Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjsports-2014-094036).

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Accepted 28 October 2014
Published Online First 21 November 2014

ABSTRACT

Background The effectiveness of platelet-rich plasma (PRP) injections for osteoarthritis (OA) is still controversial. We investigated the effect of PRP injections in patients with knee OA based on decreasing pain, improving function, global assessment and changes regarding joint imaging.

Methods We performed a comprehensive, systematic literature search in computerised databases (MEDLINE, EMBASE, CINAHL, CENTRAL, Web of Science and PEDro) until June 2014 for randomised or non-randomised controlled trials. These were graded for risk of bias and a level of evidence was provided. If possible, meta-analysis was performed.

Results Ten trials were included. In these, intra-articular PRP injections were more effective for pain reduction (mean difference (MD) −2.45; 95% CI −2.92 to −1.98; p value <0.00001 and MD −2.07; 95% CI −2.59 to −1.55; p value <0.00001, single and double PRP injections, respectively) compared with placebo at 6 months postinjection. Intra-articular PRP injections were compared with hyaluronic acid and showed a statistically significant difference in favour of PRP on pain reduction based on the visual analogue scale and numeric rating scale (standardised mean difference −0.92; 95% CI −1.20 to −0.63; p value <0.00001) at 6 months postinjection. Almost all trials revealed a high risk of bias.

Conclusions On the basis of the current evidence, PRP injections reduced pain more effectively than did placebo injections in OA of the knee (level of evidence: limited due to a high risk of bias). This significant effect on pain was also seen when PRP injections were compared with hyaluronic acid injections (level of evidence: moderate due to a generally high risk of bias). Additionally, function improved significantly more when PRP injections were compared with controls (limited to moderate evidence). More large randomised studies of good quality and low risk of bias are needed to test whether PRP injections should be a routine part of management of patients with OA of the knee.

INTRODUCTION

Osteoarthritis (OA) of the knee is a progressive disease involving the intra-articular (IA) tibiafemoral and patella-femoral cartilage and all other surrounding IA and periarticular structures.[1] It is one of the most frequent causes of pain, loss of function and walking-related disability among older adults (>65 years) in the USA.[2–5]

In older patients, who are refractory to conservative management, knee replacement surgery is the primary intended treatment for severe knee OA to relieve pain and improve function. Owing to the limited lifespan of joint replacements with implant wear and the associated risk for joint revision, conservative treatment modalities are the central focus in the younger and middle-aged population with cartilage damage and OA of the knee.[6]

The American College of Rheumatology (ACR) guidelines for the treatment of OA of the knee include non-pharmacological methods and pharmacological therapies.[7] These modalities are effective but not without limitations. Non-pharmacological approaches such as exercise and lifestyle modification are often associated with poor compliance.[8] Pharmacological therapies including analgesics, non-steroid and steroid anti-inflammatory drugs and corticosteroid injections provide only temporary benefit and often have side effects.[9–11]

There is an increasing clinical interest in autologous growth factor treatment such as the use of platelet-rich plasma (PRP) injections in OA of the knee.[12 13] PRP is an autologous blood product with an elevated platelet concentration.[14] Platelet-derived growth factors, stored in the α granulate of these increased concentration of platelets, regulate some biological processes in tissue repair.[15–18]

The preparation of platelets from autologous blood is a simple procedure by using laboratory centrifuge or cell separators. The application of this growth factor treatment is safe and minimally invasive.[14]

Several case series have shown favourable results of IA PRP injections in patients with cartilage damage and OA of the knee.[19–27] However, a number of controlled studies have demonstrated positive and negative outcomes. Due to these mixed results, we performed a systematic search of the literature to assess the effectiveness and safety over long and short time of PRP injections in patients with OA of the knee.

METHODS

Types of studies: Randomised controlled or non-randomised controlled clinical trials in full text were potentially eligible for inclusion.

Types of participants: We considered patients (>18 years) diagnosed with monolateral or bilateral OA of the knee based on the criteria described by the ACR, Altman *et al*'s[28] classification criteria and clinical and radiological information.

Types of interventions: Studies of interest were all IA injections (preparations) with PRP or similar products (ie, autologous blood, platelet-leucocyte

To cite: Laudy ABM, Bakker EWP, Rekers M, *et al*. *Br J Sports Med* 2015;**49**:657–672.

gel, platelet concentrate, platelet gel or PRGF-Endoret (Plasma Rich in Growth Factors-Endoret)) compared with control treatments including placebo, exercise treatment, joint lavage, IA hyaluronic acid (HA), IA corticosteroid, other IA PRP or doses of other IA PRP.

Types of outcomes: Studies reporting one of the OMERACT III core sets of outcome measures were eligible for inclusion: (1) pain; (2) physical function; (3) patient global assessment and (4) joint imaging.[29]

In addition, information about other outcome measures were extracted and analysed.

For assessment of adverse events, the following variables of interest were included: (1) short time local and systemic reactions, (2) infections and (3) withdrawals due to adverse events.

Search methods for identification of studies: We performed a comprehensive, systematic literature search in the electronic databases of MEDLINE, EMBASE, CINAHL, Web of Science and the Cochrane library without language or time restrictions until June 2014. Our search strategy (see addendum) was developed with help with a clinical librarian. For additional relevant studies, we examined the reference list of all included publications, consulted experts on this topic and used the 'related articles' feature in the used databases.

We searched the national (http://www.trialregister.nl) and international trial registries (http://www.controlled-trials.com); ClinicalTrials.gov and http://apps.who.int/trialsearch/ to identify ongoing studies. When an ongoing study was found, attempts were made to contact its primary investigator to collect further information.

Conference abstracts were searched to identify relevant unpublished studies in: OpenSigle (http://opensigle.inist.fr/); British Library Inside (http://www.bl.uk/inside); Web of Science and BIOSIS Previews (http://www.ovid.com). Also, we hand searched presentations and abstracts from annual meetings of the American Academy of Orthopaedic Surgeons (AAOS), the American Academy of Physical Medicine and Rehabilitation (AAPM&R), the ACR and the Osteoarthritis Research Society International (OARSI). The search was performed independently by two reviewers (ABML, MR).

Study selection: After removing duplicates, all titles and abstracts were screened independently for potentially eligible studies by two reviewers (ABML, MHM). Reports of studies that were considered potentially relevant by at least one reviewer were retrieved in full text. The eligibility of the retrieved full-text articles for final inclusion was assessed independently by two reviewers (ABML, MHM). Disagreement was resolved through discussion and if no consensus was reached, a third reviewer (EWPB or MR) made the final decision.

Data extraction: Two reviewers (ABML, MHM) independently extracted the data of all the included studies using a standardised data extraction form to ensure uniform data collection.

The following data were extracted from all eligible studies:

- General study information: title, authors and publication year;
- Study characteristics: study design, study setting, inclusion/exclusion criteria;
- Details of the interventions: dose, frequency of administration and duration of treatment;
- Primary and secondary outcome measures including the results in the intervention and the comparison groups from baseline to follow-up with the effect sizes and p values;
- Information regarding variables in the production of PRP used in the study protocols, such as the presence of white cells count, activation status, platelet concentration and the use of anticoagulants;
- Adverse events.

Differences in results of data extracted were resolved in an agreement meeting by the two reviewers. If questions remained after reading and extracting an article, the original authors of the study were contacted.

Quality assessment: Two independent reviewers (ABML, MHM) assessed the quality of the included randomised and non-randomised studies using the Cochrane Collaboration risk of bias tool.[30] This tool contains the following domains: sequence generation—allocation sequence concealment—blinding of participants, personnel and outcome assessors—incomplete outcome data—selective outcome reporting and other potential threats to validity. We assessed risk of bias in each domain of all included studies using a risk of bias table. We determined an item as 'low risk' of bias (+), 'high risk' of bias (−) or 'unclear risk' of bias (?), respectively.[30] Trials were considered as low risk of bias when on every single item of bias a '+' was scored; if studies scored '−' or '?' on one or two items of bias, a moderate bias was considered. Studies with more than two '−' or '?' were considered as high risk of bias. Differences were settled by discussion and in case of disagreement, the third reviewer (EWPB) made the final decision.

To assess the level of evidence for an intervention, best-evidence synthesis was used.[31] The results of the risk-of-bias assessments of the individual studies were used to classify the level of evidence.[32] This qualitative analysis was performed with five levels of evidence based on the risk of bias and results of the included studies:

1. Strong evidence: provided by two or more studies with a low risk of bias and by generally consistent findings in all studies (≥75% of the studies reported consistent findings).
2. Moderate evidence: provided by one study with a low risk of bias and/or two or more studies with a high risk of bias, and by generally consistent findings in all studies (≥75% of the studies reported consistent findings).
3. Limited evidence: provided by only one study with a high risk of bias.
4. Conflicting evidence: inconsistent findings in multiple studies (≥75% of the studies reported consistent findings).
5. No evidence: when no studies could be found.

Data syntheses: The results of the studies were analysed using RevMan 5.2. If the data were sufficiently homogeneous (clinical and statistical), we summarised these in a meta-analysis. Continuous outcomes were calculated and expressed as the mean difference (MD) or as the standardised MD (SMD) depending on the similarity of the used scales. Dichotomous data were expressed as the relative risk (RR).To measure heterogeneity between studies, we used the χ^2 (p value less than 0.10 indicates heterogeneity) and I^2 statistic (a value of less than 40% represents low heterogeneity and a value of 75% or more indicates high heterogeneity). The outcomes were pooled using random-effects models. Fixed-effects models were used when less than five studies could be included.

In case of heterogeneity, we planned a subgroup and meta-regression analysis to explore possible differences in PRP preparation, dose of PRP, age of study population, duration of follow-up or methodological features and the results are presented in a descriptive summary of findings table.

For pain, we identified pain on a visual analogue scale (VAS) or the numeric rating scale (NRS). If this was not available, we used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (percentage of people with a 50% decrease, VAS or Likert). For function, we used the WOMAC physical function subscale (50% decrease,

VAS or Likert) as the primary measure of function followed by the WOMAC total score and the Lequesne index.

RESULTS

Results of the search

The search of electronic databases and other sources in June 2014 resulted in 371 articles (see figure 1). After combining the results, removing duplicates and selections based on the title and abstract, 14 full-text articles remained. Four studies were excluded after reviewing the full text. Two were excluded because they did not examine the intervention of interest[33 34] and one was a point/counterpoint discussion.[35] The search in the trial registers resulted in three trials, two ongoing trials and one trial which was characterised as completed. We were unable to obtain additional information regarding this trial for inclusion in this systematic review. In total, 10 studies with 1110 patients met the predefined inclusion criteria.[36–45] The trials were published between 2011 and 2013.

Description of studies

See online supplementary materials: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Design

Six studies were reported to be randomised controlled trials (RCT). One of these compared PRP with placebo,[37] whereas the other five studies compared PRP with HA.[36 38–40 43]

Four studies were non-randomised clinical trials. Three included comparisons of PRP with HA[41 42 45] and one study compared single versus double spinning in the preparation of the PRP.[44]

Sample sizes

The mean number of patients randomised was 102 and ranged from 30 to 176.[40 43] The total follow-up of seven trials[37 39–43 45] was 6 months and that of three trials[36 38 44] had a duration of 12 months.

Participants

The average age in the randomised and non-randomised controlled trials was 59.5 years (range 52.8–66.4) and 53.4 years (range 52.1–55.7), respectively.

Both clinical criteria, as proposed by the recommendations of the ACR, and two different radiological grading systems were used to include patients with OA. The severity of OA was classified with the Ahlbäck classification by Patel *et al*[37] and Sánchez *et al*[40] (mode of grade OA in both the PRP group and the control group was 1), whereas five authors[36 39 41–43] used the Kellgren and Lawrence (K&L) classification system (mode of grade OA in the PRP group and the control group was 2; figure 2A, B). Three studies were excluded in the pooling of OA severity. Filardo *et al*[23] and Kon *et al*[16 45] grouped grading scales and Filardo *et al*[38 44] reported mean values.

Intervention

In five of the 10 trials the single spin procedure for the preparation of the PRP was used[36 37 39–41] whereas three trials reported a double spin procedure.[38 43 45] One trial used both techniques and compared them (single spinning vs double spinning approach).[44] Spaková *et al*[42] used a three spinning technique.

Most trials used a dosage of three IA injections on a one, two or three weekly basis.[36 38 40 42–45] In the Patel *et al*[37] and the Say *et al*[41] trials, a dosage of one IA injection was used, whereas Cerza *et al*[39] used a dosage of four injections at weekly intervals.

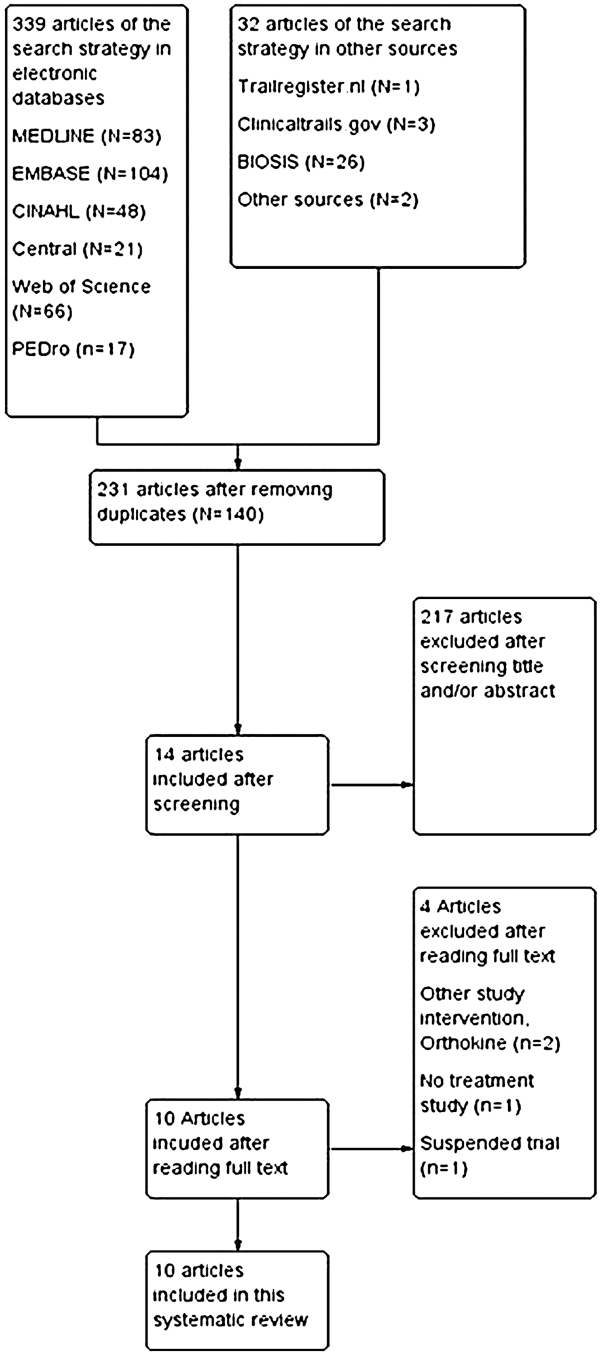


Figure 1 Study flow diagram.

In addition, the authors of the included studies were contacted by mail to obtain more detailed information of the used PRP. The results were categorised following the Mishra *et al*[46] classification system (table 1).

Outcomes

All trials reported a minimal one of the OMERACT III core sets of outcome measures. Primary outcome measures to assess pain and function were the VAS or NRS for pain and the WOMAC physical function subscale, respectively. Secondary outcome measures for pain included the WOMAC pain subscale, and those for function were inclusive of the WOMAC total index and Lequesne index.

