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REVIEW ARTICLE (META-ANALYSIS)

Comparative Effectiveness of Platelet-Rich Plasma Injections for Treating Knee Joint Cartilage Degenerative Pathology: A Systematic Review and Meta-Analysis

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Abstract

Objective: To explore the effectiveness of platelet-rich plasma (PRP) in treating cartilage degenerative pathology in knee joints.

Data Sources: Electronic databases, including PubMed and Scopus, were searched from the earliest record to September 2013.

Study Selection: We included single-arm prospective studies, quasi-experimental studies, and randomized controlled trials that used PRP to treat knee chondral degenerative lesions. Eight single-arm studies, 3 quasi-experimental studies, and 5 randomized controlled trials were identified, comprising 1543 participants.

Data Extraction: We determined effect sizes for the selected studies by extracting changes in functional scales after the interventions and compared the PRP group pooled values with the pretreatment baseline and the groups receiving placebo or hyaluronic acid (HA) injections.

Data Synthesis: PRP injections in patients with knee degenerative pathology showed continual efficacy for 12 months compared with their pretreatment condition. The effectiveness of PRP was likely better and more prolonged than that of HA. Injection doses $\leq$2, the use of a single-spinning approach, and lack of additional activators led to an uncertainty in the treatment effects. Patients with lower degrees of cartilage degeneration achieved superior outcomes as opposed to those affected by advanced osteoarthritis.

Conclusions: PRP application improves function from basal evaluations in patients with knee joint cartilage degenerative pathology and tends to be more effective than HA administration. Discrepancy in the degenerative severity modifies the treatment responses, leading to participants with lower degrees of degeneration benefiting more from PRP injections.

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The knee is the most common joint in the lower extremity affected by cartilage degeneration, with severity ranging from degenerative chondropathy to advanced osteoarthritis (OA). The progression of articular chondral lesions results in pain, stiffness, swelling, and restricted joint motion, greatly affecting the quality of life and socioeconomic well-being.[1] A variety of pain-relieving oral medications are available and appear effective in the early disease stages, including acetaminophen, nonsteroidal anti-inflammatory drugs, and weak opioid analogues.[2] Injection therapies are usually reserved for patients with unsatisfactory responses to oral regimens.[3,4] Intra-articular corticosteroid injections have been widely used in the management of symptomatic knee OA, but their effectiveness seems to be limited to 1 month.[5] Synthetic hyaluronic acid (HA), whose natural form is present in healthy joint fluid, has been used to treat knee OA for decades based on the theoretical benefits of viscosupplementation and modulation of inflammatory reactions. Although an antecedent meta-analysis disclosed the superiority of HA over corticosteroids in terms of longer efficacy, a recent large-scaled meta-analysis[6] discouraged

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the use of viscosupplementation because of a clinically irrelevant advantage and an increased risk of serious adverse events after HA injections.

Platelet-rich plasma (PRP), a natural concentrate of autologous growth factors from the blood, is an emerging regenerative therapy for tissue injury and degeneration.[7] Degranulation of platelets causes the release of various growth factors and cytokines, which play a crucial role in joint homeostasis and healing processes. Current evidence synthesized by performing several meta-analyses[8,9] showed positive effects of PRP on lateral epicondylitis and periodontal and sinus bone grafts, but less favorable outcomes in arthroscopic rotator cuff repair, joint arthroplasty, reconstruction of cruciate ligaments, and chronic tendinopathy.[10-12] Accordingly, the efficacy of PRP likely varies in different pathologic conditions and body sites. Research on PRP treatment for articular cartilage lesions has been published since 2010.[13] The efficacy is of interest to musculoskeletal specialists because of its potential disease-modifying and regenerative capability, compared with conventional injection regimens. However, to our knowledge, no meta-analytic research has quantified the effectiveness of PRP treatment and analyzed the factors that modify the outcomes. Therefore, we undertook a systematic review and meta-analysis to investigate the clinical results in patients with knee chondral degenerative lesions, with regard to functional changes, compared with the pretreatment condition, after PRP injections, placebo controls, and HA administration.

Methods

Study selection

We systematically searched for all relevant articles in 2 online databases, PubMed and Scopus, from the earliest record to September 2013. PubMed is a free database mainly derived from MEDLINE and is considered an optimal tool in biomedical electronic research. Compared with another free access database, Google Scholar, PubMed offers results of better accuracy. We used Scopus, an online database that covers a wider range of journals, to confirm that all relevant trials were retrieved.[14] The key terms, including *cartilage, knee, osteoarthritis, gonarthrosis, platelet, PRP,* and *platelet-rich plasma,* were entered as medical subject headings and text words for searches. Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, ClinicalTrials.gov, and bibliographies of included trials and related meta-analyses were manually scrutinized for additional references.

The review included randomized controlled trials, quasi-experimental studies, and prospective follow-up studies without language restriction. Case reports without a well-designed intervention scheme or outcome measurement were excluded. Studies were eligible if they enrolled adult participants with knee cartilage degenerative disorders diagnosed through clinical and image findings. Trials presenting data on people with other causes of knee pain such as sprain, tendinopathy, and meniscus tear were ruled out. The included studies were required to use PRP at least in 1 treatment arm. Research was eliminated if PRP was not applied through injection. All selected trials were required to have serial functional measurements such as the International Knee Documentation Committee (IKDC) Subjective Knee Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before and after the administration of PRP.

List of abbreviations:

CI	**confidence interval**
HA	**hyaluronic acid**
IKDC	**International Knee Documentation Committee**
KL	**Kellgren-Lawrence**
KOOS	**Knee Injury and Osteoarthritis Outcome Score**
OA	**osteoarthritis**
PRP	**platelet-rich plasma**
WOMAC	**Western Ontario and McMaster Universities Osteoarthritis Index**

Data extraction and quality assessment

Two authors (K.-V.C., C.-Y.H.) independently evaluated all articles eligible for inclusion. The data extracted from the selected studies included patient characteristics, information on PRP administration, and details of outcome measurements. The Jadad scale was used to assess the quality of the randomized controlled trials. The aggregate scores ranged from 0 to 5 points. Trials with scores <3 were assumed to have a lower methodological quality.[15] Prospective follow-up and quasi-experimental studies were evaluated by using the Newcastle-Ottawa Scale to assess the quality of selection, comparability, exposure, and outcome. The maximum scores observed were 9 points, and total scores <4 points were considered low in quality.[16] Discrepancies between the 2 independent evaluations for potential articles were resolved through discussion and consensus.

