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

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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1 **Comparative Effectiveness of Platelet-Rich Plasma Injections for Treating Knee**

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3

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Abstract

Objectives: 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, and randomized controlled trials that employed PRP to treat knee chondral degenerative lesions. Eight single-arm studies, 3 quasi-experimental, 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 following the interventions and compared the PRP group pooled values with the pre-treatment 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 pre-treatment condition. The effectiveness of PRP was likely better and more prolonged than HA. Injection doses equal to or less than 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 to benefit more from PRP injections.

Keywords: platelet-rich plasma, osteoarthritis, cartilage, knee

List of Abbreviations: PRP: platelet-rich plasma; HA**:** hyaluronic acid; OA: osteoarthritis

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, leading to serious impacts on the quality of life and social-economic wellbeing.[1] A variety of pain relieving oral medications are available and appear effective in the early disease stages, including acetaminophen, non-steroidal 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 one month.[5] Synthetic hyaluronic acid (HA), whose natural form is present in healthy joint fluid, has been employed against 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 discouraged the use of viscosupplementation due to a clinically irrelevant advantage and an increased risk of serious adverse events following HA injections.[6]

Platelet-rich plasma (PRP), a natural concentrate of autologous growth factors

from the blood, is an emerging regenerative therapy against 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 showed positive effects of PRP on lateral epicondylitis and periodontal and sinus bone grafts[8, 9], but less favorable outcomes regarding arthroscopic rotator cuff repair, joint arthroplasty, reconstruction of cruciate ligaments, and chronic tendinopathy.[10-12] Accordingly, the efficacy of PRP likely varies in different pathological 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 due to its potential disease modifying and regenerative capability, compared to conventional injection regimens. However, to the best of 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 to the pretreatment condition, following 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 employed 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 of the selected trials were required to have serial functional measurements such as the International Knee Documentation Committee Subjective Knee Form (IKDC), Knee injury and Osteoarthritis Outcome Score (KOOS), or Western Ontario and McMaster Universities Arthritis Index (WOMAC) before and after the administration of PRP.

Data Extraction and Quality Assessment

Two authors (K.V.C and 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 less than 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 less than 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 month following 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 pre-treatment condition, we used the standardized mean difference between the baseline and status following therapy. Data were derived from the ratio of the difference between baseline and post-treatment functional scores to the standard deviation (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 {[(participant numbers in baseline – 1)*(standard deviation of scores in baseline)^2 + (participant numbers after treatment – 1)*(standard deviation of scores after treatment)^2]/ [(participant numbers in baseline – 1)+ (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 post-treatment 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 <0.1 for chi-squared 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 if the action caused serious changes in the overall result. We used a funnel plot and the Begg's test to exam 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 (StataCorp, Texas, USA [a]).

Results

Of the 73 non-duplicate citations identified from the literature, 18 clinical trials were screened for eligibility (Figure 1). One study was excluded due to introducing PRP by performing a miniarthrotomy[21] (not by an injection technique), and the other was removed because of inability to extract data from box plots.[22] 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 compared PRP with HA injections,[33-36] 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 employed 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 (Tables 1 and 2)

The 16 included studies had a total enrollment of 1543 patients, 840 of whom (54.4%) were males. The duration from the onset of knee pain to be registered 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 following PRP injections. Most studies recruited knee OA patients 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 (Figures 2, 3, and 4)

Compared with the pre-injection 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 0.97, 4.79) at 12 months, which all favored the status following PRP treatment. 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 0.51, 4.20) at 12 months. In the HA group, the effect sizes were 1.15 (95% CI 0.78, 1.52) at 2 months, 0.75 (95% CI 0.62, 0.88) at 6 months, and 0.85 (95% CI 0.46, 1.24) at 12 months. A significant superiority of 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 (Figure 4 and Table 3), the PRP group still demonstrated a significantly higher effect size of 1.55 (95% CI 0.97, 2.12), compared to 0.75 (95% CI 0.62, 0.88) in the HA group, at 6 months. Only 1 study used normal saline for placebo controls. The effect sizes were -0.29 (95% CI -0.68, 0.10) at 2 months and -0.48 (95% CI -0.89, -0.07) at 6 months, whose point estimates and 95% CI appeared inferior to the PRP and HA group values.