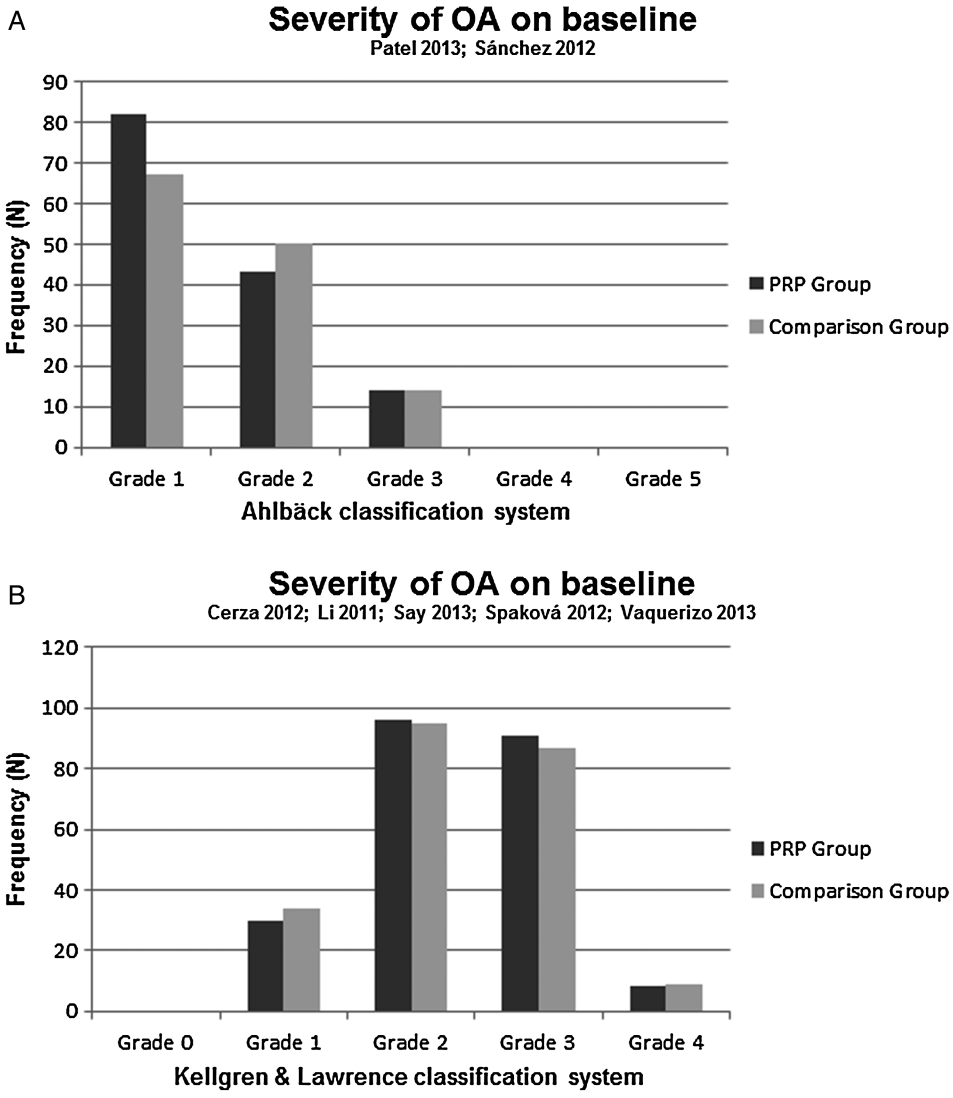


Figure 2 Severity of osteoarthritis (OA) on baseline classified by the Ahlbäck system.

Table 1 Details of the used PRP compilation and Mishra classification of PRP

References	Injections (N)/interval (weeks)/volume (mL)	Spinning approach	White cells count	Activation	Platelet concentration	Type PRP (Mishra classification)
Vaquerizo *et al*[36]*	3/2/8	Single spinning	–	+	<5×baseline	4B
Patel *et al*[37]*	1(2)/–(3)/8	Single spinning	–	+	<5×baseline	4B
Filardo *et al*[38 44]*	3/1/5	Double spinning	+	+	5×baseline	2A
Cerza *et al*[39]*	4/1/5.5	Single spinning	–	–	>5×baseline	3A
Sánchez *et al*[40]*	3/1/8	Single spinning	–	+	<5×baseline	4B
Say *et al*[41]	1/–/2.5	Single spinning	–	+	<5×baseline	4B
Spaková *et al*[42]	3/1/3	3 spinnings	+	–	<5×baseline	1B
Li *et al*[43]	3/3/3.5	NA	NA	+	NA	NA
Filardo *et al*[23]	3(3)/3(3)/5(5)	Single vs double spinning	– (+)	+(+)	<5×baseline	4B (2B)
Kon *et al*[16 45]	3/2/5	Double spinning	+	+	>5×baseline	2A

Type 1 PRP: increased white cells count and no activation; type 2 PRP: increased white cells count and activated; type 3 PRP: minimal/no white cells count and no activation; type 4 PRP: minimal/no white cells count and activated.
A: contains an increased platelet concentration at or above five times baseline (extracted venous blood).
B: contains an increased platelet concentration less than five times baseline (extracted venous blood).
*Included randomised controlled trials.
Values in brackets in the Patel's study: group B (2 platelet-rich injections).
Values in brackets in the Filardo's study: comparison group (double-spinning approach).
NA, not applicable; PRP, platelet-rich plasma.

Table 2 Overview of outcome measures per study

		OMERACT III set of outcome measures						
		Pain		Function			Global assessment	Joint imaging
Study type	Intervention/ comparison	VAS/ NRS	WOMAC pain	WOMAC physical function	WOMAC total	Lequesne index	Patient satisfaction	Scoring radiographs or demonstrably superior imaging techniques
RCTs	PRP-placebo	√1	√1*	√1*	√1*	–	√1	–
	PRP-HA		√2, 3	√2, 3	√2, 3, 4, 5	√2, 3, 5	√6*	–
CCTs	PRP-HA	√7, 8	–	–	√8	–	√7,*9	–
CCTs	PRP-PRGF	–	–	–	–	–	√10	–

1, Patel *et al*;[37] 2, Sánchez *et al*;[40] 3, Vaquerizo *et al*;[36] 4, Cerza *et al*;[39] 5, Li *et al*;[43] 6, Filardo *et al*;[38 44] 8, Spaková *et al*;[42] 9, Kon *et al*;[16 45] 10, Filardo *et al*.[23]
*Outcome measure not applicable or not reported in the included study.
–, No primary or secondary outcome measure in included study; √, study on outcome measure; CCT, non-randomised controlled trial; HA, hyaluronic acid; NRS, numeric rating scale; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; RCT, randomised controlled trial; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Postinjection follow-up moments varied between studies. All included studies, however, reported pain, function or global assessment at 6 months postinjection.

An overall summary regarding the outcome measures used in the included studies is provided in table 2.

Quality assessment

All randomised and non-randomised trials, except Sánchez's *et al*[40] trial which achieved a moderate risk of bias, obtained a high risk of bias.

A summary of the risk of bias of the included studies can be found in figure 3A, B. A more detailed justification for assigning low risk, high risk or unclear risk to each domain of bias is described and provided in the characteristics of the included studies table.

Effect of intervention

The included randomised and non-randomised trials assessed the effect of IA PRP injections compared with placebo and HA, respectively. For an overview of their effects, see table 3 and figures 4–23. One non-randomised trial assessed the effect of PRP compared with another IA PRP.

Data analysis

Fixed-effect models were used to estimate the effect of PRP versus HA. No statistical heterogeneity was present on the outcome pain identified on a VAS or the NRS (forest plot comparison 3, outcome 3.1). When pooled the outcome measures WOMAC pain subscale (percentage of people with a 50% decrease, VAS or Likert), WOMAC physical function, WOMAC total or Lequesne index, considerable heterogeneity was present (forest plot comparison 2 outcomes: 2.2–2.3–2.6–2.7–2.10). No meta-regression or subgroup analyses to test heterogeneity could be performed because four or less studies assessed the effect of PRP with a similar outcome and follow-up.

No statistical heterogeneity was present when pooling data on the outcome adverse events (forest plot comparison 2, outcome 2.16).

PRP versus placebo

Patel *et al*[37] detected a statistically significant difference on a 0–10 cm VAS in favour of the single PRP injection and the two PRP injections compared with saline at 6 months postinjection (MD −2.45; 95% CI −2.92 to −1.98; p value <0.00001, MD −2.07; 95% CI −2.59 to −1.55; p value <0.00001).

Patel *et al*[37] reported that for both pain and physical function, as assessed by WOMAC,[47] the improvement at 6 weeks, 3 and 6 months, was greater in the single spin and double spin procedure compared to placebo (p<0.001). Since no measure of dispersion (ie, SD, SE) was reported, these outcomes were not included in the RevMan analysis.

The same trial reported the percentage of patients who were satisfied with the procedure at 6 months postinjection. A statistically significant difference was detected in favour of the single PRP injection and the two PRP injections compared with saline. RR was 8.40 (95% CI 2.19 to 32.24; p value 0.002), RR was 7.82 (95% CI 2.02 to 30.20; p value 0.003).

Finally, no statistically significant difference was detected in the total number of patients with short time local and systemic reactions during and after the injections between the one PRP injection group and the saline group. RR was 11.14 (95% CI 0.66 to 187.75; p value 0.09). A statistically significant difference was detected between the two PRP injections group and the saline group; RR was 21.23 (95% CI 1.32 to 341.04; p value 0.03). For details, please see the effect estimates (see online supplementary materials).

Level of evidence (pain and function)

Limited evidence (one study with a high risk of bias) is available that PRP injections reduce pain significantly more than do placebo injections. Limited evidence (one study with a high risk of bias) is available that function (WOMAC) is improved significantly better after PRP injections compared with placebo.

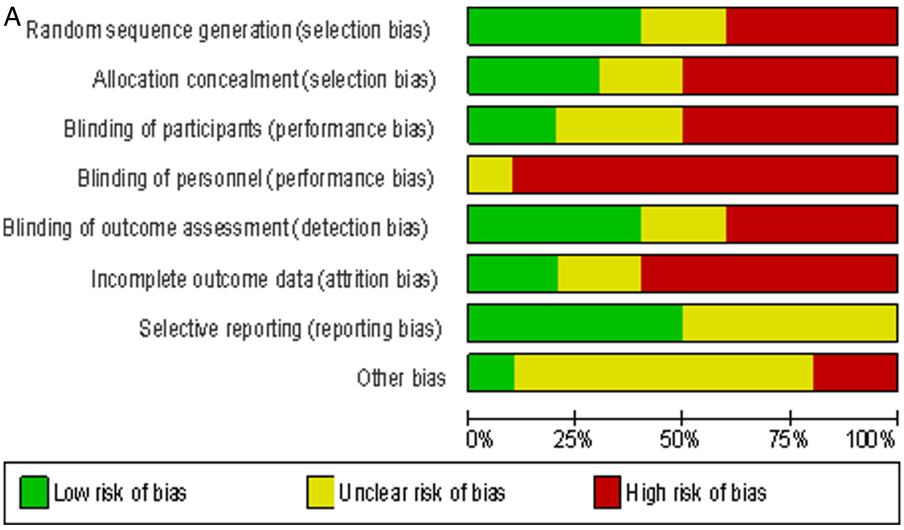
PRP versus HA

For details, please see table 3 and figures 10–22.

Level of evidence (pain)

Moderate evidence (≥75% of the studies had consistent findings but displayed a high risk of bias) is available that PRP injections reduce pain significantly more than do HA injections.

Regarding physical function, Vaquerizo *et al*[36] reported a statistically significant difference between PRP and HA in the number of patients reporting a 50% decrease in the WOMAC physical function score at both 6 months and 48 weeks postinjection (RR 3.80; 95% CI 1.54 to 9.35; p value 0.004 and RR 27.20; 95% CI 1.68 to 441.24; p value 0.02, respectively). This trial also detected a statistically significant difference in favour of PRP for the WOMAC physical function (0–68 Likert) at 6 months and 48 weeks postinjection (MD −16.50; 95% CI −22.20 to −10.80; p value <0.00001, MD −17.00; 95% CI



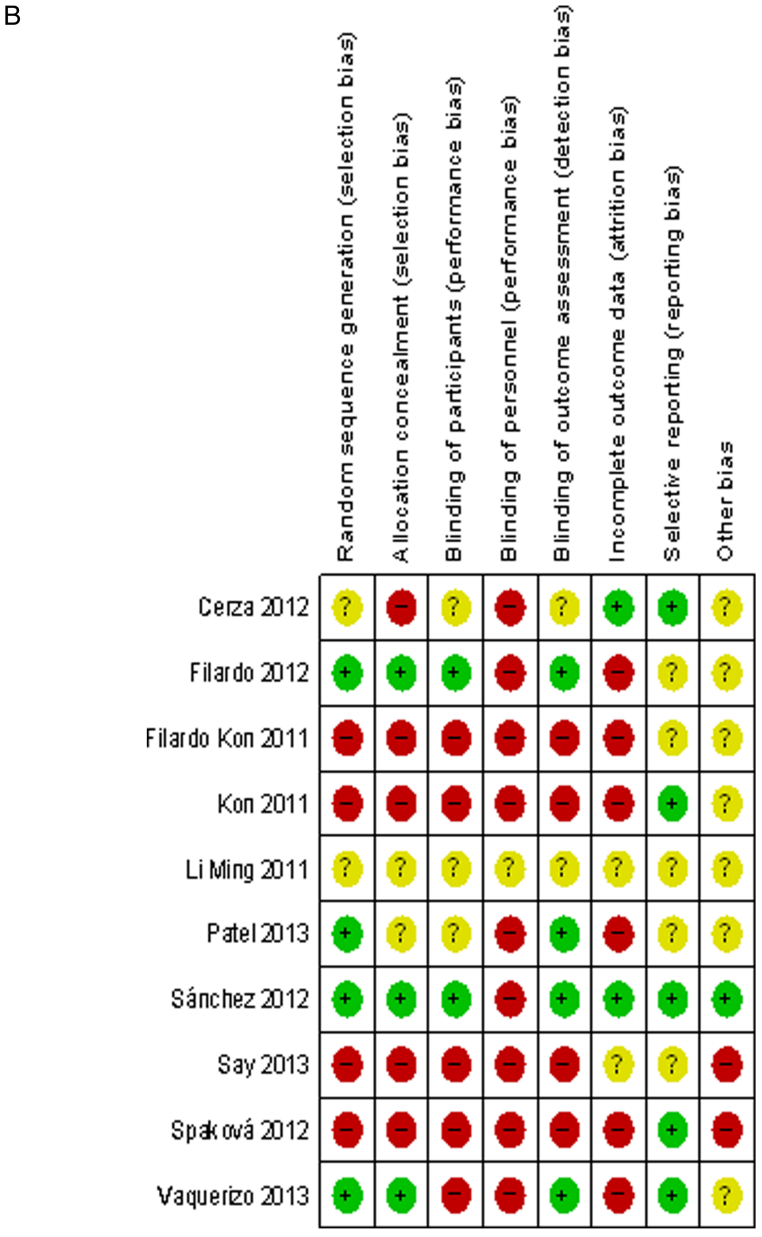


Figure 3 (A) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (B) Risk of bias graph: review authors' judgements about each risk of bias item for each included study.

Table 3 Overview of intervention effect per study in time

Study	Outcome	Subgroup	3 months postinjection	6 months postinjection	12 months postinjection
Vaquerizo *et al*[36]	Pain	Percentage of patients having a 50% decrease in the WOMAC pain subscale		+	+
	Function	Percentage of patients having a 50% decrease in the WOMAC physical function subscale		+	+
		Percentage of patients having a 50% decrease in the Lequesne index		+	+
		WOMAC total score		+	+
		Lequesne index		+	+
Cerza *et al*[39]	Function	WOMAC total score	+	+	
Sánchez *et al*[40]	Pain	Percentage of patients having a 50% decrease in the WOMAC pain subscale		+	
		WOMAC pain subscale		–	
	Function	WOMAC physical function subscale		–	
		WOMAC total score		–	
		Lequesne index		–	
Li *et al*[43]	Function	WOMAC total score	–	+	
		Lequesne index	–	+	
Spaková *et al*[42]	Pain	NRS	+	+	
	Function	WOMAC total score	+	+	
Say *et al*[41]	Pain	VAS	+	+	

+, indicates positive effect derived from the p value (p value <0.05);
–, indicates negative effect derived from the p value (p value >0.05);
NRS, numeric rating scale; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

−22.35 to −11.65; p value <0.00001, respectively). No statistically significant differences between PRP and HA were detected on the normalised WOMAC physical subscale (0–100) at 6 months postinjection in Sánchez *et al*'s[40] trial (MD −1.10; 95% CI −6.00 to 3.80; p value 0.66). When pooling these data, heterogeneity was present (SMD −0.41; 95% CI −0.65 to −0.17; p value 0.001, $\chi^2$16.40 df=1, I^2=94%).

Function, assessed with the WOMAC total score (0–96 Likert), showed a statistically significant difference in favour of PRP compared with HA at 3 months (pooled SMD −0.93; 95% CI −1.27

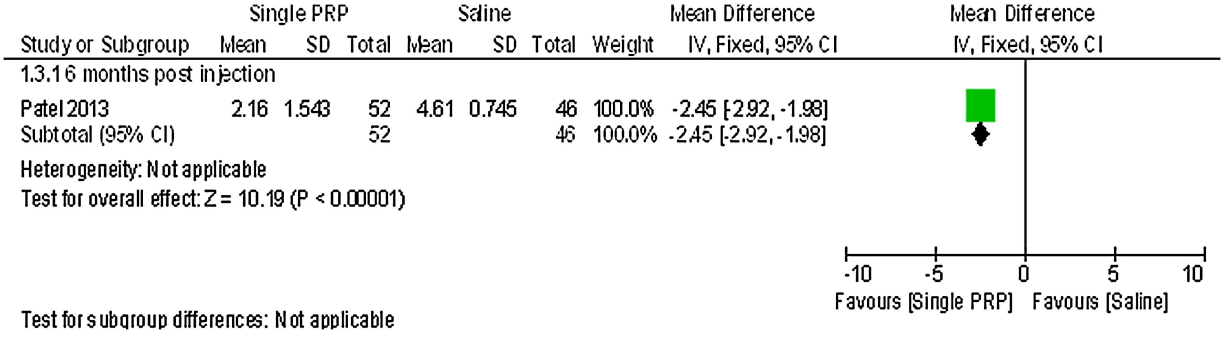


Figure 4 Forest plot of comparison: 1 platelet-rich plasma (PRP) versus placebo, outcome: 1.3; pain: visual analogue scale (single PRP vs saline).