Data synthesis and analysis

Data were extracted from 3 points at or closest to the 2nd, 6th, and 12th months after the interventions. Effect sizes were estimated from functional knee joint scales and applied to compare the results across studies or between different therapeutic approaches. If more than 1 functional scale was available for a study, we selected only 1 measurement according to the order of IKDC, KOOS, and then WOMAC. Since some studies had multiple treatment arms, we treated each arm as a separate data set for analysis. To evaluate the effectiveness of PRP treatment, compared with the pretreatment condition, we used the standardized mean difference between the baseline and status after therapy. Data were derived from the ratio of the difference between baseline and posttreatment functional scores to the SD of the pooled results. Positive and negative values of the effect sizes indicated a functional improvement and decline, respectively. For cases in which the functional score SD was deficient, the value was computed from the P value of the corresponding hypothesis testing. The pooled SD resulted from the square root $\{[(\text{participant numbers in baseline} - 1)*(\text{SD of scores in baseline})^2 + (\text{participant numbers after treatment} - 1)*(\text{SD of scores after treatment})^2]/[(\text{participant numbers in baseline} - 1) + (\text{participant numbers after treatment} - 1)]\}$.[16,17] Because the pooled SD was calculated based on the rule of intention to treat, the dropout rate was not considered, and the participant numbers remained unchanged between the baseline and posttreatment data sets.

The effect sizes were pooled by using a random-effect model and were represented by a point estimate with a 95% confidence interval (CI). Regarding the comparison with the baseline condition, an advantage of PRP referred to a positive summed effect

size with a 95% CI above a zero value. In terms of comparison with HA injection or placebo treatment, a superiority of intervention was determined by a higher summed effect size in the intervention group without an overlap of the 95% CI in the comparative group.[18] The heterogeneity across studies was tested by using I-square and Cochran's Q tests. A P value $<.10$ for chi-square testing of the Q statistic or an I-square $>50\%$ was regarded as the existence of significant heterogeneity.[19] We performed a subgroup analysis according to the different dosages, regimens, and preparations of PRP, as well as the severity of knee degenerative lesions. A sensitivity analysis was conducted by removing some studies with extreme effect size values to observe whether the action caused serious changes in the overall result. We used a funnel plot and the Begg's test to examine the publication bias, which was defined as the tendency for positive trials to be published and the tendency for negative and null trials not to be published.[20] All analyses were performed by using Stata 10.0.[a]

Results

Of the 73 nonduplicate citations identified from the literature, 18 clinical trials were screened for eligibility (fig 1). One study[21] was excluded because PRP was introduced by performing a mini-arthrotomy (not by an injection technique), and the other study[22] was removed because of an inability to extract data from box

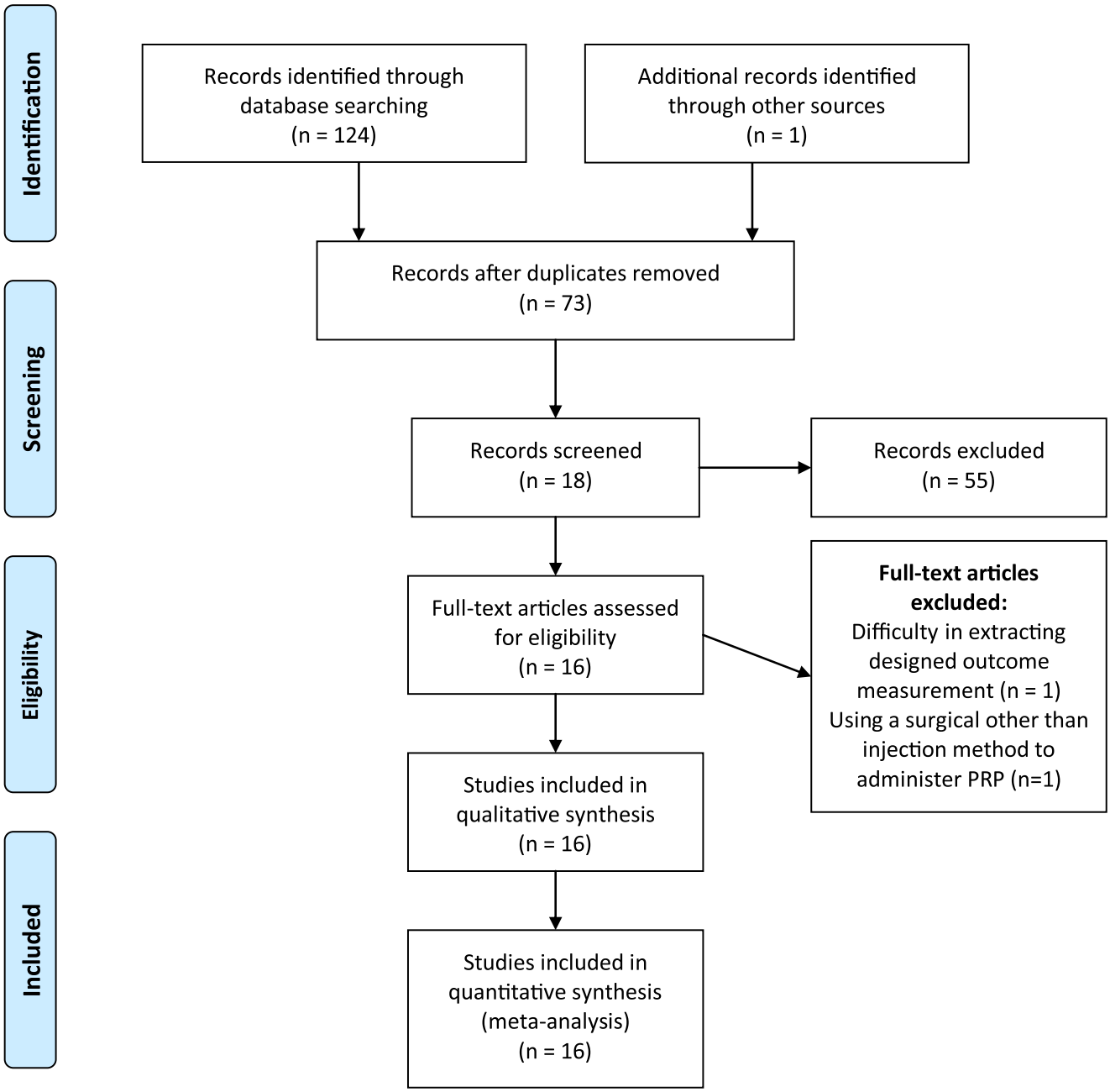

Fig 1 Flow diagram of the evaluation process for the inclusion or exclusion of studies.