Stratified analysis (Table 3)

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. The point estimate 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 used equal or fewer than 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 either 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, grade I-II, and grade III-IV were defined as degenerative chondropathy, early osteoarthritis, and advanced osteoarthritis, respectively. The degenerative chondropathy group had the highest effect size point estimate at all time

points, followed by early and advanced osteoarthritis. 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 osteoarthritis group (effect size, 1.59, 95% CI, 0.85, 2.32).

Adverse Effect

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 following PRP treatment was 1.19 (95% CI, 0.85, 1.66) compared with HA administration, indicating no significant difference between the regimens in eliciting post-injection discomfort.

Publication bias (Figure 5)

Asymmetry was observed in the funnel plots based on the effect sizes of changes in the functional scales from baseline in the PRP group. P values, determined by using a Begg's test, were 0.028 at 2 months, 0.017 at 6 months, and 0.84 at 12 months,

242 which indicated the existence of significant publication bias regarding the measured
243 outcome at 2 and 6 months.
244
245
246 **Discussion**
247 The current meta-analysis comparing PRP injections in patients with knee
248 degenerative pathology, with their pre-treatment condition, showed a continual
249 efficacy for at least 12 months. Compared with HA administration, the PRP group
250 exhibited better and prolonged beneficial effects, and the advantages remained after
251 excluding single arm and quasi-experimental trials. Injection doses equal to or less
252 than 2, the use of a single-spinning approach, and lack of activation agents led to an
253 uncertainty of the treatment effectiveness. Furthermore, patients with a lower degree
254 of cartilage degeneration achieved superior results compared to those with advanced
255 OA. Finally, PRP treatment did not elicit a higher risk of adverse reactions relative to
256 HA administration.
257
258 Four meta-analytic research articles investigating the efficacy of PRP in the
259 treatment of orthopedic disorders have been recently published. Krogh et al.
260 compared a variety of injection therapies against lateral epicondylitis and found that

PRP administration was significantly superior to placebo for pain relief.[8] Chahal et al.[12] and Zang et al.[10] reviewed studies comprising participants with full-thickness rotator cuff tendon tears, who were treated with arthoscopic repair with or without concomitant PRP supplementation, and failed to demonstrate a benefit of additional PRP in reducing overall re-tear rates and improving shoulder-specific outcomes. Sheath et al. compared PRP interventions with controls in various orthopedic conditions such as anterior cruciate ligament reconstruction, spinal fusion, total knee arthroplasty, humeral epicondylitis, and Achilles tendinopathy, and concluded that the available evidence was insufficient to support PRP as a treatment option for orthopedic or soft tissue injuries.[11] To the best of our knowledge, none of these meta-analyses targeted the issue of PRP prescription against knee degenerative lesions. A focused review regarding PRP for the treatment of cartilage pathology has been recently published and did not favor PRP as a first-line treatment for moderate to severe knee OA.[13] 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 effective sizes is the overestimation of true values due to a lack of control. Only 1 of the included trials employed saline as a placebo control, whose effect size was -0.29 (95% CI -0.68, 0.10) at 2 months and -0.48 (95% CI -0.89, -0.07) 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 following 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 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 with 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