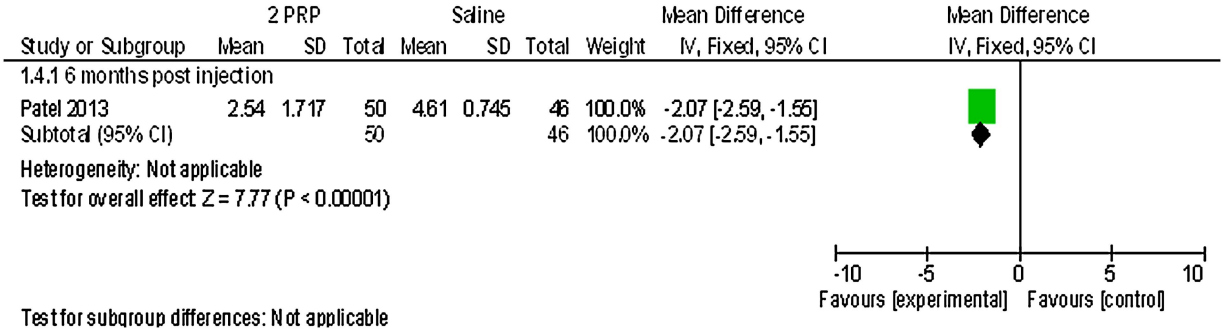


Figure 5 Forest plot of comparison: 1 platelet-rich plasma (PRP) versus placebo, outcome: 1.4; pain: visual analogue scale (2 PRP vs saline).

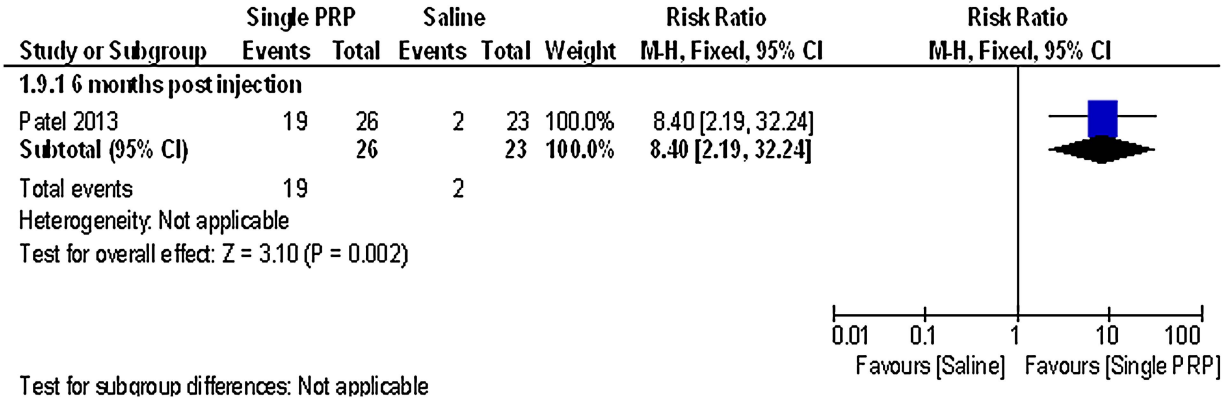


Figure 6 Forest plot of comparison: 1 platelet-rich plasma (PRP) versus placebo, outcome: 1.9; global assessment: patient satisfaction, number of patients who were satisfied (single PRP vs saline).

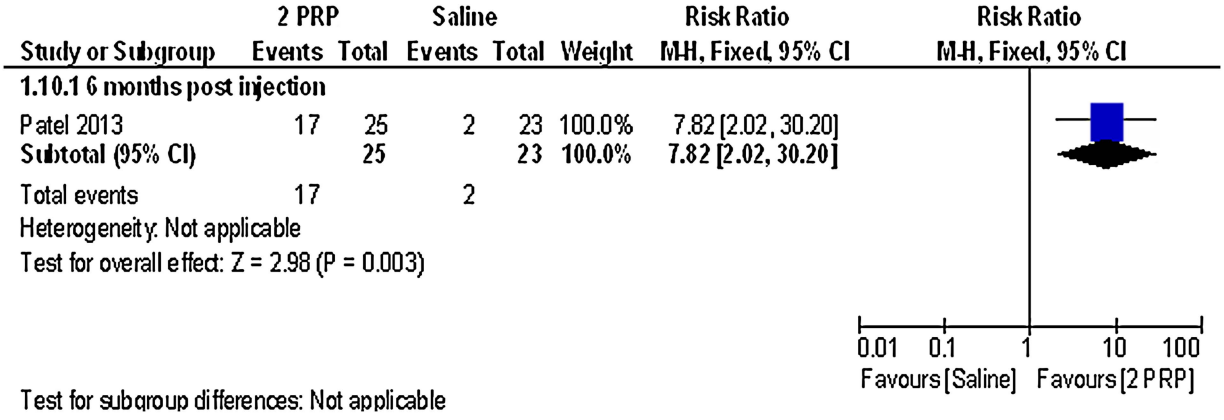


Figure 7 Forest plot of comparison: 1 platelet-rich plasma (PRP) versus placebo, outcome: 1.10; global assessment: patient satisfaction, number of patients who were satisfied (2 PRP vs saline).

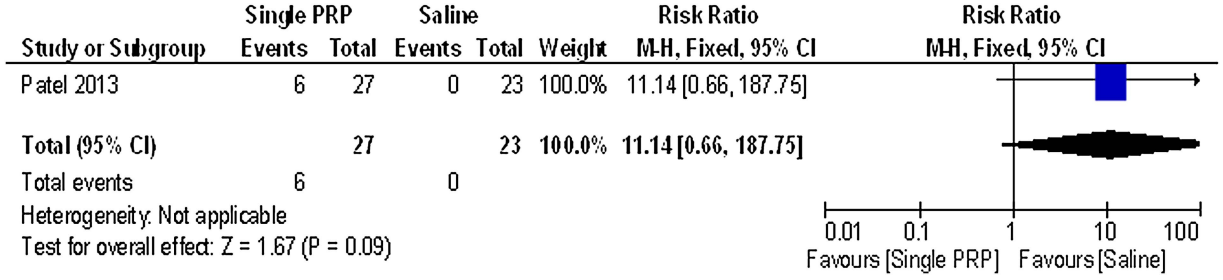


Figure 8 Forest plot of comparison: 1 platelet-rich plasma (PRP) versus placebo, outcome: 1.13; adverse effects: number of patients with local or systemic reactions related to treatment (single PRP vs saline).

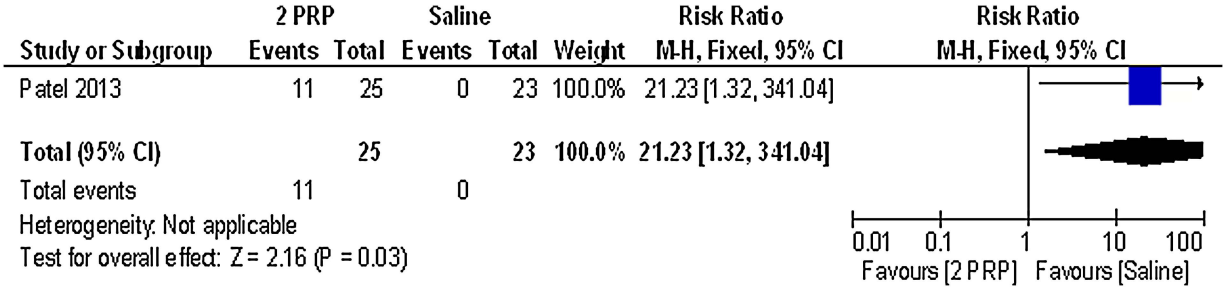


Figure 9 Forest plot of comparison: 1 platelet-rich plasma (PRP)versus placebo, outcome: 1.14; adverse effects: number of patients with local or systemic reactions related to treatment (2 PRP vs saline).

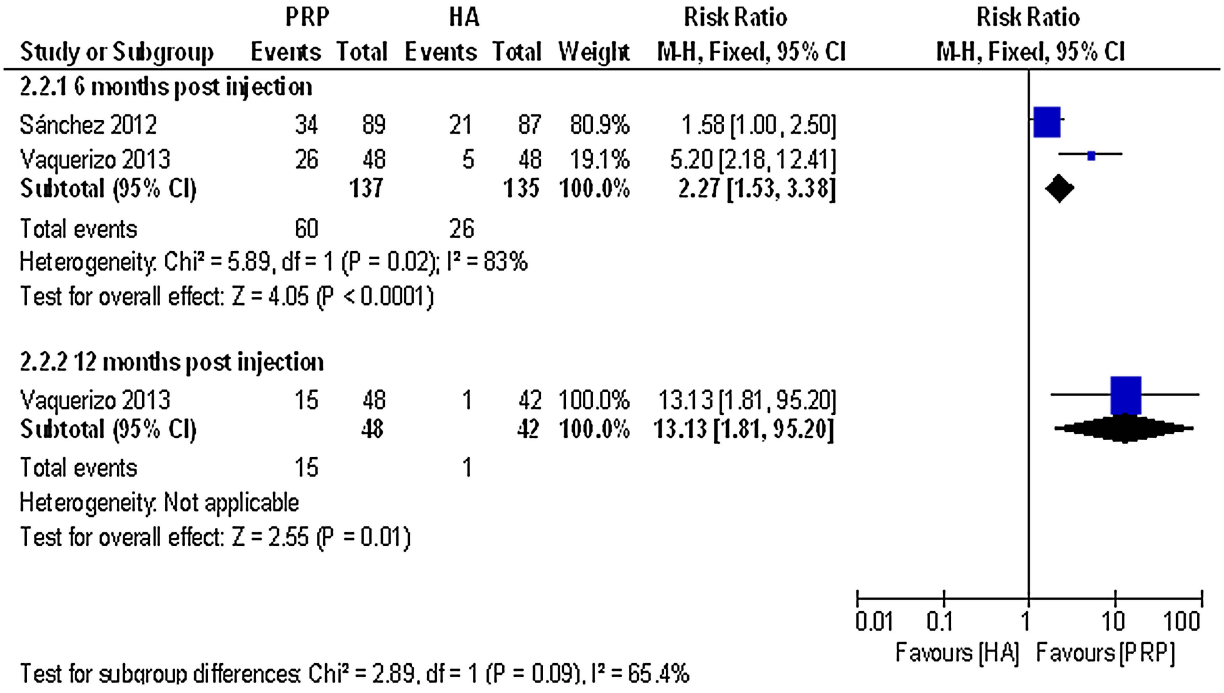


Figure 10 Forest plot of comparison: 2 platelet rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.2; pain: number of patients with 50% decrease on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale.

to −0.59; p value 0.00001)[39 43] and 6 months (pooled SMD −0.81; 95% CI −1.02 to −0.61; p value <0.00001).[36 39 40 43] However, considerable heterogeneity was present (χ^2=7.20 df=1, I^2=86% and χ^2=51.09 df=3, I^2=94%, respectively). At 48 weeks postinjection, the Vaquerizo *et al*[36] trial also showed a statistically significant difference using the WOMAC total score (0–96 Likert; SMD −1.34; 95% CI −1.80 to −0.88; p value <0.00001).

Considerable heterogeneity was also present in the Lequesne index (0–24) at 6 months postinjection (pooled MD −1.24; 95% CI −1.90 to −0.58; p value <0.00001, χ^2=20.71 df=1, I^2=90%) in the Vaquerizo *et al*[36], Sánchez *et al*[40] and Li *et al*[43] trials.

Vaquerizo *et al* also detected a statistically significant difference in favour of PRP in the number of patients reporting a 50% decrease in the Lequesne index at 6 months (RR 7.00; 95% CI 1.68 to 29.15; p value 0.008), but no statistically significant difference was found at 48 weeks postinjection (RR 7.88; 95% CI 1.04 to 59.61; p value 0.05).

Regarding the non-randomised trials, Spaková *et al*[42] assessed function with the WOMAC total score at 3 and 6 months postinjection. A statistically significant difference in favour of PRP was found at both postinjection follow-up periods (MD −11.82; 95% CI −17.51 to −6.13; p value <0.00001 and MD −12.05; 95% CI −17.55 to −6.55; p value <0.00001). For details, please see the effect estimates (see online supplementary materials).

Level of evidence (function)

Limited to moderate evidence is available that function (expressed as a 50% decrease of the WOMAC physical function

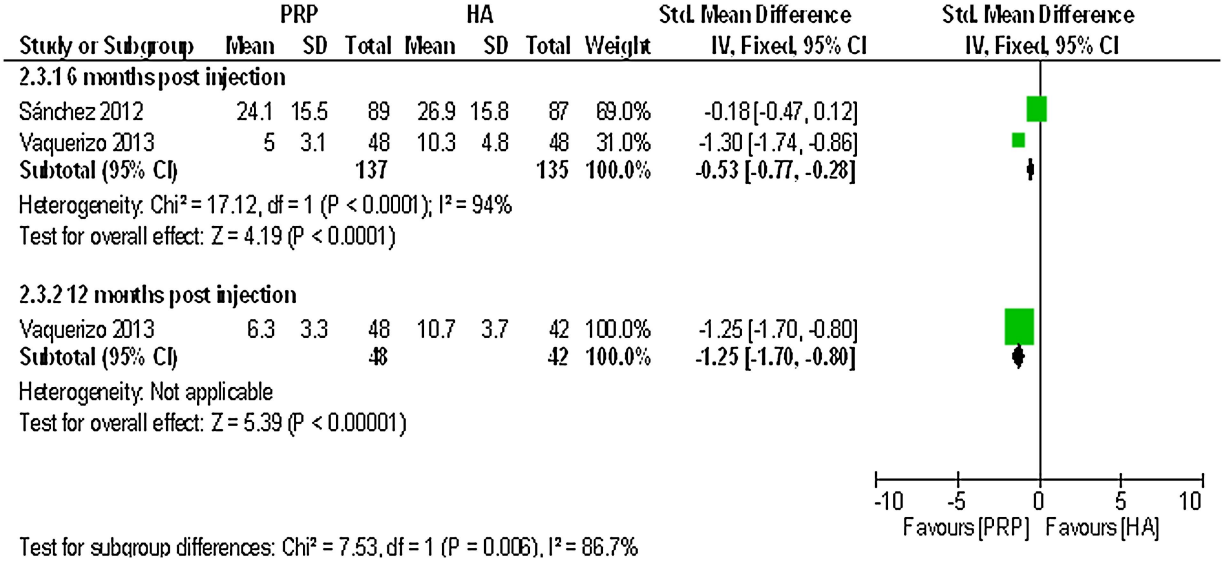


Figure 11 Forest plot of comparison: 2 platelet rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.3; pain: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale.

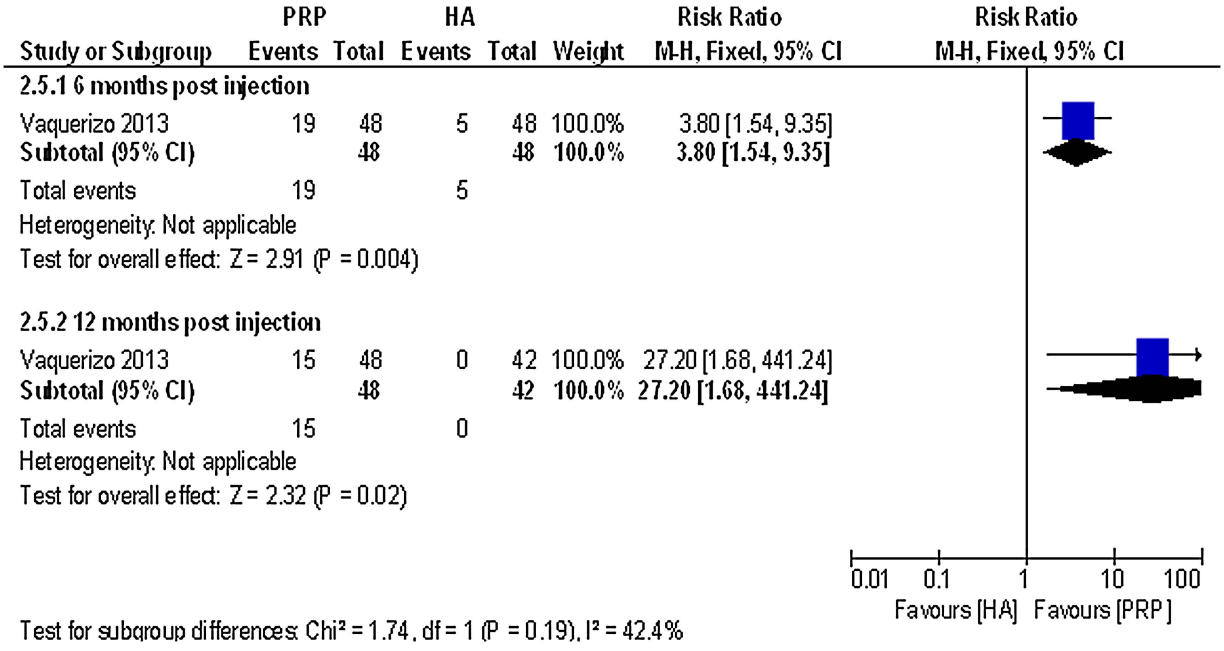


Figure 12 Forest plot of comparison: 2 platelet rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.5; function: number of patients with 50% decrease on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscale.

score or assessed with the WOMAC total score) is improved significantly better after PRP injections compared with HA. Limited evidence (one study with a high risk of bias) is available that the Lequesne score is significantly higher after PRP injections compared with HA.