plots. An assessment of the remaining 16 articles revealed that 8 used a single-arm, open-label, and prospective follow-up design.[23-30] Two quasi-experimental studies[31,32] and 4 randomized controlled trials[33-36] compared PRP with HA injections, 1 randomized controlled trial compared different doses of PRP with normal saline,[37] and 1 quasi-experimental trial compared a single-spinning approach of PRP with a double-spinning approach.[38] The 16 included trials comprised 26 treatment arms, of which 18 used PRP treatments, 7 administered HA, and 1 used saline for placebo controls. Regarding knee-specific outcome measures, we extracted data from IKDC in 8, KOOS in 1, and WOMAC in 7 of the 16 studies.

Characteristics of the included patients

The 16 included studies had a total enrollment of 1543 patients, 840 of whom (54.4%) were men (tables 1 and 2). The duration from the onset of knee pain to registration in each trial was listed from 3 months to more than 1 year. The follow-up period ranged from 6 to 24 months, and the latest point of assessment for most trials was at 12 months after PRP injections. Most studies recruited patients with knee OA with a severity less than grade III on the Kellgren-Lawrence (KL) scale, and some of them also enrolled participants affected by cartilage degenerative lesions with a grade of 0 on the KL scale.

Effects of interventions

Compared with the preinjection condition, we found a pooled effect size of 2.31 (95% CI, 1.53−3.09) at 2 months, 2.52 (95% CI, 1.94−3.09) at 6 months, and 2.88 (95% CI, .97−4.79) at 12 months, which all favored the status after PRP treatment (fig 2). If we deleted an outlier with an extremely high effect size,[24] the beneficial effects from PRP injections remained, with an effect size of 1.84 (95% CI, 1.53−3.09) at 2 months, 2.19 (95% CI, 1.73−2.66) at 6 months, and 2.35 (95% CI, .51−4.20) at 12 months. In the HA group, the effect sizes were 1.15 (95% CI, .78−1.52) at 2 months, .75 (95% CI, .62−.88) at 6 months, and .85 (95% CI, .46−1.24) at 12 months (fig 3). A significant superiority of the PRP intervention was demonstrated by a higher summed effect size in the PRP group without an overlap of the 95% CI of the HA group at months 2 and 6. In addition, after excluding the data from quasi-experimental and single-arm longitudinal follow-up studies and only using the data from randomized controlled trials (fig 4, table 3), the PRP group still demonstrated a significantly higher effect size of 1.55 (95% CI, .97−2.12), compared with .75 (95% CI, .62−.88) in the HA group, at 6 months. Only 1 study used normal saline for placebo controls. The effect sizes were −.29 (95% CI, −.68 to .10) at 2 months and −.48 (95% CI, −.89 to −.07) at 6 months, whose point estimates and 95% CI appeared inferior to the PRP and HA group values.

Stratified analysis

The participants receiving PRP treatments were stratified according to the study design, cycles of centrifugation, kind of activation agents, administration doses, and severity of cartilage degeneration (see table 3). The point estimates of the pooled effect size in the single-arm prospective studies and quasi-experimental trials seemed to be higher than those in the randomized controlled trials, and a significant difference was identified at 12 months between the quasi-experimental and randomized controlled trials. The stratified analysis failed to demonstrate a dose-responsiveness relationship in the injection numbers, superiority of double-spinning to single-spinning techniques, and additional activation agents to an activator-free preparation. However, an uncertainty in the treatment effectiveness emerged regarding participants who received ≤2 injection doses, a single-spinning approach, or lack of additional activators, since the 95% CI of the summed effect sizes in these subgroups crossed the value of 0 at any of the 3 time points.

Eight of the 16 trials, including 9 arms of PRP treatment, divided their participants into 2 or 3 subgroups based on knee OA severity. In the present meta-analysis, KL grade 0, grades I and II, and grades III and IV were defined as degenerative chondropathy, early OA, and advanced OA, respectively. The degenerative chondropathy group had the highest effect size point estimate at all time points, followed by the early OA group and the advanced OA group. A significantly better treatment effectiveness was identified at 6 months in the degenerative chondropathy group (effect size, 3.90; 95% CI, 2.54−5.26) compared with the advanced OA group (effect size, 1.59; 95% CI, .85−2.32).

Adverse effects

Eight of the 16 trials reported adverse events after injection, most of which were local swelling and transient regional pain, and the overall incidence was 9.59% (95% CI, 7.79%−11.32%) per person undergoing 1 PRP treatment cycle. The pooled relative risk of adverse reactions after PRP treatment was 1.19 (95% CI, .85−1.66) compared with HA administration, indicating no significant difference between the regimens in eliciting postinjection discomfort.

Publication bias

Asymmetry was observed in the funnel plots based on the effect sizes of changes in the functional scales from baseline in the PRP group (fig 5). *P* values, determined by using a Begg's test, were .028 at 2 months, .017 at 6 months, and .84 at 12 months, which indicated the existence of significant publication bias regarding the measured outcome at 2 and 6 months.

Discussion

The current meta-analysis comparing the conditions of patients with knee degenerative pathology before and after treatment with PRP injections showed a continual efficacy for at least 12 months. Compared with patients receiving HA, those in the PRP group exhibited better and prolonged beneficial effects, and the advantages remained after excluding single-arm and quasi-experimental trials. Injection doses ≤2, the use of a single-spinning approach, and lack of activation agents led to an uncertainty of the treatment effectiveness. Furthermore, patients with a lower degree of cartilage degeneration achieved superior results compared with those with advanced OA. Finally, PRP treatment did not elicit a higher risk of adverse reactions relative to HA administration.