299 effect of HA in relieving pain in patients with knee OA probably through the
300 mechanism of viscosupplementation and modulation of the early inflammatory
301 response.[6] Compared with the HA group, patients treated by using PRP demonstrated
302 better effectiveness at 2 time points and the trend of improvement was sustained until
303 12 months (Figure 4). The advantage of PRP over HA remained at 6 months even
304 when only the results from randomized controlled trials were analyzed. In-vitro
305 experiments have demonstrated the capability of PRP in the temporary modulation of
306 cytokine levels and stimulation of chondral anabolism, which may lead to short-term
307 pain relief and long-term functional improvement, respectively.[40] When comparing
308 the temporal changes in clinical outcomes between the 2 regimens, PRP injections
309 provided a more prompt symptomatic relief than HA. Since the main action of HA
310 derives from the restoration of visicoelasticity of synovial fluid, the prolonged
311 efficacy of PRP might imply a regenerating or disease modifying potential, which has
312 rarely reported in studies using HA preparations.
313
314 Several factors mentioned by antecedent research might modify the effect of PRP
315 injections. In terms of the study design, the pooled effect sizes in single arm and
316 quasi-experimental studies were likely to be higher than that in randomized controlled
317 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 lack of activation agents tended to generate an effect size covering the zone of ineffective treatment (Table 3). Regarding the number of PRP injections, a dose-responsiveness relationship was unclear. Likewise, uncertainty of effectiveness existed with doses equal or less than 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 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 employed 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. Secondly, 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 negative for 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 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 the interpretation should be cautious due to the low methodology quality of included trials. The effectiveness of PRP is likely superior to 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. Future studies are suggested to target the population with mild to moderate knee OA based on the consideration of clinical utility.

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Figure Legends

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

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

Figure 3. Forest plot of the effect sizes (ES) of functional changes from baseline following HA injections.

Figure 4. Temporal relationships of effect sizes of functional changes following PRP, HA, and placebo injections. We also analyzed the treatment arm only comprising randomized controlled trials (RCT) of PRP interventions.

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

Table 1. Summary of studies using platelet-rich plasma injection to treat chondral degenerative lesions in knee joints

Author, year	Enrolled sample number	Average age, years	Disease duration	Double blind	Intention-to-treat analysis	Outcome measure	Follow-up timing	Adverse event	Quality assessment
Single arm prospective follow-up studies									
Halpern et al, 2013	22, (17 M, 5 F)	54.7	Averaged 14 months	No	No	VAS, WOMAC	1 week, 1, 3, 6, 12 months	Not mentioned	4†
Jang et al, 2013	65 (12 M, 53 F)	59.7 (32-85)	Not mentioned	No	Yes	IKDC, VAS	1, 3, 6, 9, 12 months	Mild swelling or pain in 41 patients. Mild local heat in 7 patients	4†
Gobbi et al, 2012	50 (31 M, 19 F)	47.7 ± 5.2	Not mentioned	No	Yes	IKDC, KOOS, Marx, Tegner, VAS	6, 12 months	Nil	4†
Napolitano et al, 2012	27 (21 M, 6 F)	Arthritis group (n=13): 64 ± 11; cartilage disease group (n=14): 26.2 ± 2	More than 1 year	No	Not mentioned	NRS, WOMAC	1, 6 months	Nil	4†
Filardo et al, 2011	90 (57 M, 33 F)	50 ± 14	At least 4 months	No	No	IKDC, VAS	2, 6, 12, 24 months	Pain with swelling in one patient	4†
Sampson et al, 2011	14 (12 M, 2 F)	51.8 (18-87)	At least 3 months	No	No	VAS, KOOS, ultrasound measured cartilage thickness	2, 5, 11, 18, 52 weeks	Moderate pain in one patient	4†
Wang-Saegusa et al, 2011	261 (152 M, 109 F)	48.4 ± 16.7	At least 3 months	No	Not mentioned	Lequesne index, SF-36, VAS, WOMAC	6 months	Nil	4†
Kon et al, 2010	91 (57 M, 34 F at follow-up)	47 (24-82)	At least 4 months	No	No	IKDC	2, 6, 12 months	Pain with swelling in one patient	4†

Quasi-experimental studies									
Filardo et al, 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 4 months	No	Not mentioned	IKDC, KOOS, VAS	2, 6, 12 months	Nil	5†
Spakova et al, 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 12 months	No	Not mentioned	NRS, WOMAC	3, 6 months	Temporary mild worsening of knee pain after PRP injections in 6 cases	5†
Kon et al, 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 54.9 ± 12.6	At least 4 months	No	Not mentioned	IKDC, VAS	2, 6 months	Nil	5†
Randomized controlled trials									
Patel et al, 2013	74 (single PRP injection group: 10 M, 16 F; double PRP injections group: 5 M, 20 F; normal saline group: 6 M, 17 F)	Single PRP injection group: 53.1 ± 11.6; double PRP injections group: 51.6 ± 9.2; normal saline group: 53.7 ± 8.2	Not mentioned	Yes	No	VAS, WOMAC	6 weeks, 3, 6 months	Post-injective pain in 4 patients in the single PRP injection group and in 3 patients in the double PRP injection group	5*
Cerza et al, 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, 12 months	Nil	2*