Kon *et al* reported patient satisfaction as a measure of patient global assessment. No statistically significant differences were found between PRP and HA (both high-weight and low-weight HA) on the number of patients satisfied at 6 months (RR was 1.24; 95% CI 0.98 to 1.58; p value=0.07 and 1.28; 95% CI 1.00 to 1.64; p value=0.05).[45]

Additionally, no statistically significant differences were detected for the number of patients reporting postinjective pain reaction (pooled RR 1.00; 95% CI 0.65 to 1.53; p value 1.00).[36 40 43]

Filardo *et al*[38] reported a statistically significantly higher postinjective pain reaction in the PRP group (p value 0.039). Since no measure of dispersion was reported, this outcome was not analysed in RevMan.

PRP versus PRP

Only one non-randomised controlled trial comparing PRP with another PRP reported data on global assessment that could be used in this review. Filardo *et al*[44] reported the percentage of patients satisfied with the procedure at 12 months postinjection. No statistically significant difference was detected between the single-spinning approach (76.4% PRGF group) and the double-spinning approach (80.6% PRP group), (RR 1.05; 95% CI 0.89

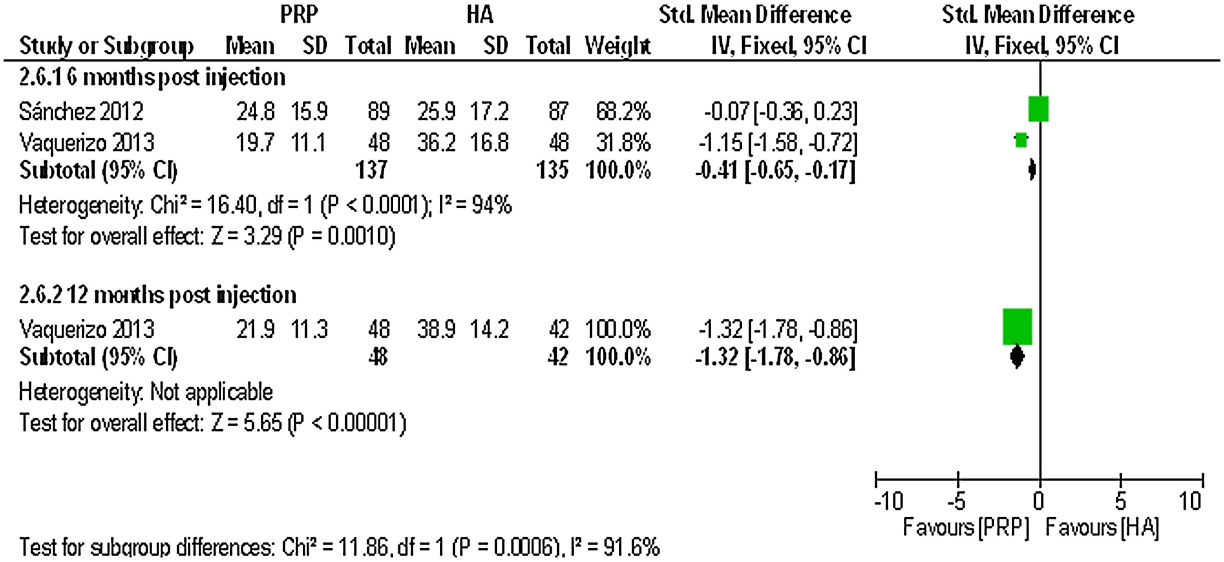


Figure 13 Forest plot of comparison: 2 platelet rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.6; function: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscale.

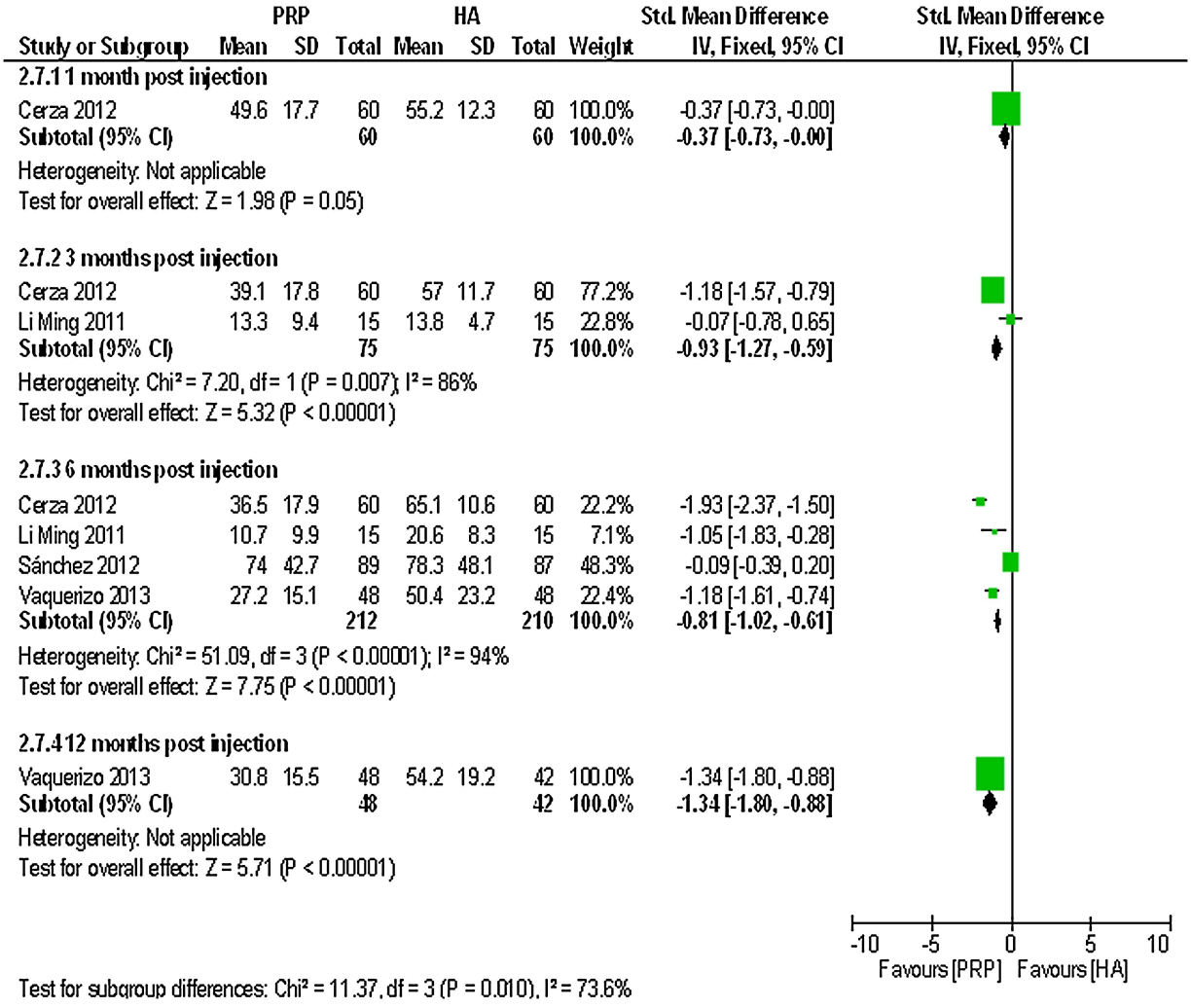


Figure 14 Forest plot of comparison: 2 platelet rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.7; function: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total.

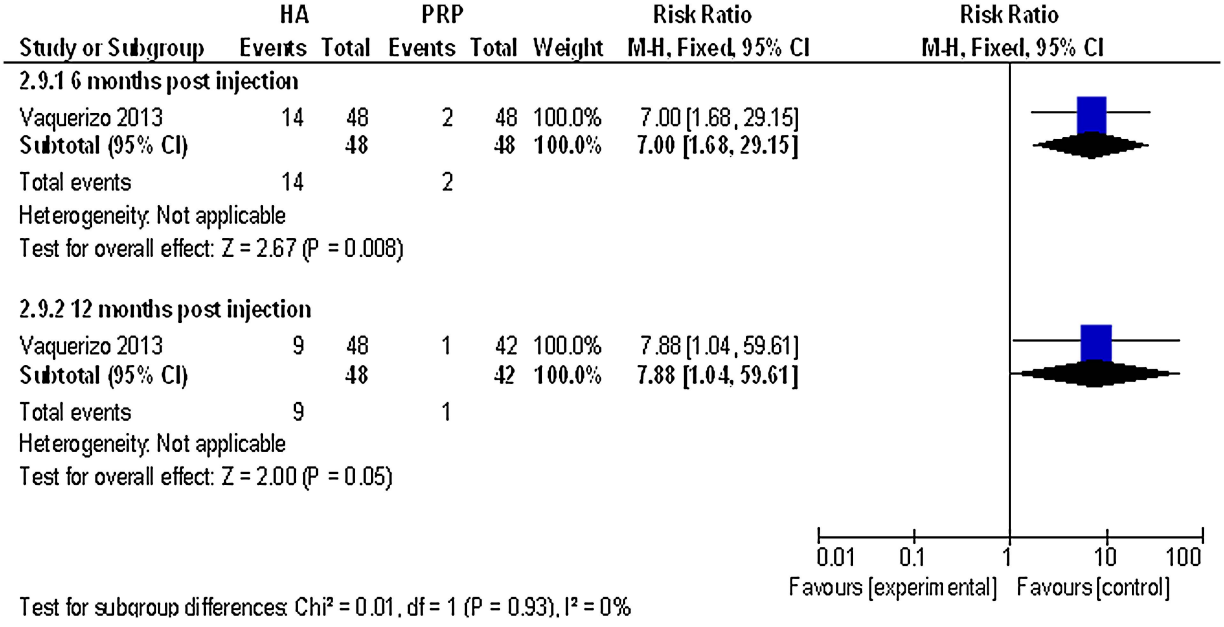


Figure 15 Forest plot of comparison: 2 platelet rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.9; function: number of patients with a 50% decrease on the Lequesne index.

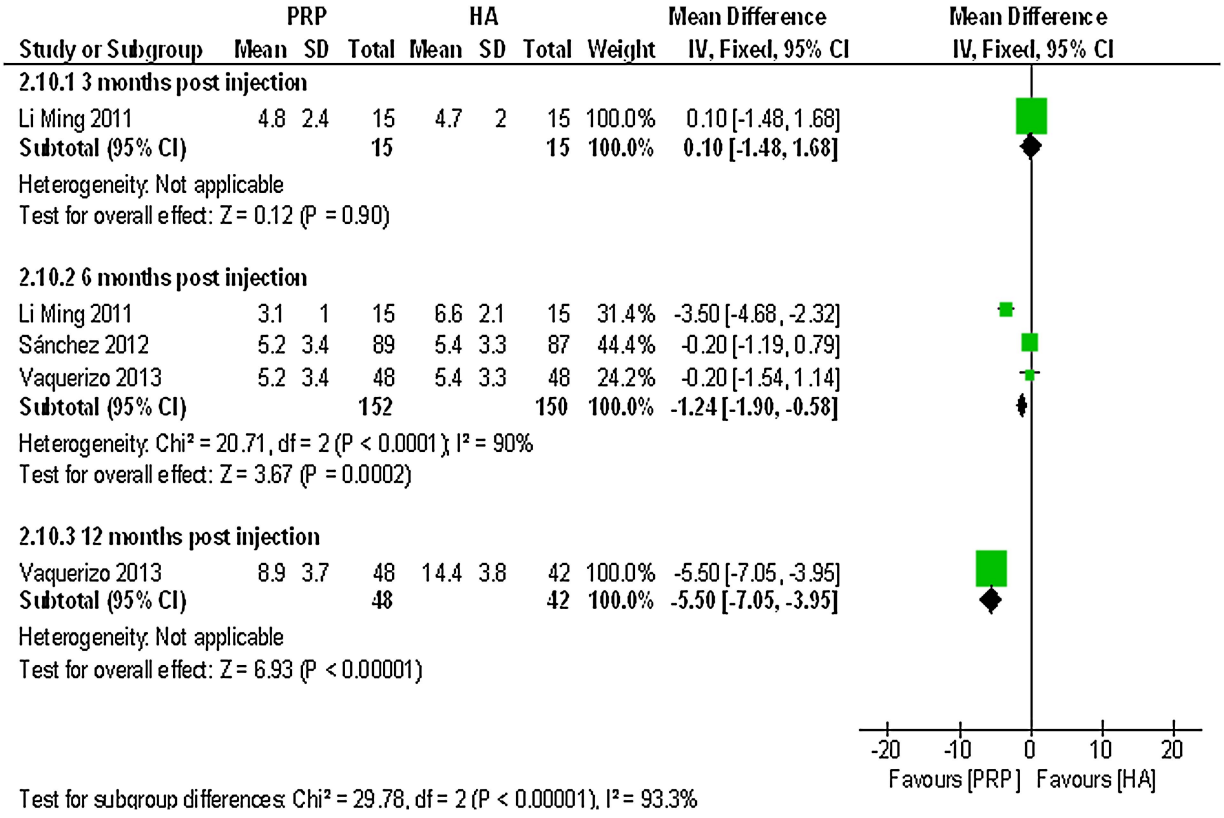


Figure 16 Forest plot of comparison: 2 platelet rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.10; function: Lequesne index (0–24 Likert).

to 1.25; p value 0.54). For details, please see the effect estimates (see online supplementary materials) and figure 23.

DISCUSSION

This systematic review assessed the effectiveness of PRP studied in five RCTs and five non-randomised trials. A general positive effect on pain reduction and function was found in favour of PRP injections compared with control groups. However, the level of evidence regarding the effectiveness of PRP in the treatment of OA of the knee was limited to moderate when PRP injections were compared with placebo or HA.

One RCT compared PRP with placebo and reported data from 78 patients.[37] There was evidence of benefit for pain reduction and global assessment at 6 months postinjection. The analyses do not provide evidence for effects on function due to the lack of data for functional improvement. There was no statistical significant difference in the total number of patients with short time local and systemic reactions during and after the injections between a single PRP injection and placebo.

In comparisons between IA PRP injections and HA, a beneficial effect was found regarding pain reduction in favour of PRP at 6 months postinjection.[41 42] Pooled comparisons using the WOMAC pain subscale, WOMAC physical function scale or Lequesne index outcome measures were not possible because of the presence of considerable heterogeneity. When unpooled, there was no trend for functional measures (International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS) and Tegner) to have improved with PRP treatment.[38 41 43 45] A summary of intervention effects per study in time is provided in table 3.

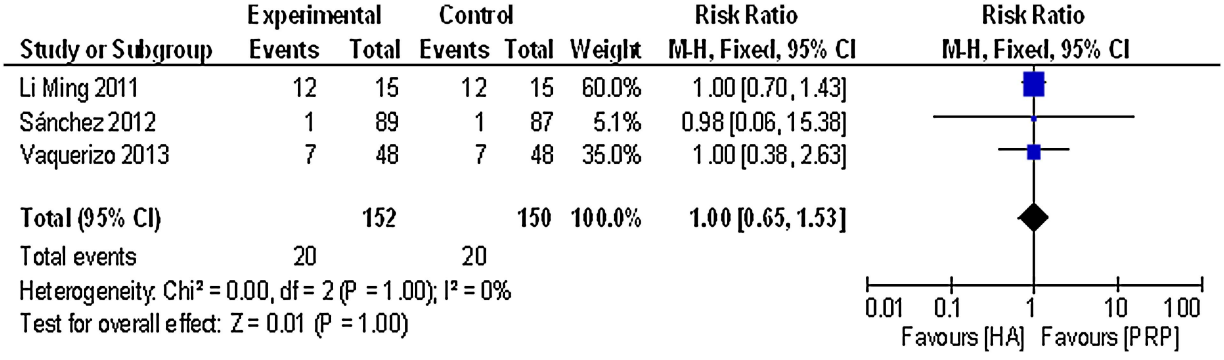


Figure 17 Forest plot of comparison: 2 platelet-rich plasma (PRP) versus hyaluronic acid (HA), outcome: 2.16; adverse effects: number of patients with local or systemic reactions related to treatment.