Four meta-analytic research articles investigating the efficacy of PRP in the treatment of orthopedic disorders have been recently published. Krogh et al[8] compared a variety of injection therapies for lateral epicondylitis and found that PRP administration was significantly superior to placebo for pain relief. Chahal[12] and Zang[10] and colleagues reviewed studies comprising participants

Table 1 Summary of studies using PRP injection to treat chondral degenerative lesions in knee joints

Author, Year	Enrolled Sample No.	Average Age (y)	Disease Duration	Double Blind	Intention-to-Treat Analysis	Outcome Measure	Follow-Up Timing	Adverse Event	Quality Assessment
Single-arm, prospective follow-up studies									
Halpern[29] 2013	22 (17 M, 5 F)	54.7	Averaged 14mo	No	No	VAS, WOMAC	1wk; 1, 3, 6, 12mo	Not mentioned	4*
Jang[30] 2013	65 (12 M, 53 F)	59.7 (32–85)	Not mentioned	No	Yes	IKDC, VAS	1, 3, 6, 9, 12mo	Mild swelling or pain in 41 patients. Mild local heat in 7 patients	4*
Gobbi[27] 2012	50 (31 M, 19 F)	47.7±5.2	Not mentioned	No	Yes	IKDC, KOOS, Marx, Tegner, VAS	6, 12mo	Nil	4*
Napolitano[28] 2012	27 (21 M, 6 F)	Arthritis group (n=13): 64±11; cartilage disease group (n=14): 26.2±2	More than 1y	No	Not mentioned	NRS, WOMAC	1, 6mo	Nil	4*
Filardo[24] 2011	90 (57 M, 33 F)	50±14	At least 4mo	No	No	IKDC, VAS	2, 6, 12, 24mo	Pain with swelling in 1 patient	4*
Sampson[25] 2011	14 (12 M, 2 F)	51.8 (18–87)	At least 3mo	No	No	VAS, KOOS, ultrasound measured cartilage thickness	2, 5, 11, 18, 52wk	Moderate pain in 1 patient	4*
Wang-Saegusa[26] 2011	261 (152 M, 109 F)	48.4±16.7	At least 3mo	No	Not mentioned	Lequesne index, SF-36, VAS, WOMAC	6mo	Nil	4*
Kon[23] 2010	91 (57 M, 34 F at follow-up)	47 (24–82)	At least 4mo	No	No	IKDC	2, 6, 12mo	Pain with swelling in 1 patient	4*
Quasi-experimental studies									
Filardo[38] 2012	144 (single-spinning PRP group: 52 M, 20 F; double-spinning PRP group: 43 M, 29 F)	Single-spinning PRP group: 53.8±14.9; double-spinning PRP group: 50.3±14.4	At least 4mo	No	Not mentioned	IKDC, KOOS, VAS	2, 6, 12mo	Nil	5*

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Table 1 (*continued*)

Author, Year	Enrolled Sample No.	Average Age (y)	Disease Duration	Double Blind	Intention-to-Treat Analysis	Outcome Measure	Follow-Up Timing	Adverse Event	Quality Assessment
Spakova[32] 2012	120 (PRP group: 33 M, 27 F; HA group: 31 M, 29 F)	PRP group: 52.8±12.4; HA group: 53.2±14.5	At least 12mo	No	Not mentioned	NRS, WOMAC	3, 6mo	Temporary mild worsening of knee pain after PRP injections in 6 cases	5*
Kon[31] 2011	150 (PRP group: 30 M, 20 F; LWHA group: 27 M, 23 F; HWHA group: 25M, 25 F)	PRP group: 50.6±13.8; LWHA group: 53.2±13; HWHA group: 54.9±12.6	At least 4mo	No	Not mentioned	IKDC, VAS	2, 6mo	Nil	5*
Randomized controlled trials									
Patel[37] 2013	74 (single PRP injection group: 10 M, 16 F; double PRP injection group: 5 M, 20 F; normal saline group: 6 M, 17 F)	Single PRP injection group: 53.1±11.6; double PRP injection group: 51.6±9.2; normal saline group: 53.7±8.2	Not mentioned	Yes	No	VAS, WOMAC	6wk; 3, 6mo	Postinjective pain in 4 patients in the single PRP injection group and in 3 patients in the double PRP injection group	5†
Cerza[34] 2012	120 (PRP group: 25 M, 35 F; HA group: 28 M, 32 F)	PRP group: 66.5±1.3; HA group: 66.2±10.6	Not mentioned	No	Yes	WOMAC	1, 3, 12mo	Nil	2†
Filardo[35] 2012	109 (PRP group: 37 M, 17 F; HA group: 31 M, 24 F)	PRP group: 55; HA group: 58	At least 4mo	Yes	Yes	IKDC, KOOS, Tegner, VAS	2, 6, 12mo	A significantly higher postinjective pain reaction was observed in the PRP group.	5†
Sanchez[36] 2012	176 (PRP group: 43 M, 46 F; HA group: 42 M, 45 F)	PRP group: 60.5±7.9; HA group: 58.9±8.2	Not mentioned	Yes	Yes	WOMAC	1, 2, 6mo	Mild adverse event (26 in PRP group; 24 in HA group)	5†
Li[33] 2011	30 (PRP group: 6 M, 9 F, HA group: 7 M, 8 F)	PRP group: 57.6 (36—76); HA group: 58.2 (39—76)	At least 4mo	Not mentioned	Yes	IKDC, Lequesne index, WOMAC	3, 4, 6mo	Pain, swelling, and limited range (12 in PRP group and 12 in HA group)	2†

Abbreviations: F, female; HWHA, high—molecular weight HA; LWHA, low—molecular weight HA; M, male; NRS, numeric rating scale; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; VAS, visual analog scale.

* Quality scores derived from the Newcastle-Ottawa Scale.

† Quality scores derived from the Jadad scale.