Filardo et al, 2012	109 (PRP group 37 M, 17 F; HA group 31 M, 24 F)	PRP group: 55; HA group 58	At least 4 months	Yes	Yes	IKDC, KOOS, Tegner, VAS	2, 6, 12 months	A significantly higher post-injective pain reaction was observed in the PRP group	5*
Sanchez et al, 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, 6 months	Mild adverse event (26 in PRP group; 24 in HA group)	5*
Li Ming, 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 4 months	Not mentioned	Yes	IKDC, Lequesne index, WOMAC	3, 4, 6 months	Pain, swelling and limited range (12 in PRP group and 12 in HA group)	2*

Note: * indicated that the quality scores derived from the Jadad scale. † indicated that the quality scores derived from the Newcastle-Ottawa Scale. Abbreviation: M, male; F, female; PRP, platelet-rich plasma; HA, hyaluronic acid; LWHA, low–molecular weight hyaluronic acid; HWHA, high–molecular weight hyaluronic aicd; IKDC, International Knee Documentation Committee Subjective Knee Form; KOOS, Knee Injury and Osteoarthritis Outcome Score; NRS, numeric rating scale; SF-36, 36-item short-form health survey; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Table 2. Summary of the preparations and injection details of platelet-rich plasma in the retrieved trials

Author, year	Total injection dose	Volume per dose (mL)	Interval of injection	Centrifugation time	Activation agent	Comparison
Single arm prospective follow-up studies						
Halpern et al, 2013	1	6	NA	Not mentioned	Not mentioned	Nil
Jang et al, 2013	1	3	NA	Not mentioned	Not mentioned	Nil
Gobbi et al, 2012	2	4	1 month	1 centrifugation, 3500 rpm for 9 minutes	Nil	Nil
Napolitano et al, 2012	3	5	1 week	1 centrifugation, 3100 rpm for 8 minutes	Calcium gluconate	Nil
Filardo et al, 2011	3	5	3 weeks	2 centrifugations: 1800 rpm for 15 minutes and 3500 rpm for 10 minutes	Calcium chloride	Nil
Sampson et al, 2011	3	6	4 weeks	1 centrifugation for 15 minutes	Calcium chloride	Nil
Wang-Saegusa et al, 2011	3	5	2 weeks	1 centrifugation, 1800 rpm for 8 minutes	Calcium chloride	Nil
Kon et al, 2010	3	5	3 weeks	2 centrifugations, the first: 1800 rpm for 15 minutes; the second: 3500 rpm for 10 minutes	Calcium chloride	Nil
Randomized controlled trials or quasi-experimental studies						
Patel et al, 2013	1 in group A, 2 in group B	8	3 weeks in group B	1 centrifugation, 1500 rpm for 15 minutes	Calcium chloride	Group A: single PRP injection; group B: double PRP injections; group C: single normal saline injection
Cerza et al, 2012	4	5.5	1 week	Not mentioned	Not mentioned	HA (Hyalgan; Fidia, Abano Terme, Italy)
Filardo et al, 2012	3	5	1 week	2 centrifugations, the first: 1480 rpm for 6 minutes; the second: 3400 rpm for 15 minutes	Not mentioned	HA (Hyalubrix; Fidia, Abano Terme, Italy)
Filardo et al, 2012	3	5	3 weeks	Single-spinning group: 1 centrifugation for 8 minutes; double-spinning group: 2 centrifugations, 1800 rpm for 15 minutes and 3500 rpm for 10 minutes	Calcium chloride	Single-spinning vs. double spinning
Sanchez et al, 2012	3	2	1 week	1 centrifugation for 8 minutes	Calcium chloride	HA (Euflexxa; Copenhagen,