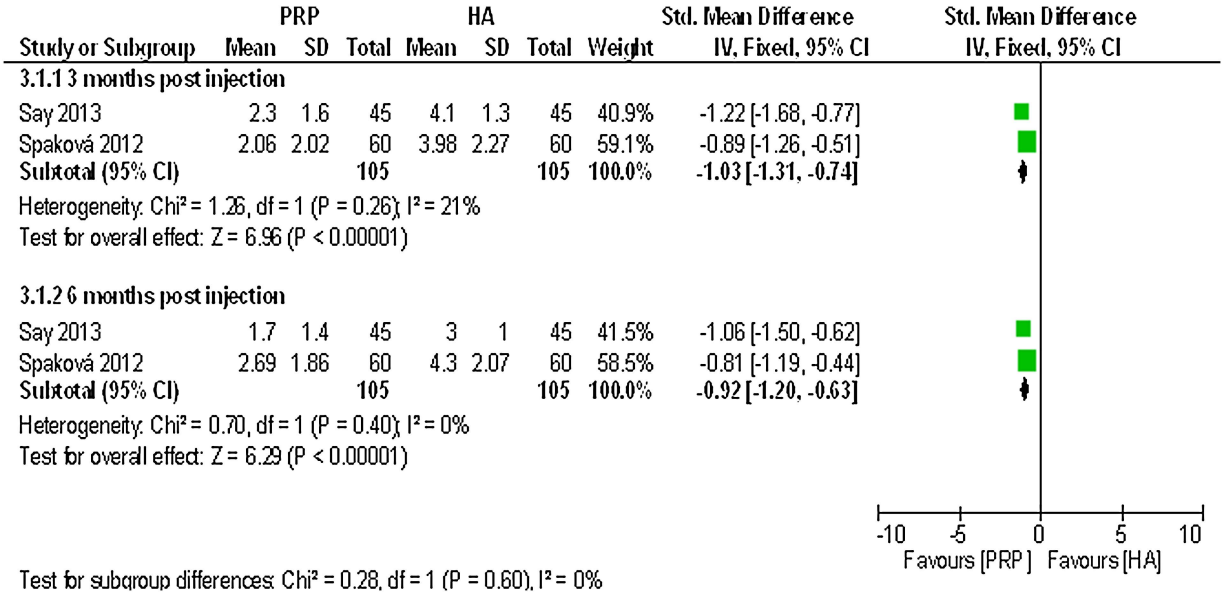


Figure 18 Forest plot of comparison: 3 platelet-rich plasma (PRP) versus hyaluronic acid (HA; non-randomised controlled trail (CCT)), outcome: 3.1; pain: visual analogue scale/numeric rating scale.

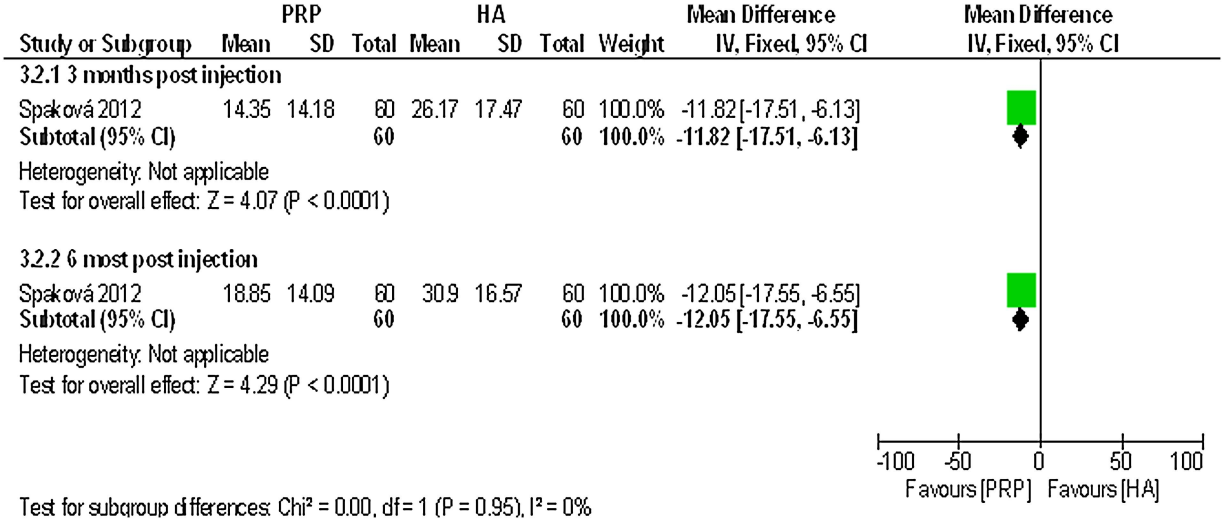


Figure 19 Forest plot of comparison: 3 platelet-rich plasma (PRP) versus hyaluronic acid (HA; non-randomised controlled trail (CCT)), outcome: 3.2; function: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total.

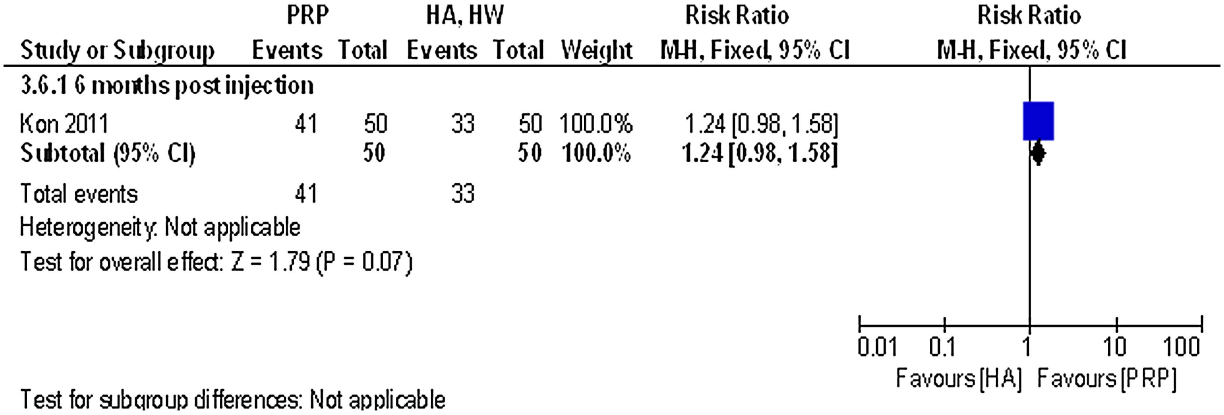


Figure 20 Forest plot of comparison: 3 platelet-rich plasma (PRP) versus hyaluronic acid (HA; non-randomised controlled trail (CCT)), outcome: 3.6; global assessment: patient satisfaction, number of patients who were satisfied (PRP vs high-weight (HW) HA).

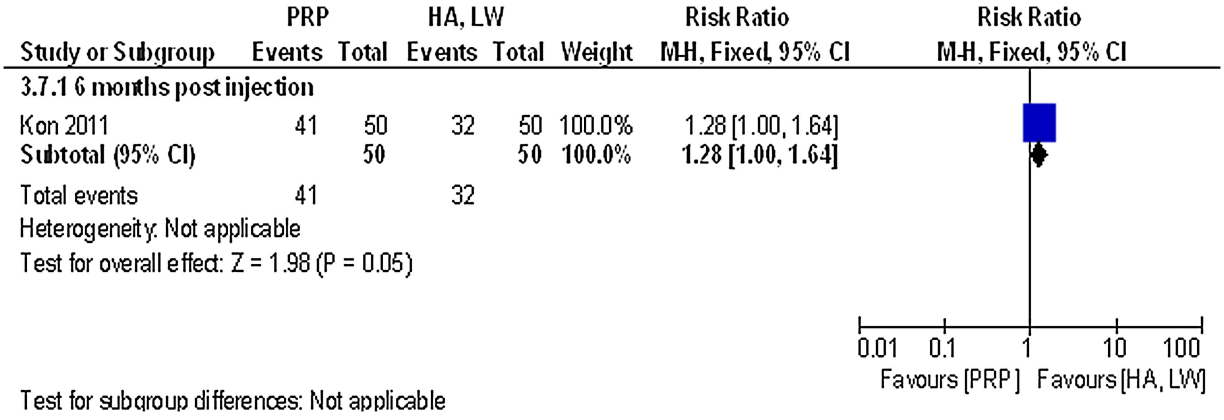


Figure 21 Forest plot of comparison: 3 platelet-rich plasma (PRP) versus hyaluronic acid (HA; non-randomised controlled trail (CCT)), outcome: 3.7; global assessment: patient satisfaction, number of patients who were satisfied (PRP vs low weight (LW) HA).

The variance of patient reported outcome measures (PROMs[48]) used in the included studies made it difficult to compare the results. As recommended by the OMERACT III conference, four domains should be evaluated in OA clinical trials: pain, physical function, patient global assessment, and, for studies of 1 year or longer, joint imaging.[29] Although the WOMAC is the instrument currently used, other valid and reliable instruments can be used to measure the domains as indicated in patients with OA.[49 50] In addition to this, no superiority of any outcome measure to another has been studied in patients with OA as yet.[49] All included studies reported a minimal one of the first three OMERACT domains. None of them evaluated changes on joint imaging. Follow-up moments of 6 months were too short to investigate whether PRP injections are associated with changes in MRI. Halpern *et al*[20] detected, in a prospective non-comparative study with 22 patients, no change per compartment in at least 73% of cases at 12 months follow-up.

The level of degeneration of the knee in all studies was one of the inclusion criteria. On the basis of this level of degeneration, a few studies reported more promising results for the use of PRP in knees with a lower level of joint degeneration.[38 40 45] The K&L classification criteria and the Ahlbäck classification criteria are two different classification systems used in the included studies to classify the level of joint degeneration.[51] Not only the differences in descriptions between classification systems but also differences in descriptions of grades of knee OA within a classification system are reported by Schiphof *et al*.[52] The included studies in this review mentioned only classification grades of knee OA or referred to original studies without a narrow description. In addition to these two studies, the level of degeneration was categorised in three groups: cartilage degeneration, early OA and advanced OA.[44 45] Regarding this variance of level of degeneration between and probably within the included studies, no conclusions can be drawn about the possible effect of PRP injections on a specific classification of OA.

Platelets contain growth factors, cytokines, chemokines, as well as dense and lisosomal granules.[53–55] The release of these may play a special role in cartilage repair including modulating inflammatory processes, cell proliferation, chemotaxis, migration, differentiation and syntheses of matrix.[16 17 56] Although the results of these laboratory studies are encouraging and set the rationale for the treatment of platelet concentrates, there is still uncertainty about the optimal formulation of PRP. Most of the included studies in this review employed a different type of PRP based on the preparation method (single or double spinning) and cellular content (concentration of platelets, whether or not activated prior to injection and the presence of leucocytes). The influence of various variables in the comparison of different types of PRP will lead to different biological and physiological processes and with this probably different effectiveness.[14] In addition, the different therapeutic protocols used in the studies introduce further confounding factors.

Safety is an important aspect considering PRP as conservative treatment. This review was detected in the placebo-controlled study as well as in the comparison with HA studies with no statistically significant differences in the total number of patients with short time local and systemic reactions during and after the injections.[36–40] Controversially, Patel *et al*'s study reported more short time local and systematic reactions in the two PRP injections group.[36] It is obvious that more injections are probably

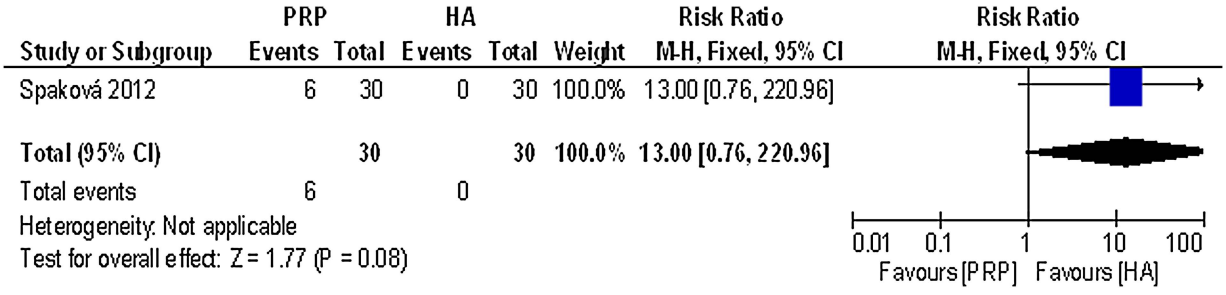


Figure 22 Forest plot of comparison: 3 platelet-rich plasma (PRP) versus hyaluronic acid (HA; non-randomised controlled trail (CCT)), outcome: 3.10; adverse effects: number of patients with local or systemic reactions related to treatment.

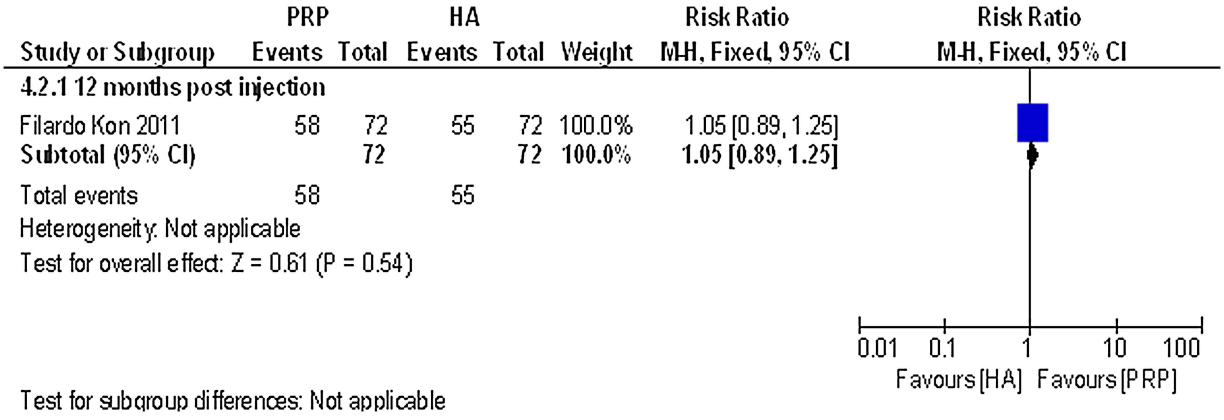


Figure 23 Forest plot of comparison: 4 PRP—single spinning—versus PRP—double spinning—(CCT), outcome: 4.2; global assessment: patient satisfaction, number of patients who were satisfied (CCT, non-randomised controlled trail; HA, hyaluronic acid; PRP, platelet-rich plasma).

responsible for the higher amount of adverse reactions, but regarding this one study, no conclusions can be made about the dose response relationship.

Another important aspect to consider when interpreting the results is the study quality. Except for the study by Sánchez *et al*[40] all RCTs and all non-randomised controlled trials revealed a high risk of bias.

All RCTs, except Sánchez *et al*'s trial, presented performance bias due to the impossibility to blind personnel and participants. Patel *et al* aimed to blind the participants; however, the differently used dosage in one PRP group made it difficult to blind the participants and it remains unclear if performance bias is present.

Two RCTs were deficient in the reporting of randomisation procedures.[37 39] Cerza *et al* only reported that participants were randomised, but they gave no explanation regarding the procedure. Both studies did not report the method used to conceal the allocation sequence in sufficient detail. This makes it difficult to assess the study quality. In general, the effects found in the studies comparing PRP with placebo and PRP with HA were probably influenced by several biases.

Both the three non-randomised controlled trials that assessed the effect of PRP injections comparing HA and the non-randomised trial comparing two different types of PRP had many systemic errors including selection, performance, attrition and detection bias.[41 42 44 45] In all studies without randomisation, both participants and personnel were unblinded to the treatments. Also, blinding the outcome assessor was not reported and this can lead to detection bias. Additional selection bias may have been present in the studies by Filardo *et al*[44] and Kon *et al*[45] The patient treatment allocation was determined by the hospital at which the patients were seen. No further information was present regarding the treatment to which the groups were assigned. There are reliable criteria to identify and grade OA used in this studies. No statistically significant differences were found among the groups regarding the grade of OA. Therefore, we conclude that this inequality may not have been present. All the biases described may have led to the treatment effects found in the studies comparing PRP with HA and other types of PRP.

Limitations of this systematic review

This review was limited by the small number of studies included (n=10) and the fact that only one RCT compared PRP with placebo. A second limitation is that our review used the Cochrane Collaboration's tool for assessing risk of bias for both RCTs and non-randomised trials. Owing to the lack of a widely acceptable tool to assess non-randomised trials, we decided to use a domain based evaluation instead of a scale or checklist.[30]

Another limitation is that an included study published in the Chinese language was not translated.[43] The results of this trial could be extracted because they were reported in the English language. However, quality assessment could not be made and that made it impossible to draw conclusions about the results that were found because of the probable undetectable systematic error.