Table 2 Summary of the preparations and injection details of PRP in the retrieved trials

Author, Year	Total No. of Injection Doses	Volume per Dose (mL)	Interval of Injection	Centrifugation Time	Activation Agent	Comparison
Single-arm, prospective follow-up studies						
Halpern[29] 2013	1	6	NA	Not mentioned	Not mentioned	Nil
Jang[30] 2013	1	3	NA	Not mentioned	Not mentioned	Nil
Gobbi[27] 2012	2	4	1mo	1 centrifugation, 3500rpm for 9min	Nil	Nil
Napolitano[28] 2012	3	5	1wk	1 centrifugation, 3100rpm for 8min	Calcium gluconate	Nil
Filardo[24] 2011	3	5	3wk	2 centrifugations, 1800rpm for 15min and 3500rpm for 10min	Calcium chloride	Nil
Sampson[25] 2011	3	6	4wk	1 centrifugation for 15min	Calcium chloride	Nil
Wang-Saegusa[26] 2011	3	5	2wk	1 centrifugation, 1800rpm for 8min	Calcium chloride	Nil
Kon[23] 2010	3	5	3wk	2 centrifugations, the first: 1800rpm for 15min; the second: 3500rpm for 10min	Calcium chloride	Nil
Randomized controlled trials or quasi-experimental studies						
Patel[37] 2013	1 in group A, 2 in group B	8	3wk in group B	1 centrifugation, 1500rpm for 15min	Calcium chloride	Group A: single PRP injection; group B: double PRP injection; group C: single normal saline injection
Cerza[34] 2012	4	5.5	1wk	Not mentioned	Not mentioned	HA
Filardo[35] 2012	3	5	1wk	2 centrifugations, the first: 1480rpm for 6min; the second: 3400rpm for 15min	Not mentioned	HA
Filardo[38] 2012	3	5	3wk	Single-spinning group: 1 centrifugation for 8min; double-spinning group: 2 centrifugations, 1800rpm for 15min and 3500rpm for 10min	Calcium chloride	Single-spinning vs double spinning

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Table 2 (*continued*)

Author, Year	Total No. of Injection Doses	Volume per Dose (mL)	Interval of Injection	Centrifugation Time	Activation Agent	Comparison
Sanchez[36] 2012	3	2	1wk	1 centrifugation for 8min	Calcium chloride	HA
Spakova[32] 2012	3	3	1wk	3 centrifugations, 3200rpm for 15min, 1500rpm for 10min, and 3200rpm for 10min	Nil	HA
Kon[31] 2011	3	5	2	2 centrifugations, 1480rpm for 6min and 3400rpm for 15min	Calcium chloride	HWHA (molecular weight 1000–2900kDa) and LWHA (molecular weight 500–730kDa)
Li[33] 2011	3	4	3wk	2 centrifugations, both 2000rpm for 10min	Calcium chloride	HA (1500–2500kDa)

Abbreviations: HWHA, high–molecular weight HA; LWHA, low–molecular weight HA; NA, not applicable; rpm, revolutions per minute.

with full-thickness rotator cuff tendon tears who were treated with arthroscopic repair with or without concomitant PRP supplementation, and they failed to demonstrate a benefit of additional PRP in reducing overall retear rates and improving shoulder-specific outcomes. Sheath et al[11] compared PRP interventions with control interventions in various orthopedic conditions such as anterior cruciate ligament reconstruction, spinal fusion, total knee arthroplasty, humeral epicondylitis, and Achilles' tendinopathy, and they concluded that the available evidence was insufficient to support PRP as a treatment option for orthopedic or soft tissue injuries. To our knowledge, none of these meta-analyses targeted the issue of PRP prescription for knee degenerative lesions. A focused review[13] of PRP for the treatment of cartilage pathology has recently been published and did not favor PRP as a first-line treatment for moderate to severe knee OA. However, a quantitative analysis in terms of potential symptom-relieving and disease-modifying effects is still deficient. Therefore, we standardized the functional change from baseline at various time points in an effort to obtain more accurate estimates on the effectiveness of intra-articular PRP injection for the treatment of knee degenerative pathology.

Our meta-analysis suggested that PRP injection significantly improved the functional status, relative to basal evaluations, in patients with knee degenerative pathology, and the beneficial effect was maintained for 1 year after treatment. The major concern regarding our pooled effect sizes is the overestimation of true values because of a lack of control treatments. Only 1 of the included trials used saline as a placebo control, whose effect size was −.29 (95% CI, −.68 to .10) at 2 months and −.48 (95% CI, −.89 to −.07) at 6 months. We believed that the estimated effect of saline injection was reliable since it was derived from a double-blind, randomized controlled trial. The result implies a gradual functional decline with a significant deterioration identified at 6 months after placebo treatment. In contrast, the PRP group revealed a continual improvement until 12 months. Therefore, the present meta-analysis suggests that the effectiveness of PRP derived from a biological benefit, which could not simply be explained by a placebo effect.

The HA effect size pooled in the present meta-analysis indicated that the efficacy reached a highest point at 2 months after injection but declined over time. The change in HA efficacy is comparable to that found in previous meta-analytic research despite a greater effect size,[5,39] since we used the patients' baseline as the reference point and included more small, uncontrolled trials. Current evidence suggests a modest effect of HA in relieving pain in patients with knee OA probably through the mechanism of viscosupplementation and modulation of the early inflammatory response.[6] Compared with the HA group, patients treated with PRP demonstrated better effectiveness at 2 time points, and the trend of improvement was sustained until 12 months (see fig 4). The advantage of PRP over HA remained at 6 months, even when only the results from randomized controlled trials were analyzed. In vitro experiments have demonstrated the capability of PRP in the temporary modulation of cytokine levels and stimulation of chondral anabolism, which may lead to short-term pain relief and long-term functional improvement, respectively.[40] When comparing the temporal changes in clinical outcomes between the 2 regimens, PRP injections provided a more prompt symptomatic relief than HA. Since the main action of HA derives from the restoration of viscoelasticity of synovial fluid, the prolonged efficacy of PRP might imply a regenerating or disease-modifying potential, which has rarely been reported in studies using HA preparations.