						Denmark)
Spakova et al, 2012	3	3	1 week	3 centrifugations, 3200 rpm for 15 minutes, 1500 rpm for 10 minutes and 3200 rpm for 10 minutes	Nil	HA (Erectus; CSC Pharmaceuticals Handels GmbH)
Kon et al, 2011	3	5	2	2 centrifugations,1480 rpm for 6 minutes and 3400 rpm for 15 minutes	Calcium chloride	HWHA (molecular weight 1000 to 2900 kDa) and LWHA (molecular weight 500 to 730 kDa)
Li Ming, 2011	3	4	3 weeks	2 centrifugations, both 2000 rpm for 10 minutes	Calcium chloride	HA (1500-2500 kDa)

Note: Abbreviation: NA, Not applicable; rpm, revolutions per minute; PRP, platelet-rich plasma; HA, hyaluronic acid; LWHA, low–molecular weight hyaluronic acid; HWHA, high–molecular weight hyaluronic acid

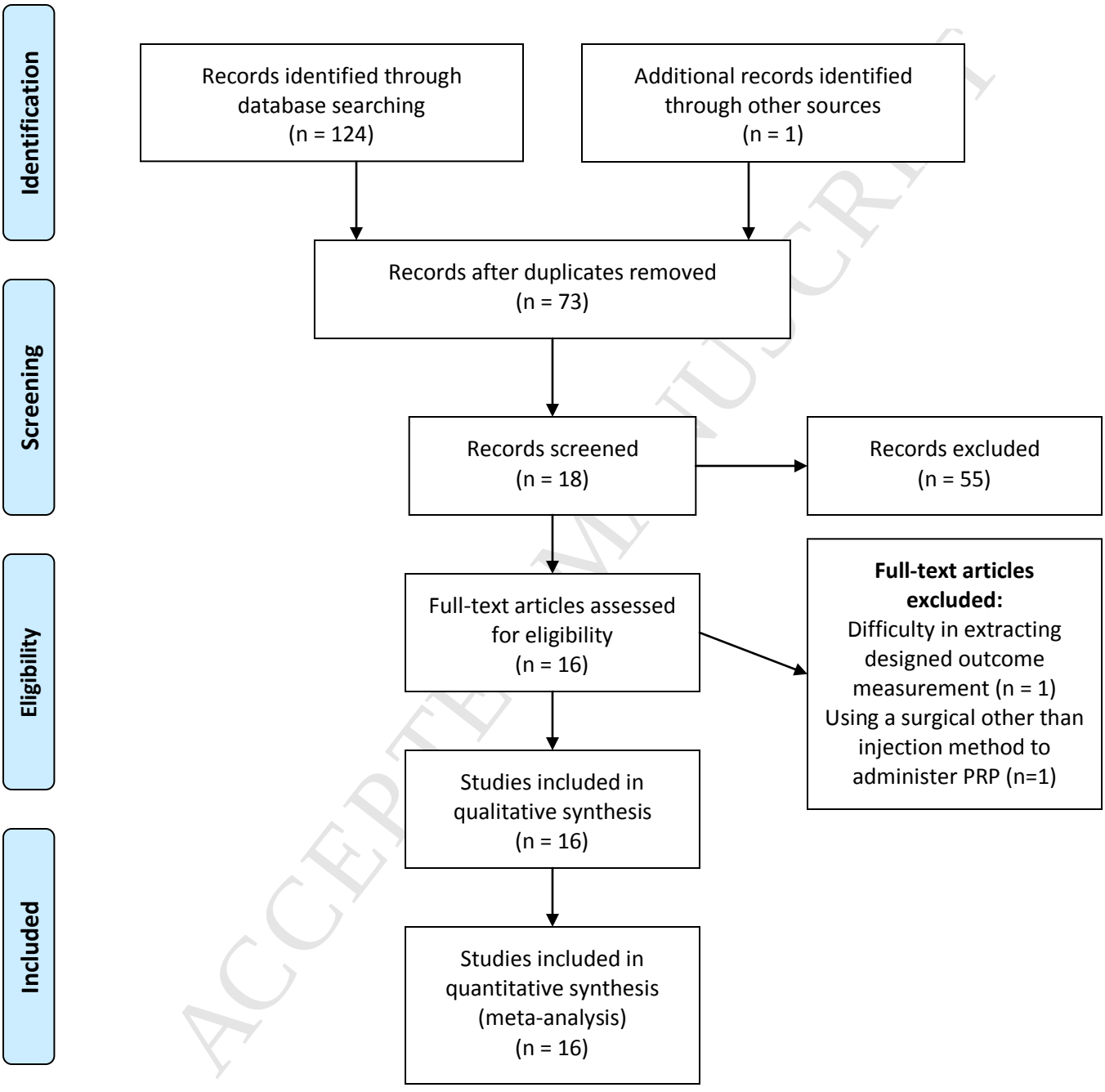
Table 3. Analysis of the effect sizes of platelet-rich plasma treatment stratified by their study design, dose of injection, cycle of centrifugation, additional activation agent and severity of degenerative pathology.