Recommendations for research

All included studies described an equal explanation of the biological basis for the chosen intervention. Although there is consensus about the potential beneficial effect of PRP, the exact mechanisms of how a high platelet concentration coordinates an inflammatory, proliferative or remodelling response are still unknown. A better understanding of how platelets affect these healing mechanisms in degenerative cartilage tissues is important to develop more precise formulations and applications of PRP. More specifically, questions regarding the optimal platelet concentration, activation procedure, inclusion or exclusion of leucocytes and the optimal preparation, dosage and number of applications need to be addressed. Therefore, more detailed in vitro studies will be necessary before proper interventions can be assessed in future research.

These intervention studies should use equal validated disease specific and PROMs. A potential guideline in outcome measures in studies with patients with OA could be the criteria as recommended by the task force of the OARSI.[49]

Finally, there is a need for large high-quality RCTs to avoid potential bias in selection, performance and attrition.

Conclusion

On the basis of the current evidence, PRP injections reduced pain more effectively than did placebo injections in OA of the knee (level of evidence: limited due to the high risk of bias). This significant effect on pain was also seen when PRP injections were compared with HA injections (level of evidence: moderate due to the generally high risk of bias). Additionally, function improved significantly more when PRP injections were compared with controls (limited to moderate evidence). More large randomised studies of good quality and low risk of bias are needed to test whether PRP injections should be a routine part of management of patients with OA of the knee.

What this study adds

- A thorough systematic review about the effects of platelet-rich plasma on knee osteoarthritis (OA).
- An insight into the high risk of bias in the available studies on this topic.
- A possible addition to conservative treatment options for knee OA.

Contributors ABML conducted the study, analysed the data and wrote the manuscript. EWPB planned the study and was available for parts of the data analysis and corrected the manuscript. MR analysed the data and corrected the manuscript. MHM planned the study, analysed the data, and corrected and submitted the manuscript.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Lane NE, Brandt K, Hawker G, *et al*. OARSI-FDA initiative: defining the disease state of osteoarthritis. *Osteoarthritis Cartilage* 2011;19:478–2.
2 Suri P, Morgenroth DC, Hunter DJ. Epidemiology of osteoarthritis and associated comorbidities. *PM&R* 2012;4:S10–19.
3 Arden N, Nevitt MC. Osteoarthritis: epidemiology. *Best Prac Res Clin Rheumatol* 2006;20:3–25.
4 Felson DT, Lawrence RC, Dieppe PA, *et al*. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635–46.
5 Lawrence RC, Felson DT, Helmick CG, *et al*. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35.
6 Carr AJ, Robertsson O, Graves S, *et al*. Knee replacement. *Lancet* 2012;379:1331–40.
7 ACR 2000 American College of Rheumatology Subcommittee on osteoarthritis guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. 2000 Update. *Arthritis Rheum* 2000;43:1905–15.
8 Felson DT, Zhang Y, Anthony JM, *et al*. Weight loss reduces the risk for symptomatic knee osteoarthritis in woman. The Framingham Study. *Ann Intern Med* 1992;116:535–9.
9 Zang W, Moskowitz RW, Nuki G, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis. Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137–62.
10 Bellamy N, Campbell J, Robinson V, *et al*. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Sys Rev* 2006;19:CD005328.
11 Hepper CT, Halvorson JJ, Duncan ST, *et al*. The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies. *J Am Acad Orthop Surg* 2009;17:638–46.
12 Fortier LA, Barker JU, Strauss EJ, *et al*. The role of growth factors in cartilage repair. *Clin Orthop Relat Res* 2011;469:2706–15.
13 Smelter E, Hochberg MC. New treatments for osteoarthritis. *Curr Opin Rheumatol* 2013;25:310–16.
14 Mishra A, Harmom K, Woodall J, *et al*. Sports medicine applications of platelet rich plasma. *Curr Pharm Biotechnol* 2012;13:1185–95.
15 Andia I, Sánchez M, Maffulli N. Joint pathology and platelet-rich plasma therapies. *Expert Opin Biol. Ther* 2012;12:7–22.
16 Kon E, Filardo G, Di Martino A, *et al*. Platelet-rich plasma (PRP) to treat sports injuries: evidence to support its use. *Knee Surg Sports Traumatol Arthrosc* 2011;19:516–27.
17 Cole BJ, Seroyer ST, Filardo G, *et al*. Platelet-rich plasma: where are we now and where are we going. *Sports Health* 2010;2:203–10.
18 Woodell-May JE, Pietrzak WS. Platelet-rich plasma in orthopaedics. In: Pietrzak WS, ed. *Orthopedic biology and medicine: muskuloskeletal tissue regeneration*. Totawa, NJ: Humana Press, 2008:547–68.
19 Jang S-J, Kim J-D, Cha S-S. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. *Eur J Orthop Surg Traumatol* 2013;23:573–80.
20 Halpern B, Chaudhury S, Rodeo SA, *et al*. Clinical and MRI outcomes after platelet-rich plasma treatment for knee osteoarthritis. *Clin J Sport Med* 2013;23:238–39.
21 Gobbi A, Karnatzikos G, Mahajan V, *et al*. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. *Sports Health* 2012;4:162–72.
22 Sampson S, Reed M, Silvers H, *et al*. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *Am J Phys Med Rehabil* 2010;89:961–9.
23 Filardo G, Kon E, Buda R, *et al*. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthosc* 2011;19:528–35.
24 Wang-Saegusa A, Cugat R, Ares O, *et al*. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. *Arch Orthop Trauma Surg* 2011;131:311–17.
25 Kon E, Buda R, Filardo G, *et al*. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc* 2010;18:472–9.
26 Napolitano M, Matera S, Bossio M, *et al*. Autologous platelet gel for tissue regeneration in degenerative disorders of the knee. *Blood Transfus* 2012;10:72–7.
27 Buhr M, Siekmann W. Intra-articular injection of platelet rich plasma for cartilage repair [Intraartikuläre Injection von thrombozytenangereichertem Plasma zur Behandlung von Knorpelschäden]. *Orthopädische Praxis* 2009;45:10–16.
28 Altman R, Asch E, Bloch D, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;29:1039–49.
29 Bellamy N, Kirwan J, Boers M, *et al*. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* 1997;24:799–802.
30 Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions, version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, 2011.
31 Slavin RE. Best evidence synthesis: an intelligent alternative to meta-analysis. *J Clin Epidemiol* 1995;48:9–18.
32 Van Tulder M, Furlan A, Bombardier C, *et al*.; Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. *Spine* 2003;28:1290–9.
33 Yang KGA, Raijmakers NJH, van Arkel ERA, *et al*. Autologous interleukin-1 receptor antagonist improves function and symptoms in osteoarthritis when compared to placebo in a prospective randomized controlled trial. *Osteoarthritis Cartilage* 2008;16:498–505.
34 Baltzer AW, Moser C, Jansen SA, *et al*. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. *Osteoarthritis Cartilage* 2009;17:152–60.
35 Klatt BA, Lopez HL, Segal NA, *et al*. Treatment options in knee osteoarthritis: total knee arthroplasty versus platelet-rich plasma. *PM R* 2011;3:377–86.
36 Vaquerizo V, Placencia MA, Arribas I, *et al*. Comparison of intra-articular injections of plasma rich in growth factors versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trail. *Arthroscopy* 2013;29:1635–43.
37 Patel S, Dhillon MS, Aggerwal S, *et al*. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trail. *Am J Sports Med* 2013;41:356–4.
38 Filardo G, Kon E, Di Martino A, *et al*. Platelet-rich plasma versus hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trail. *BMC Musculoskelet Disord* 2012;13:229.
39 Cerza F, Carnì S, Carcangiu A, *et al*. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 2012;40:2822–7.
40 Sánchez M, Fiz N, Azofra J, *et al*. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070–8.
41 Say F, Gürler D, Yener K, *et al*. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Čech* 2013;80:278–3.
42 Spaková T, Rosocha J, Lacko M, *et al*. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil* 2012;91:411–17.
43 Li M, Zhang C, Ai Z, *et al*. Therapeutic effectiveness of intra-knee-articular injection of platelet rich plasma on knee articular cartilage degeneration. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2011;25:1192–6.
44 Filardo G, Kon E, Ruiz MTP, *et al*. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc* 2012;20:2082–91.
45 Kon E, Mandelbaum B, Buda R, *et al*. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy* 2011;27:1490–501.
46 Mishra A, Harmon K, Woodall J, *et al*. Sports medicine applications of platelet rich plasma. *Curr Pharm Biotech* 2012;13:1185–95.
47 Collins N, Misra D, Felson D, *et al*. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity

Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken)* 2011;63(Suppl 11):S208–28.
48 Davidson M, Keating J. Patient-reported outcome measures (PROMs): how should I interpret reports of measurement properties? A practical guide for clinicians and researchers who are not biostatisticians. *Br J Sports Med* 2014;48:792–6.
49 Pham T, Heijde D, Lassere M, *et al*. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. *J Rheumatol* 2003;30:1648–54.
50 Williams V, Piva S, Irrgang J, *et al*. Comparison of reliability and responsiveness of patient-reported clinical outcome measures in knee osteoarthritis rehabilitation. *J Orthop Sports Phys Ther* 2012;42:716–23.
51 Petersson IF, Boegård T, Saxne T, *et al*. Radiographic osteoarthritis of the knee classified by the Ahlbäck and Kellgren & Lawrence systems for the tibiofemoral joint in people aged 35–54 years with chronic knee pain. *Ann Rheum Dis* 1997;56:493–6.
52 Schiphof D, Boers M, Biersma-Zeinstra S. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. *Ann Rheum Dis* 2008;67:1034–6.
53 Boswell S, Cole B, Sundman E, *et al*. Platelet rich plasma: a milieu of bioactive factors. *Arthroscopy* 2012;28:429–39.
54 Foster T, Puskas B, Mandelbaum B, *et al*. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med* 2009;37:2259–72.
55 Anitua E, Andia I, Ardanza B, *et al*. Autologous platelets as a source of proteins for healing and tissue regeneration. *Tromb Haemost* 2004;91:4–15.
56 Eppley B, Woodell J, Higgens J. Platelet quantification and growth factor analysis from platelet rich plasma: implications for wound healing. *Plast Reconstr Surg* 2004;114:1502–8.

Search strategies

MEDLINE

((("Platelet-Rich Plasma"[Mesh] OR Platelet-rich plasma[tiab] OR "Platelet Transfusion"[Mesh] OR platelet transfusion[tiab] OR PRP[tiab] OR "Blood Transfusion, Autologous"[MeSH Terms] OR plasma rich[tiab] OR autologous conditioned plasma[tiab] OR autologous blood[tiab])) **AND** ("Osteoarthritis"[Mesh] OR osteoarthritis[tiab] OR osteoarthrosis[tiab] OR osteoarthroses[tiab] OR "Arthritis"[Mesh] OR arthritis[tiab] OR arthroses[tiab] OR arthrosis[tiab] OR "Cartilage Diseases"[Mesh] OR chondropathy[tiab] OR chondropathies[tiab] OR chondropathia[tiab] OR "Cartilage"[Mesh] OR cartilage*[tiab] OR gonarthroses[tiab] OR gonarthrosis[tiab] OR (chondral[tiab] AND (defect*[tiab] OR lesion*[tiab] OR injur*[tiab] OR repair[tiab])))) **AND** ("Knee Joint"[Mesh] OR "Knee"[Mesh] OR knee*[tiab] OR articulatio genu*[tiab] OR articulatic genu*[tiab]) **AND** ("Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR trial*[tiab] OR (clinical[tiab] AND trial[tiab]) OR "Clinical Trials as Topic"[Mesh] OR random*[tiab] OR random allocation[MeSH Terms] OR "therapeutic use" [Subheading] OR research design [mh:noexp] OR "Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR prospective[tiab] OR cohort stud*[tiab] OR case-control[tiab]) (83)

EMBASE

1 thrombocyte rich plasma/ or thrombocyte transfusion/ or blood autotransfusion/(23783)
2 (platelet-rich plasma or platelet transfusion or PRP or plasma rich or autologous conditioned plasma or autologous blood).ti,ab,kw. (26343)
3 1 or 2 (40806)
4 exp osteoarthritis/ or exp arthritis/ or exp chondropathy/ or exp cartilage/(469068)
5 (osteoarthritis or osteoarthrosis or osteoarthroses or arthritis or arthroses or arthrosis or chondropathy or chondropathies or chondropathia or cartilage* or gonarthroses or gonarthrosis).ti,ab,kw. (295162)
6 4 or 5 (526867)
7 knee/ or (knee* or articulatio genu* or articulatic genu*).ti,ab,kw. (134557)
8 exp clinical trial/ or clinical article/ or clinical study/ or controlled study/ or controlled clinical trial/ or randomized controlled trial/ or major clinical study/ or double blind procedure/ or multicenter study/ or single blind procedure/ or crossover procedure/ or placebo/ or randomization/ or cohort analysis/ or exp case control study/ or (clinical trial* or random* or prospective or cohort stud* or case-control).ti,ab,kw. (7509301)
9 3 and 6 and 7 and 8 (104)

CINAHL

S17 S5 AND S11 AND S16 (48)
S16 S13 OR S14 OR S15 (474333)
S15 (MH "Prospective Studies+") OR (MH "Double-Blind Studies") OR (MH "Case Control Studies+") (275277)
S14 TI clinical trial* OR AB clinical trial* OR TI random* OR AB random* OR TI prospective OR AB prospective OR TI cohort stud* OR AB cohort stud* OR TI case-control OR AB case-control (222431)
S13 (MH "Clinical Trials+") OR (MH "Randomized Controlled Trials") (167281)
S12 S5 AND S11 (111)
S11 S6 OR S7 OR S8 OR S9 OR S10 (53524)
S10 (TI osteoarthritis OR AB osteoarthritis) OR (TI osteoarthrosis OR AB osteoarthrosis) OR (TI osteoarthroses OR AB osteoarthroses) OR (TI arthritis OR AB arthritis) OR (TI arthroses OR AB arthroses) OR (TI artrosis OR AB artrosis) OR (TI chondropathy OR AB chondropathy) OR (TI chondropathies OR AB chondropathies) OR (TI chondropathia OR AB chondropathia) OR (TI cartilage* OR AB cartilage*) OR (TI gonarthroses OR AB gonarthroses) OR (TI gonarthrosis OR AB gonarthrosis) OR ((TI chondral OR AB chondral) AND (TI repair OR AB repair)) OR ((TI chondral OR AB chondral) AND (TI injur* OR AB injur*)) OR ((TI chondral OR AB chondral) AND (TI lesion* OR AB lesion*)) OR ((TI chondral OR AB chondral) AND (TI defect* OR AB defect*)) (31042)
S9 (MH "Cartilage+") (9562)

S8 (MH "Cartilage Diseases+") (747)
S7 (MH "Arthritis+") (39280)
S6 (MH "Osteoarthritis+") (14283)
S5 S1 OR S2 OR S3 OR S4 (2854)
S4 (TI Platelet-rich plasma OR AB Platelet-rich plasma) OR (TI platelet transfusion OR AB platelet transfusion) OR (TI PRP OR AB PRP) OR (TI plasma rich OR AB plasma rich) OR (TI autologous conditioned plasma OR AB autologous conditioned plasma) OR (TI autologous blood OR AB autologous blood) (1771)
S3 (MH "Blood Transfusion, Autologous") (801)
S2 (MH "Platelet Transfusion") (709)
S1 (MH "Platelet-Rich Plasma") (51)

The Cochrane Library
1 Cochrane review, 20 Trials (Central)
#1 MeSH descriptor: [Platelet-Rich Plasma] explode all trees
#2 MeSH descriptor: [Platelet Transfusion] explode all trees
#3 platelet-rich plasma:ti,ab,kw (Word variations have been searched)
#4 platelet transfusion:ti,ab,kw (Word variations have been searched)
#5 PRP:ti,ab,kw (Word variations have been searched)
#6 plasma rich:ti,ab,kw (Word variations have been searched)
#7 autologous conditioned plasma:ti,ab,kw (Word variations have been searched)
#8 autologous blood:ti,ab,kw (Word variations have been searched)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Osteoarthritis] explode all trees
#11 MeSH descriptor: [Arthritis] explode all trees
#12 MeSH descriptor: [Cartilage Diseases] explode all trees
#13 MeSH descriptor: [Cartilage] explode all trees
#14 osteoarthritis or osteoarthrosis or osteoarthroses:ti,ab,kw (Word variations have been searched)
#15 arthritis or arthroses or arthrosis:ti,ab,kw (Word variations have been searched)
#16 chondropathy or chondropathies or chondropathia:ti,ab,kw (Word variations have been searched)
#17 cartilage* or gonarthroses or gonarthrosis:ti,ab,kw (Word variations have been searched)
#18 chondral and (defect* or lesion* or injur* or repair):ti,ab,kw (Word variations have been searched)
#19 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 MeSH descriptor: [Knee Joint] explode all trees
#21 MeSH descriptor: [Knee] explode all trees
#22 knee* or articulatio genu* or articulatic genu*:ti,ab,kw (Word variations have been searched)
#23 #20 or #21 or #22
#24 #9 and #19 and #23