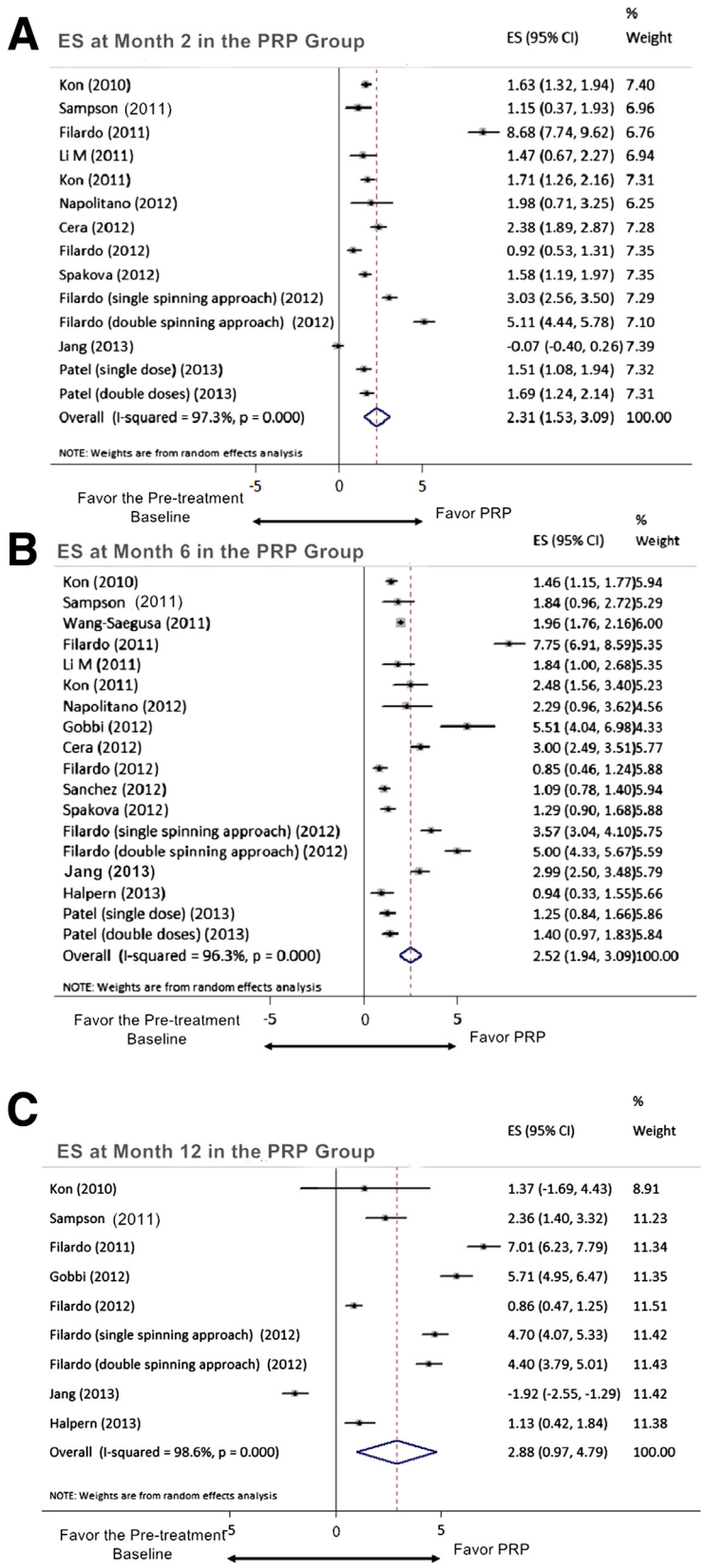

Fig 2 Forest plot of the ES of functional changes from baseline at (A) 2 months, (B) 6 months, and (C) 12 months after PRP injections. Abbreviation: ES, effect sizes.

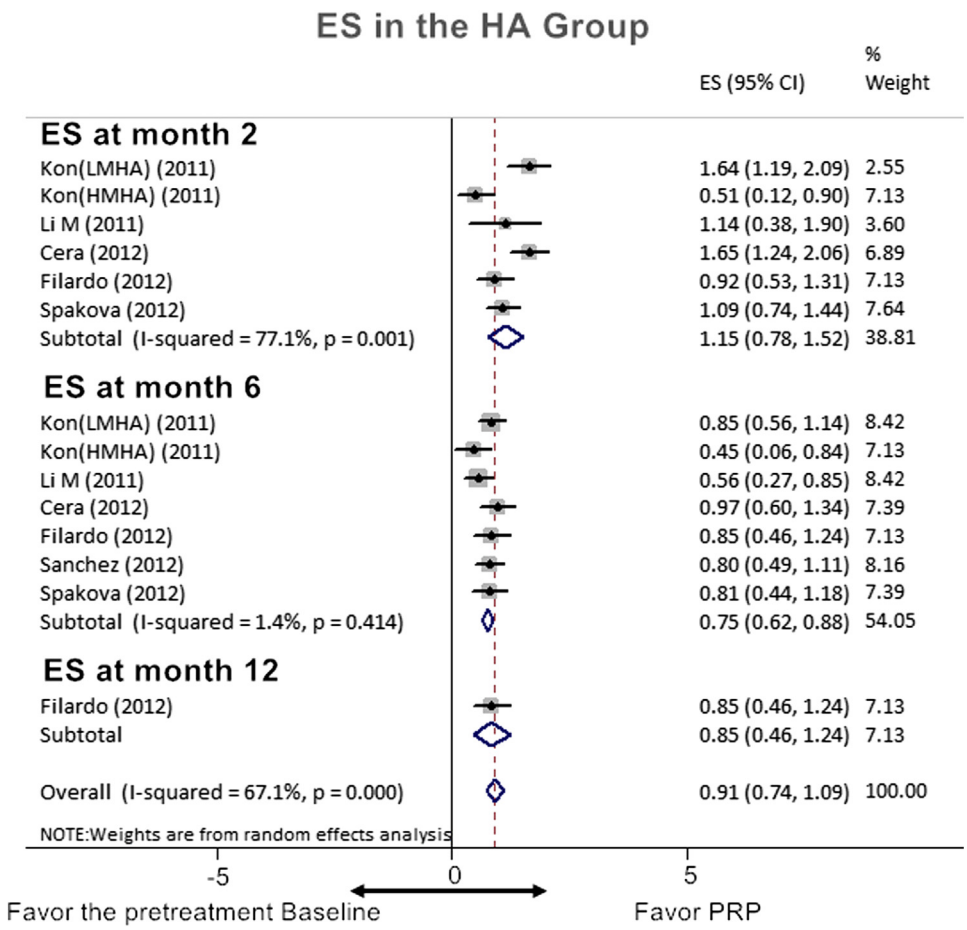

Fig 3 Forest plot of the ES of functional changes from baseline after HA injections. Abbreviation: ES, effect sizes.