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, 4.75)	3.02 (1.99, 4.06)	2.64 (-0.44, 5.71)[#]
Quasi-experimental study	2.84 (1.48, 4.19)	3.08 (1.36, 3.81)	4.55 (4.11, 4.98)[a]
Randomized controlled trial	1.59 (1.09, 2.09)	1.55 (0.97, 2.12)	0.86 (0.47, 1.25)[a]
Dose of PRP administrations			
Four	2.38 (1.89, 2.87)	3.00 (2.49, 3.51)	Nil
Three	2.70 (1.68, 3.72)	2.59 (1.83, 3.35)	3.54 (1.43, 5.65)
Two	1.69 (1.24, 2.14)	3.39 (-0.63, 7.42)[#]	5.71 (4.95, 6.47)
One	0.71 (-0.83, 2.26)[#]	1.73 (0.50, 2.97)	-0.40 (-3.39, 2.59)[#]
Cycle of centrifugation			
One	1.53 (0.51, 2.56)	2.28 (1.69, 2.88)	2.71 (-0.95, 6.37)[#]
Two	3.22 (1.58, 4.85)	3.21 (1.44, 4.99)	3.50 (0.37, 6.64)
Three	1.58 (1.19, 1.97)	1.29 (0.90, 1.68)	Nil
Not mentioned	2.38 (1.89, 2.87)	1.98 (-0.04, 4.00)[#]	1.13 (0.42, 1.84)
Additional activation agent			
Calcium chloride	3.00 (1.78, 4.23)	2.68 (1.85, 3.50)	4.24 (2.75, 5.75)
Calcium gluconate	1.74 (1.32, 2.17)	2.42 (1.66, 3.18)	Nil
Nil	0.75 (-0.87, 2.37)[#]	3.11 (1.37, 4.85)	1.89 (-5.59, 9.37)[#]
Not mentioned	1.64 (0.21, 3.07)	1.60 (0.20, 2.99)	0.92 (0.58, 1.27)

Severity of degeneration			
Degenerative chondropathy	3.34 (1.64, 5.04)	3.90 (2.54, 5.26)[b]	3.41(0.86, 5.96)
Early osteoarthritis	2.23 (1.51, 2.94)	2.37 (1.96, 2.78)	1.60 (0.11, 3.08)
Advanced osteoarthritis	1.58 (1.08, 2.08)	1.59 (0.85, 2.32)[b]	0.96(0.13, 1.80)

Note: The values were expressed by their point estimates with a 95% confidence interval. “a” indicated significant difference of the effect size at 12 months between the quasi-experimental studies and randomized controlled trials. “b” indicated significant difference of the effect size at 6 months between degenerative chondropathy and advanced osteoarthritis. “#” indicated that the 95% confidence interval covered a zero value, which implied an uncertainty of treatment effectiveness compared with the pretreatment baseline. Abbreviation: PRP, platelet-rich plasma.

PRISMA 2009 Flow Diagram



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