Effect estimates overview

Comparison 1 Platelet rich plasma versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Pain: WOMAC pain subscale (single PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 6 weeks post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.1.2 3 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.1.3 6 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Pain: WOMAC pain subscale (2 PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 6 weeks post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2.2 3 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2.3 6 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Pain: Visual Analogue Scale (Single PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 6 months post injection	1	98	Mean Difference (IV, Fixed, 95% CI)	-2.45 [-2.92, -1.98]
1.4 Pain: Visual Analogue Scale (2 PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 6 months post injection	1	96	Mean Difference (IV, Fixed, 95% CI)	-2.07 [-2.59, -1.55]
1.5 Function: WOMAC physical function subscale (Single PRP vs Salin)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 6 weeks post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.5.2 3 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.5.3 6 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.6 Function: WOMAC physical function subscale (2 PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 6 weeks post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.6.2 3 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.6.3 6 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.7 Function: WOMAC total (Single PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.7.1 6 weeks post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable

1.7.2 3 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.7.3 6 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.8 Function: WOMAC total (2 PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.8.1 6 weeks post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.8.2 3 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.8.3 6 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.9 Global assessment: patient satisfaction, number of patients that were satisfied (Single PRP vs Saline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9.1 6 months post injection	1	49	Risk Ratio (M-H, Fixed, 95% CI)	8.40 [2.19, 32.24]
1.10 Global assessment: patient satisfaction, number of patients that were satisfied (2 PRP vs Saline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 6 months post injection	1	48	Risk Ratio (M-H, Fixed, 95% CI)	7.82 [2.02, 30.20]
1.11 WOMAC stiffness subscale (Single PRP vs Salin)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.11.1 6 weeks post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.11.2 3 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.11.3 6 months post injection	1	49	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.12 WOMAC stiffness subscale (2 PRP vs Saline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.12.1 6 weeks post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.12.2 3 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.12.3 6 months post injection	1	48	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.13 Adverse effects: Number of patients with local or systemic reactions related to treatment (Single PRP vs Saline)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	11.14 [0.66, 187.75]
1.14 Adverse effects: Number of patients with local or systemic reactions related to treatment (2 PRP vs Saline)	1	48	Risk Ratio (M-H, Fixed, 95% CI)	21.23 [1.32, 341.04]

Comparison 2 Platelet rich plasma versus Hyaluronic Acid

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Pain: Number of patients with 30% decrease on WOMAC pain subscale	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 6 months post injection	1	96	Risk Ratio (M-H, Fixed, 95% CI)	5.71 [2.85, 11.46]
2.1.2 12 months post injection	1	90	Risk Ratio (M-H, Fixed, 95% CI)	4.90 [2.08, 11.54]
2.2 Pain: Number of patients with 50% decrease on WOMAC pain subscale	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 6 months post injection	2	272	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [1.53, 3.38]
2.2.2 12 months post injection	1	90	Risk Ratio (M-H, Fixed, 95% CI)	13.13 [1.81, 95.20]
2.3 Pain: WOMAC pain subscale	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 6 months post injection	2	272	Std. Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.77, -0.28]
2.3.2 12 months post injection	1	90	Std. Mean Difference (IV, Fixed, 95% CI)	-1.25 [-1.70, -0.80]
2.4 Function: Number of patients with 30% decrease on WOMAC physical function subscale	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 6 months post injection	1	96	Risk Ratio (M-H, Fixed, 95% CI)	4.14 [2.01, 8.53]
2.4.2 12 months post injection	1	90	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [1.57, 6.71]
2.5 Function: Number of patients with 50% decrease on WOMAC physical function subscale	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.5.1 6 months post injection	1	96	Risk Ratio (M-H, Fixed, 95% CI)	3.80 [1.54, 9.35]
2.5.2 12 months post injection	1	90	Risk Ratio (M-H, Fixed, 95% CI)	27.20 [1.68, 441.24]
2.6 Function: WOMAC physical function subscale	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.6.1 6 months post injection	2	272	Std. Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.65, -0.17]
2.6.2 12 months post injection	1	90	Std. Mean Difference (IV, Fixed, 95% CI)	-1.32 [-1.78, -0.86]
2.7 Function: WOMAC total	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.7.1 1 month post injection	1	120	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.73, -0.00]
2.7.2 3 months post injection	2	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.93 [-1.27, -0.59]
2.7.3 6 months post injection	4	422	Std. Mean Difference (IV, Fixed, 95% CI)	-0.81 [-1.02, -0.61]
2.7.4 12 months post injection	1	90	Std. Mean Difference (IV, Fixed, 95% CI)	-1.34 [-1.80, -0.88]

2.8 Function: Number of patients with 30% decrease on Lequesne index	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.8.1 6 months post injection	1	96	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [2.47, 10.13]
2.8.2 12 months post injection	1	90	Risk Ratio (M-H, Fixed, 95% CI)	20.13 [2.84, 142.71]
2.9 Function: Number of patients with 50% decrease on Lequesne index	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.9.1 6 months post injection	1	96	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [1.68, 29.15]
2.9.2 12 months post injection	1	90	Risk Ratio (M-H, Fixed, 95% CI)	7.88 [1.04, 59.61]
2.10 Function: Lequesne index (0-24 Likert)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.10.1 3 months post injection	1	30	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.48, 1.68]
2.10.2 6 months post injection	3	302	Mean Difference (IV, Fixed, 95% CI)	-1.24 [-1.90, -0.58]
2.10.3 12 months post injection	1	90	Mean Difference (IV, Fixed, 95% CI)	-5.50 [-7.05, -3.95]
2.11 Adverse effects: Number of patients with local or systemic reactions related to treatment	3	302	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.65, 1.53]

Comparison 3 Platelet rich plasma versus Hyaluronic Acid (non-randomized trials)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Pain: Visual Analogue Scale/Numeric Rating Scale	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1.1 3 months post injection	2	210	Std. Mean Difference (IV, Fixed, 95% CI)	-1.03 [-1.31, -0.74]
3.1.2 6 months post injection	2	210	Std. Mean Difference (IV, Fixed, 95% CI)	-0.92 [-1.20, -0.63]
3.2 Function: WOMAC total	1		Mean Difference (IV, Fixed,	Subtotals only

			95% CI)	
3.2.1 3 months post injection	1	120	Mean Difference (IV, Fixed, 95% CI)	-11.82 [-17.51, -6.13]
3.2.2 6 months post injection	1	120	Mean Difference (IV, Fixed, 95% CI)	-12.05 [-17.55, -6.55]
3.3 Global assessment: Patient satisfaction, number of patients that were satisfied (PRP vs High Weight HA)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 6 months post injection	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.98, 1.58]
3.4 Global assessment: Patient satisfaction, number of patients that were satisfied (PRP vs Low Weight HA)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.4.1 6 months post injection	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.00, 1.64]
3.5 Adverse effects: number of patients with local or systemic reactions related to treatment	1	60	Risk Ratio (M-H, Fixed, 95% CI)	13.00 [0.76, 220.96]

Comparison 4 Platelet rich plasma -single spinning- versus Platelet rich plasma -double spinning- (non-randomized trials)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Global assessment: Patient satisfaction, number of patients that were satisfied	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 12 months post injection	1	144	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.25]

Characteristics of included and excluded studies

Characteristics of included studies

Cerza 2012	
Study type/Country/Treatment	Randomized, two arm, controlled trial Single Center, Italy PRP versus Hyaluronic Acid,
Participants	Mean age: 66.4, % Female: 55.8% Mean disease duration: NR Number Randomized: 120 Follow-up: 1, 3 and 6 months <u>Inclusion:</u> Age: NR Duration clinical symptoms : NR Symptomatic OA of the knee , radiological **Kellgren Lawrence** grade I-III <u>Baseline values:</u> Kellgren Lawrence grade (n(%)): I: PRP: 21(35) HA: 25(42) II: PRP: 24(40) HA: 22(37) III: PRP: 15(25) HA: 13(21) WOMAC score (mean(SD): Total: PRP: 79.6(9.5) HA: 75.4(10.7)
Intervention	<u>Intervention (n=60):</u> 4 PRP (ACP)(type NA) intra articular injections (5,5mL) Interval: weekly <u>Comparison (n=60):</u> 4 HA intra articular injections Interval: weekly
Outcomes	Primary outcome: WOMAC total score (0-96) Adverse effects
Results	WOMAC total score 1, 3 and 6 months resp. (mean(SD)): PRP:49.6(17.7), 39.1(17.8), 36.5(17.9) HA: 55.2(12.3), 57(11.7), 65.1(10.6) *P<0.001, P<0.001, P<0.001* Adverse effects: No short time side effects observed

Risk of bias (Cerza 2012)		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were consecutively randomized..." Comment: The report states that allocation was random. Method of sequence generation process was not specified. Insufficient information about the sequence generation process to permit judgement of low risk or high risk.
Allocation concealment (selection bias)	High risk	Comment: It is not stated that allocation was concealed. Probably not done
Blinding of participants (performance bias)	Unclear risk	No reporting regarding blinding the participants. Comment: It is not stated that the participants were blind for treatment. Insufficient information about the blinding of participants to permit judgement of low risk or high risk.
Blinding of personnel (performance bias)	High risk	Quote: "The injections were performed by the unblinded physician..." Comment: Probably not done
Blinding of outcome assessment (detection bias)	Unclear risk	Just reporting that the outcome assessment was managed by the same operator. Comment: Insufficient information about blinding of the observer to permit judgement of low risk or high risk.
Incomplete outcome data (attrition bias)	Low risk	Number of allocated and analyzed participants was reported. Quote: "No patients withdrew during the study period". In each group the number of subjects analyzed were reported (n=60) and no subjects excluded from analysis.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes have been reported. Primary outcome measures (WOMAC which assess pain, stiffness and fictional limitation) have been reported.
Other bias	Unclear risk	Power analysis has been calculated. (33 patients per treat arm to provide at least 80% power to detect an anticipated effect size of 0.8 on WOMACscore).

Filardo 2012	
Study type/Country/Treatment	Randomized, two arm, controlled trial Single Center, Italy PRP versus Hyaluronic Acid
Participants	Mean age: 56.5, % Female: 37.6% Mean disease duration: 63.5 months Number Randomized: 109 Follow-up: 2, 6 and 12 months <u>Inclusion:</u> Age: NR Clinical symptoms > 4 months Monolateral symptomatic OA of the knee , radiological **Kellgren Lawrence** grade 0-III <u>Baseline values:</u> Kellgren Lawrence grade (mean): PRP: 2.2 HA: 2.1 IKDC score (mean(SD)): PRP: 50.2(15.7) HA: 47.4(14.0) Tegner score (mean(SD)): PRP: 2.9(1.4) HA: 2.6(1.2)
Intervention	<u>Intervention (n=54):</u> 3 PRP (type 2A) intra articular injections (5mL) Interval: weekly <u>Comparison (n=55):</u> 3 HA intra articular injections Interval: weekly
Outcomes	<u>Primary outcome(s):</u> IKDC score (0-100) <u>Secondary outcome(s):</u> KOOS score (0-100/category) EQ-VAS (0-100) Tegner score (0-10) Range of motion Knee circumference change Patient satisfaction Adverse effects
Results	IKDC score 2, 6 and 12 months resp. (mean(SD)): PRP: 62.8(17.6), 64.3(16.4), 64.9(16.8) HA: 61.4(16.2), 61.0(18.2), 61.7(19.0) *PRP vs. HA: NS* KOOS score 2,6 and 12 months: *PRP vs. HA: Ns* EQ-VAS: NR/NS Tegner score 12 months (mean(SD)): PRP: 3.8(1.3) HA: 3.4(1.6) *PRP vs. HA: NS* Range of motion: Not reported Knee circumference: Not reported Patient satisfaction: Not reported Adverse effects: No major complications related to the injections were observed during the treatment and follow-up. Post-injective pain reaction was significantly higher in the PRP group (*p=0.039*). However this

	reaction was self-limiting.	
Risk of bias (Filardo 2012)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...according to a randomization list, provide by an independent statistician, was kept in a dedicated office". Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote: "Physician contacted statistician by a phone call just before the injective procedure". Central allocation (by telephone) Comment: Probably done
Blinding of participants (performance bias)	Low risk	Quote: "At the end of the study, the nature of the injected substance was revealed to the patients. Further: No dosage differences between groups. All of the participants underwent blood harvesting to obtain autologous PRP. Comment: Probably done
Blinding of personnel (performance bias)	High risk	Physician was not blinded. Just before the injective procedure he got informed about the treatment allocation. Comment: Probably not done
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All the clinical evaluations were performed by a medical member of staff not involved in the injective procedure" Comment: Blinding is reported and probably done.
Incomplete outcome data (attrition bias)	High risk	Number of allocated and analyzed participants was reported. 0/54 missing from PRP group, 3/55 missing from the HA group (2 due to suspected intolerance to some components of HA and 1 due to lack of efficacy).
Selective reporting (reporting bias)	Unclear risk	Primary outcomes are reported. Not all pre-specified secondary outcomes have been reported. Outcome of EQVAS, ROM, knee circumference and patients satisfaction are not reported.
Other bias	Unclear risk	Power analysis have been calculated. (96 patients per treat arm to provide at least 80% power to detect a difference of 6.7 points of the IKDC score at a 5 % level of significance and possible drop

	out of 15%).

Filardo/Kon/Ruiz 2012	
Study type/Country/Treatment	Prospective, two arm, comparative trial Multicenter, Italy PRGF (double spinning) versus PRP (single spinning)
Participants	Mean age: 52.1, % Female: 34% Mean disease duration: NR Number of participants: 144 Follow-up: 2, 6 and 12 months <u>Inclusion:</u> Age > NR Duration clinical symptoms : > 4 months Symptomatic OA of the knee, radiological **Kellgren Lawrence** grade 0-IV <u>Baseline values:</u> Kellgren Lawrence grade (N(%)): 0 (cartilage degeneration): PRP: 32(44%) PRGF: 31(43%) I-III (early OA): PRP: 24(33%) PRGF: 30(42%) VI(advanced OA): PRP: 16(22%) PRGF: 11(15%) IKDC score (mean(SD)): PRP: 42.1(13.5) PRGF: 45.0(10.1)
Intervention	<u>Intervention (n=72):</u> 3 PRP (type 2B) intra articular injections (5mL) Interval: 3 weeks <u>Comparison (n=72):</u> 3 PRP (type 4B, PRGF) intra articular injections (5mL) Interval: 3 weeks
Outcomes	<u>Primary outcome(s):</u> IKDC score (0-100) EQ VAS score (0-100) Tegner score (0-10) <u>Secondary outcome(s):</u> Patient satisfaction (%N) Adverse effects
Results	IKDC score 2, 6 and 12 months resp.(mean(SD)): PRP:60.8(16.6), 62.5(19.9), 59.9(20) PRGF: 59(16.2), 61.3(16.3), 61.6(16.2) *PRP vs. PRGF NS at all follow-up* EQ-VAS score: Not reported PRP vs. PRGF: NS Tegner score: Not reported PRP vs. PRGF: NS Patient satisfaction: PRP: 80.6% PRGF:76.4% Adverse effects: No short or long time side effects observed

	Pain (P=0.0005) and swelling (P=0.03) after injection were more frequent in the PRP group with respect to the PRGF group.

Risk of bias (Filardo/Kon/Ruiz 2012)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Hospital visit specified treatment. Comment: Probably not done
Allocation concealment (selection bias)	High risk	Quote: "...treatment allocation was due to the center the patients attended". Comment: Probably not done
Blinding of participants (performance bias)	High risk	Not reported. Comment: Probably not done
Blinding of personnel (performance bias)	High risk	Not reported. Comment: Probably not done
Blinding of outcome assessment (detection bias)	High risk	Not reported. Comment: Probably not done
Incomplete outcome data (attrition bias)	High risk	Number of participants at baseline has been reported. Number of participants at follow-up has not been reported. Exclusions and withdrawals have not been reported.
Selective reporting (reporting bias)	Unclear risk	Pre-specified primary outcomes have been reported. Secondary outcomes (EQ VAS, Tegner score) are incomplete, only significant improvent has been reported. Low risk on primary outcome reporting.
Other bias	Unclear risk	Power analyses have been calculated. (72 patients per treat arm to provide at least 80% power to detect a difference of 7.4 points of the IKDC score at a 5 % level of significance).