Several factors mentioned by antecedent research might modify the effect of PRP injections. In terms of the study design, the pooled effect sizes in single-arm and quasi-experimental studies were likely to be higher than that in randomized controlled trials. As a result, to prevent overestimation of PRP effectiveness, the present meta-analysis also interpreted the comparisons between PRP and HA based on the outcomes from randomized controlled trials. One potential modifier is the centrifugation method. Some authors advocate a double-spinning technique instead of a single-spinning method because the former might generate a higher platelet concentration and thus result in better efficacy.[38] Another issue is the addition of activation agents, which potentially contribute to an increase in growth factor release.[13] Our stratified analysis did not identify a significant discrepancy in effectiveness between groups by using different centrifugation methods or activation agents. However, the use of a single spinning method and a lack of activation agents tended to generate an effect size covering the zone of ineffective treatment (see table 3). Regarding the number of PRP injections, a dose-responsiveness relationship was unclear. Likewise, uncertainty of effectiveness existed with doses $\leq$2, suggesting a minimal requirement of 3 doses during clinical practice. Finally, our subgroup analysis showed that the efficacy varied according to the degenerative severity, which was related to the regenerative potential of damaged cartilage. Our results are compatible with those of most trials, favoring discriminative usage of PRP in cases with degenerative chondropathy and mild OA.

Study limitations

Several limitations should be considered in the interpretation of the present meta-analysis. First, most trials retrieved from the electronic database used a single-arm, prospective follow-up design without controls and randomization of the participants. These fundamental flaws rendered the studies low in research quality and level of evidence. Second, there was marked heterogeneity across the included studies regarding the PRP preparation and dosage, follow-up duration, and functional outcome assessment scales. Although we tried to compensate for methodological deficiencies by performing a stratified analysis, some results remained inconclusive since several reports lacked the documentation of the key factors mandatory for stratification. Finally, many trials recruited patients with degenerative chondropathy defined as a grade 0 on the KL scale. Without the use of magnetic resonance, the diagnosis of a chondral lesion is difficult, leading these studies to possibly enroll some subjects with knee pain without degenerative pathology. In addition, physicians seldom prescribed an injection therapy as the first line of treatment in patients with such an early lesion. Although the degenerative chondropathy group

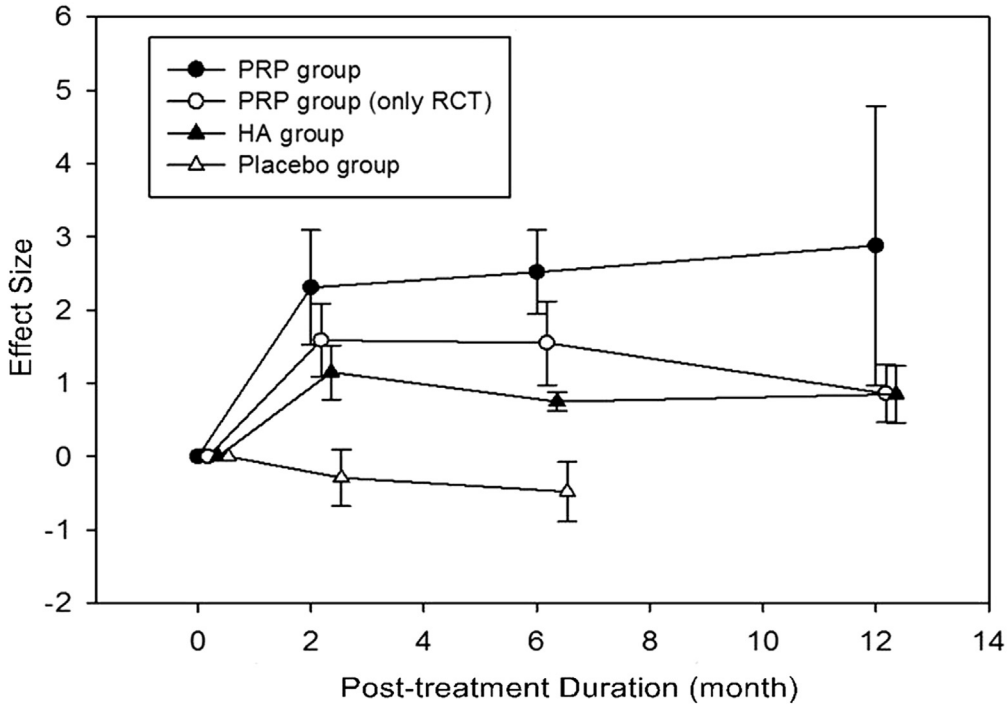

Fig 4 Temporal relationships of effect sizes of functional changes after PRP, HA, and placebo injections. We also analyzed the treatment arm only comprising RCT of PRP interventions. Abbreviation: RCT, randomized controlled trials.

Table 3 Analysis of the effect sizes of PRP treatment stratified by their study design, dose of injection, cycle of centrifugation, additional activation agent, and severity of degenerative pathology

