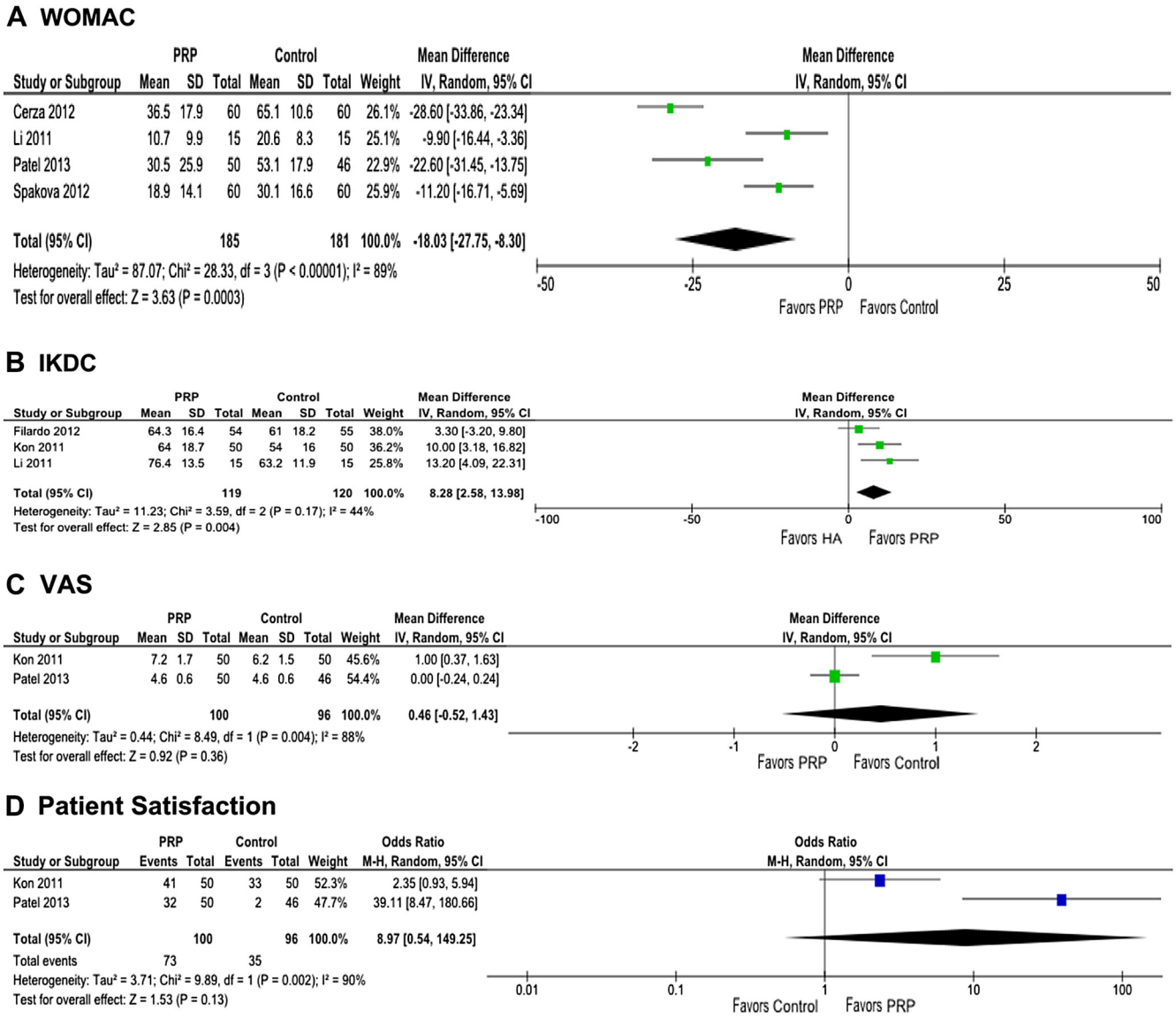

Fig 2. Forest plots showing results for PRP versus HA/placebo for (A) WOMAC, (B) IKDC, (C) VAS, and (D) patient satisfaction. (IV, inverse variance; M-H, Mantel-Haenszel.)

clinical indications.[34,35] Studies have failed to include follow-up imaging of study participants, and the role of PRP in cartilage regeneration has not been fully investigated. Furthermore, prospective studies using uniform knee-specific functional outcomes are required.[55] No studies currently exist that examine whether combining PRP and HA in an intra-articular injection could result in a synergistic effect on pertinent cartilage repair parameters.[43,56] Future studies with more long-term follow-up will allow insight into whether PRP is able to sustain the observed therapeutic effect past 6 months and whether it has any impact on the natural history of degenerative OA. Other unanswered questions include the ideal number, frequency, and timing of treatments; the grade of OA best treated; the concurrent use of nonsteroidal anti-inflammatory agents, corticosteroids, or analgesic agents; the optimal post-treatment rehabilitation protocol; and the most bioavailable delivery method.[34-36,89]

Table 7. AEs After Injection

	Sample Size (No. of Injections)		No. of AEs	
Study	PRP	Control	PRP	Control
Cerza et al.[17]	240	240	0	0
Kon et al.[22]	150	150	0	0
Kon et al.[22]*		150		0
Spakova et al.[43]	180	180	6	0
Patel et al.[36]	50	23	19	0
Li et al.[42]	45	45	31	30
Total	665	788	56	30
Percent (AE rate) (%)	45.8	54.2	8.4	3.8

*Second control cohort (LMW HA).

Limitations

This systematic review has several limitations. First, both Level I RCTs and Level II PCSs were pooled, which increases the risk of selection bias. Furthermore, the pooled sample size for this review was limited, with the control arm of HA/placebo containing 313 patients and the PRP arm containing 264 patients. This small sample size can limit the power of detecting changes that might reach the threshold for the minimal clinically important difference of an outcome measure.[90] However, we only included studies of high quality that used established outcome measures.[37] Despite this, certain outcome measures such as the VAS and patient satisfaction were only reported in a limited number of studies—hence the possibility of a type II statistical error due to an underpowered analysis cannot be ruled out. Furthermore, in the study by Patel et al.,[36] analyses were performed at a "knee level" rather than at a "patient level," which differs from other included studies. Patel et al. also introduced another source of bias because one patient in the PRP treatment group underwent a total knee arthroplasty during the study that was thereafter excluded from the study.

In addition, despite our use of a random-effects model, differences in reported effect sizes might have been the result of heterogeneity that existed in study design, patients, or treatments. Such differences could have been the result of preparation techniques (frequency/speed/length of centrifugation or the use of ancillary activat-ing/anticoagulant agents), administration techniques (volume/frequency/delivery means of administration), post-administration rehabilitation protocols, participants' baseline characteristics (age, gender, activity level, or OA grade), and the methodologic rigor of the study.

Conclusions

As compared with HA or NS injection, multiple sequential intra-articular PRP injections may have beneficial effects in the treatment of adult patients with mild to moderate knee OA at approximately 6 months. There appears to be an increased incidence of nonspecific AEs among patients treated with PRP.

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