Subgroup	Pooled Effect Size at Month 2	Pooled Effect Size at Month 6	Pooled Effect Size at Month 12
Study design			
Single-arm follow-up study	2.65 (0.55 to 4.75)	3.02 (1.99 to 4.06)	2.64 (−0.44 to 5.71)*
Quasi-experimental study	2.84 (1.48 to 4.19)	3.08 (1.36 to 3.81)	4.55 (4.11 to 4.98)†
Randomized controlled trial	1.59 (1.09 to 2.09)	1.55 (0.97 to 2.12)	0.86 (0.47 to 1.25)†
No. of PRP doses administered			
4	2.38 (1.89 to 2.87)	3.00 (2.49 to 3.51)	Nil
3	2.70 (1.68 to 3.72)	2.59 (1.83 to 3.35)	3.54 (1.43 to 5.65)
2	1.69 (1.24 to 2.14)	3.39 (−0.63 to 7.42)*	5.71 (4.95 to 6.47)
1	0.71 (−0.83 to 2.26)*	1.73 (0.50 to 2.97)	−0.40 (−3.39 to 2.59)*
Cycle of centrifugation			
1	1.53 (0.51 to 2.56)	2.28 (1.69 to 2.88)	2.71 (−0.95 to 6.37)*
2	3.22 (1.58 to 4.85)	3.21 (1.44 to 4.99)	3.50 (0.37 to 6.64)
3	1.58 (1.19 to 1.97)	1.29 (0.90 to 1.68)	Nil
Not mentioned	2.38 (1.89 to 2.87)	1.98 (−0.04 to 4.00)*	1.13 (0.42 to 1.84)
Additional activation agent			
Calcium chloride	3.00 (1.78 to 4.23)	2.68 (1.85 to 3.50)	4.24 (2.75 to 5.75)
Calcium gluconate	1.74 (1.32 to 2.17)	2.42 (1.66 to 3.18)	Nil
Nil	0.75 (−0.87 to 2.37)*	3.11 (1.37 to 4.85)	1.89 (−5.59 to 9.37)*
Not mentioned	1.64 (0.21 to 3.07)	1.60 (0.20 to 2.99)	0.92 (0.58 to 1.27)
Severity of degeneration			
Degenerative chondropathy	3.34 (1.64 to 5.04)	3.90 (2.54 to 5.26)‡	3.41 (0.86 to 5.96)
Early OA	2.23 (1.51 to 2.94)	2.37 (1.96 to 2.78)	1.60 (0.11 to 3.08)
Advanced OA	1.58 (1.08 to 2.08)	1.59 (0.85 to 2.32)‡	0.96 (0.13 to 1.80)

NOTE. Values are expressed by their point estimates with a 95% CI.

* The 95% CI covered a zero value, which implied an uncertainty of treatment effectiveness compared with the pretreatment baseline.

† Significant difference of the effect size at 12 months between the quasi-experimental studies and randomized controlled trials.

‡ Significant difference of the effect size at 6 months between degenerative chondropathy and advanced OA.

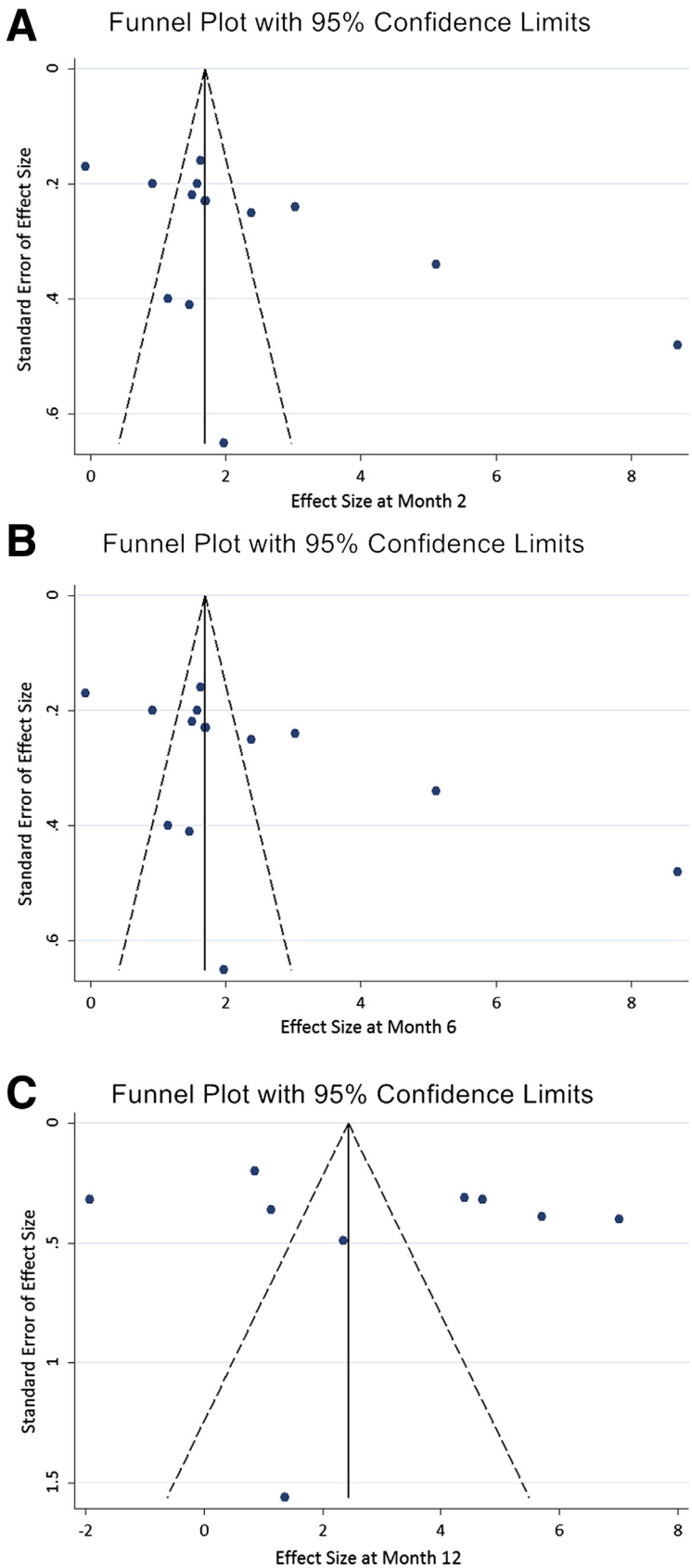

Fig 5 Funnel plots of the effective size of functional changes from baseline at (A) 2 months, (B) 6 months, and (C) 12 months after PRP injections.

had the most benefit from PRP injections in our subgroup analysis, we suggest that future trials should be conducted to focus on patients with mild to moderate knee OA based on the consideration of clinical utility.

Conclusions

The present meta-analysis demonstrates a significant functional improvement after PRP intervention in patients with knee cartilage degenerative pathology, compared with their pretreatment baseline, although this finding should be interpreted with caution because of the low methodological quality of the included trials. The effectiveness of PRP is likely superior to that of HA, with a longer effective duration. Discrepancy in the degenerative severity modified the treatment response, leading the participants with a lower degree of knee degenerative lesions to benefit more from PRP injections. We suggest that future studies target the population with mild to moderate knee OA based on the consideration of clinical utility.

Supplier

a. StataCorp LP, 4905 Lakeway Dr, College Station, TX 77845-4512.

Keywords

Cartilage; Knee; Osteoarthritis; Platelet-rich plasma; Rehabilitation

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