Kon 2011	
Study type/Country/Treatment	Prospective, three arm, comparative trial Multicenter, Italy PRP versus Hyaluronic Acid
Participants	Mean age: 52.9, % Female: 45.3% Mean disease duration: NR Number of participants: 150 Follow-up: 2 and 6 months <u>Inclusion:</u> Age: NR Duration clinical symptoms : > 4 months Symptomatic OA of the knee, radiological **Kellgren Lawrence** grade 0-IV <u>Baseline values:</u> Kellgren Lawrence grade (n): 0 PRP: 22 HAHW: 21 HALW: 19 I-III: PRP: 20 HAHW: 19 HALW: 22 IV PRP: 8 HAHW: 10 HALW: 9 IKDC score (mean(SD)): PRP: 41.2(10.9) HAHW: 47.3(13.9) HALW: 44.7(6.6) EQ-VAS score (mean(SD)): PRP: 53.6 (18.3) HAHW:52.2(12.5) HALW: 51.2(7.8)
Intervention	<u>Intervention (n=50):</u> 3 PRP (type 2A) intra articular injections (5mL) Interval: 2 weeks <u>Comparison 1 (n=50):</u> 3 HA intra articular injections (HW) Interval: 2 weeks <u>Comparison 2 (n=50):</u> 3 HA intra articular injections (LW) Interval: 2 weeks
Outcomes	<u>Primary outcome(s):</u> IKDC score (0-100) EQ-VAS score (0-100) <u>Secondary outcome(s):</u> Patient satisfaction (%N) Adverse effects
Results	IKDC score 2 and 6 months resp. (mean(SD)): PRP: 62.7(14.0), 64(18.7) HAHW: 54.8(15.6), 54(16) HALW: 61.7(13.1), 53.8(13.7) *P(6 mos follow up):PRP vs. HAHW 0.005* *P(6 mos follow up): PRP vs. HALW 0.003*

	EQ-VAS score 2 and 6 months resp. (mean(SD)): PRP: 73.0(13.9), 72.3(17.3) HAHW: 63(14.7), 62.4(15.2) HALW: 68.7(13.5), 61.7(14.8) *P(6 mos follow up):PRP vs. HAHW 0.002* *P*(*6 mos follow up*):*PRP vs. HALW 0.001* Patient satisfaction: PRP: 82% HAHW:66% HALW:64% *P=0.04* Adverse effects: No short or long time side effects observed

Risk of bias (Kon 2011)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Hospital visit specified treatment. Comment: Probably not done.
Allocation concealment (selection bias)	High risk	Each center performed only one treatment and so the patient treatment allocation was due to the center the patients attended. Comment: Probably not done.
Blinding of participants (performance bias)	High risk	Not reported. Comment: Probably not done
Blinding of personnel (performance bias)	High risk	Not reported. Comment: Probably not done
Blinding of outcome assessment (detection bias)	High risk	Not reported. Comment: Probably not done
Incomplete outcome data (attrition bias)	High risk	Number of participants at baseline has been reported. Number of participants at follow-up has not been reported. Exclusions and withdrawals have not been reported.
Selective reporting (reporting bias)	Low risk	Pre-specified primary and secondary outcomes have been reported.
Other bias	Unclear risk	Power analysis has been calculated. (50 patients per treat arm to provide at least 80% power to detect a difference of 10 points of the IKDC score at a 5 % level of significance).

Li 2011	
Study type/Country/Treatment	Randomized , two arm, controlled trial Single Center, China PRP versus Hyaluronic Acid
Participants	Mean age:57.9, % Female:56.7% Mean disease duration: > 4 months Number of participants: 30 Follow-up: 3, 4 and 6 months Inclusion: OA on basis of Kellgren Lawrence grade I-IV Baseline values: Kellgren Lawrence grade (n): I PRP: 6 HA: 6 II PRP: 2 HA: 3 III PRP: 4 HA: 3 IV: PRP: 3 HA: 3 IKDC score (mean(SD)): PRP: 55.4(8.8) HA: 57.5(9.4) WOMAC score (mean(SD): Total: PRP: 27.7(13.8) HA: 30.9(13.9) Lequesne index (mean(SD)): PRP: 8.0(3.7) HA: 9.3(2.9)
Intervention	Intervention (n=15): 3 PRP intra articular injections (3.5mL) Interval: 3 weeks Comparison (n=15): 3 HA intra articular injections (2 mL) Interval: 3 weeks
Outcomes	Primary outcome(s): IKDC score (0-100) WOMAC total (0-96) Lequesne index (0-24) Adverse effects
Results	IKDC score 3 and 6 months resp. (mean(SD)): PRP: 71.3(12.5), 76.4(13.5) HA: 70.1(12.5), 63.2(11.9) *P=0.78, P=0.00* WOMAC total score 3 and 6 months (mean(SD)): PRP: 13.3(9.4), 10.7(9.9)

	HA: 13.8(4.7), 20.6(8.3) *P=0.85, P=0.01* Lequesne index 3 and 6 months resp. (mean(SD)): PRP: 4.8(2.4), 3.1(1.0) HA: 4.7(2.0), 6.6(2.1) *P=0.87, P=0.00* Adverse effects (N/Duration(h)(SD)) PRP:12/36.2(25.1) HA:12/34.5(28.4) *P=0.86*

Risk of bias (Li 2011)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No translation available
Allocation concealment (selection bias)	Unclear risk	No translation available
Blinding of participants (performance bias)	Unclear risk	No translation available
Blinding of personnel (performance bias)	Unclear risk	No translation available
Blinding of outcome assessment (detection bias)	Unclear risk	No translation available
Incomplete outcome data (attrition bias)	Unclear risk	No translation available
Selective reporting (reporting bias)	Unclear risk	No translation available
Other bias	Unclear risk	No translation available

Patel 2013	
Study type/Country/Treatment	Randomized, three arm, controlled trial Single Center, India PRP versus Placebo (Saline)
Participants	Mean age: 52.8, % Female: 70.7% Mean disease duration: NR Number Randomized: 78 (156 knees) Follow-up: 6 weeks, 3 and 6 months <u>Inclusion:</u> Age: NR Duration clinical symptoms: NR OA of the knee according ACR criteria, radiological **Ahlbäck** grade I or II <u>Baseline values:</u> Ahlbäck grade (n): I: PRP: 37 2PRP:36 Saline:25 II: PRP 11 2PRP:10 Saline:18 WOMAC score (mean (SD)): Pain: PRP: 10.17(3.82) 2PRP: 10.62(3.73) Saline: 9.04(3.73) Stiffness: PRP: 3.06(2.08) 2PRP:3.5(2.09) Saline:2.70(2.02) Physical function: PRP: 36.12(13.08) 2PRP: 39.10(11.34) Saline: 38.80(12.44) Total: PRP: 49.56(17.83) 2PRP: 53.20(16.18) Saline: 45.54(17.29) VAS pain (mean(SD)): PRP: 4.56(0.61) 2PRP: 4.64(0.56) Saline: 4.57(0.62)
Intervention	<u>Intervention (n=27/52 knees):</u> Single PRP (type 4B) intra articular injection (8mL) <u>Comparison 1 (n=25/50 knees):</u> 2 PRP (type 4B) intra articular injections (8mL) Interval: 3 weeks

	Comparison 2 (n=23/46 knees): Single saline intra articular injection (8mL)
Outcomes	Primary outcome(s): WOMAC Subscale pain (0-20) Secondary outcome(s): WOMAC Subscale stiffness (0-8) WOMAC subscale physical function (0-68) WOMAC total (0-96) VAS pain score (0-10) Patient satisfaction (%N) (satisfied, partly satisfied, not satisfied) Adverse effects
Results	WOMAC subscale and total score 6 weeks, 3 and 6 months resp. (mean): Pain: PRP: 4.26, 3.74, 5.00 2PRP: 4.38, 4.88, 6.18 Saline: 9.48, 10.35, 10.87 *PRP vs. 2PRP: NS* *PRP vs. Saline: P<0.001* *2PRP vs. Saline: P< 0.001* Stiffness: PRP: 2.12, 1.76, 2.10 2PRP: 2.28, 2.00, 1.88 Saline: 2.76, 2.91, 2.76 *PRP vs. 2PRP: NS* *PRP vs. Saline: P<0.001* *2PRP vs. Saline: P< 0.001* Physical function: PRP: 18.98, 16.98, 20.08 2PRP: 18.30, 18.82, 22.40 Saline: 34.54, 37.43, 39.46 *PRP vs. 2PRP: NS* *PRP vs. Saline: P<0.001* *2PRP vs. Saline: P< 0.001* Total: PRP: 25.36, 22.48, 27.18 2PRP: 24.96, 25.70, 30.48 Saline: 46.78, 50.70, 53.09 *PRP vs. 2PRP: NS* *PRP vs. Saline: P<0.001* *2PRP vs. Saline: P< 0.001* VAS pain score 6 months (mean(SD)): PRP: 2.16(1.5) 2PRP: 2.54(1.7) Saline: 4.61(0.7) *PRP vs. 2PRP: P=0.410* *PRP vs. Saline: P<0.001* *2PRP vs. Saline: <0.001* Patient satisfaction 6 months: PRP :67.3% 2PRP:64.0% Saline: 4.3% Adverse effects (%): Related to infiltration PRP: 22.2% 2PRP: 44% Saline: 0% Significant difference between PRP groups and Saline

Risk of bias (Patel 2013)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants were randomly divided by computer-derived random charts into 3 groups". Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Not reported. Comment: Insufficient information to permit judgement of "low risk" or "high risk"
Blinding of participants (performance bias)	Unclear risk	Quote: "...double blinded" - "...participants were blinded" Comment: Different dosage used in comparison group 2 makes it difficult to blind these patients. Insufficient information about blinding of participants.
Blinding of personnel (performance bias)	High risk	Not reported. Reporting "double blinded" means participants and observers. Comment: Probably not done
Blinding of outcome assessment (detection bias)	Low risk	Quote: "...by a blinded observer" Comment: Blinding is reported and probably done.
Incomplete outcome data (attrition bias)	High risk	Number of allocated and analyzed participants has been reported. Reasons for missing data are reported. 1/27 was excluded from Intervention group as he underwent TKR elsewhere. 3/26 from comparison 2 group (placebo) did not received allocated intervention, refused for treatment.
Selective reporting (reporting bias)	Unclear risk	Pre-specified primary and secondary outcomes have been reported in the pre-specified way. Since no measure of dispersion (i.e. standard deviation, standard error) for primary outcome was reported, this outcome was not included in the RevMan analysis.

Other bias	Unclear risk	Power analysis has been calculated. (21 patients per treat arm to provide at least 80% power to detect a difference of 1.5 points in the VAS pain score at a 5 %level of significance).

Say 2013	
Study type/Country/Treatment	Prospective, two arm, comparative trial Single Center, Turkey PRP versus Hyaluronic Acid
Participants	Mean age: 55.7, % Female: 87.8% Mean disease duration: NR Number of participants: 90 Follow-up: 3 and 6 months <u>Inclusion:</u> Age: NR Duration clinical symptoms : > 3 months Symptomatic OA of the knee, radiological **Kellgren Lawrence** grade I-III <u>Baseline values:</u> Kellgren Lawrence grade (N): I PRP: 1 HA: 1 II PRP: 17 HA: 15 III PRP: 27 HA: 29 KOOS score (mean(SD)): PRP: 46(16.2) HA:43.8(8.6) VAS pain score (mean(SD)): PRP: 7.3(1.6) HA: 7(1.3)
Intervention	<u>Intervention (n=45):</u> Single PRP (type 4B) intra articular injection (2.5mL) <u>Comparison (n=45):</u> 3 HA intra articular injections (LW) Interval: 3 weeks
Outcomes	<u>Primary outcome(s):</u> KOOS total score (0-100) VAS pain score (0-10) <u>Secondary outcome(s):</u> Patient satisfaction Adverse effects
Results	KOOS total score 3 and 6 months resp. (mean(SD)): PRP: 76.9(7.5), 84.4(6.2) HA: 68.6(3.7), 73.2(4.6) *P=0.02, P=0.001*

	VAS pain score 3 and 6 months resp. (mean(SD)): PRP:2.3(1.6), 1.7(1.4) HA: 4.1(1.3), 3(1) *P=0.001, P=0.001* Patient satisfaction: Not Reported Adverse effects: Not reported

Risk of bias (Say 2013)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...patients were separated into two groups of ..." Comment: Probably not done.
Allocation concealment (selection bias)	High risk	Allocation concealment probably not done
Blinding of participants (performance bias)	High risk	Different dosage used in both treatment groups. Comment: Probably not done
Blinding of personnel (performance bias)	High risk	Not reported. Comment: Blinding of personnel is probably not done
Blinding of outcome assessment (detection bias)	High risk	Not reported. Comment: Blinding of outcome assessment is probably not done
Incomplete outcome data (attrition bias)	Unclear risk	Number of participants at baseline and follow up has been reported. Exclusions and withdrawals have not been reported.
Selective reporting (reporting bias)	Unclear risk	Pre-specified primary outcomes have been reported, secondary outcome have not been reported.
Other bias	High risk	No power analysis has been reported.

Spaková 2012	
Study type/Country/Treatment	Prospective, two arm, comparative trial Single Center, Slovakia PRP versus Hyaluronic Acid
Participants	Mean age: 53,0 % Female: 46.7% Mean disease duration: NR Number of participants: 120 Follow-up: 3 and 6 months Inclusion: Age: NR Duration clinical symptoms : > 12 months Symptomatic OA of the knee , radiological **Kellgren Lawrence** grade I-III Baseline values: Kellgren Lawrence grade (n): I PRP: 2 HA: 2 II PRP: 39 HA: 37 III PRP: 19 HA: 21 WOMAC score (mean(SD): PRP: 38.76(16.5) HA: 43.21(13.7) NRS pain score (mean(SD)): PRP: 5.27(1.87) HA: 6.02(1.77)
Intervention	Intervention (n=60): 3 PRP (type 1B) intra articular injections Interval: weekly Comparison (n=60): 3 HA intra articular injections Interval: weekly
Outcomes	Primary outcome(s): WOMAC total score (0-96) NRS pain score (0-10) Secondary outcome: Adverse effects
Results	WOMAC total score 3 and 6 months resp.(mean(SD)): PRP: 14.35(14.18), 18.85(14.09) HA: 26.17(17.47), 30.90(16.57)

		P<0.01, P<0.01 NRS pain score 3 and 6 months resp. (mean(SD)): PRP:2.06(2.02), 2.69(1.86) HA: 3.98(2.27), 4.3(2.07) *P<0.01, P<0.01* Adverse effects: No short or long time side effects observed

Risk of bias (Spaková 2012)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients were randomly divided into two groups. The first group of 60 patients..." Comment: Probably not done
Allocation concealment (selection bias)	High risk	No allocation concealment has been reported. Comment: Probably not done
Blinding of participants (performance bias)	High risk	No blinding of participants has been reported. Comment: Probably not done
Blinding of personnel (performance bias)	High risk	No blinding of personnel has been reported. Comment: Probably not done
Blinding of outcome assessment (detection bias)	High risk	No blinding of outcome assessment has been reported. Comment: Probably not done
Incomplete outcome data (attrition bias)	High risk	Number of participants at baseline and follow up has been reported only at 3 months of follow up. Exclusions and withdrawals have not been reported.
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes have been reported.
Other bias	High risk	No power analysis has been reported.

Sánchez 2012	
Study type/Country/Treatment	Randomized, two arm, controlled trial Multicenter, Spain PRGF-Endoret versus Hyaluronic Acid
Participants	Mean age: 59.7, % Female: 51.7% Mean disease duration: NR Number Randomized: 176 Follow-up: 1, 2 and 6 months <u>Inclusion:</u> Age: between 40 and 72 y Duration clinical symptoms : NR OA of the knee according ACR criteria, radiological **Ahlbäck** grade I- III <u>Baseline values:</u> Ahlbäck grade (n(%) I PRGF: 45(51) HA: 42(49) II PRGF: 32(36) HA: 32(38) III PRGF: 12(13) HA: 11(13) WOMAC score, normalized (mean, SD) Pain: PRGF: 40.4(16) HA: 38.4(5.6) Stiffness: PRGF: 41.8(17.3) HA: 38.5(18.3) Physical function: PRGF: 39.6(16.3) HA: 38.8(17.4) Global: PRGF: 121.8(44.4) HA: 115.6 (45.1) Lequesne index (mean(SD)): PRGF: 9.5(3.0) HA: 9.1(3.2)
Intervention	<u>Intervention (n=89):</u> 3 PRP (type 4B, PRGF) intra articular injections Interval: weekly <u>Comparison (n=87):</u> 3 HA intra articular injections

	Interval: weekly
Outcomes	Primary outcome(s): % of patients having a 50% decrease in the summed WOMAC pain subscale score Secondary outcome(s): Normalized WOMAC total score (0-300) Normalized WOMAC pain score (0-100) Normalized WOMAC stiffness score (0-100) Normalized WOMAC physical function score Lequesne index (0-24) Adverse effects
Results	50% decrease WOMAC pain score 6 months (N(%)): PRGF: 34(38.2) HA: 21(24.1) *P=0.044* Normalized WOMAC total score 6 months (mean(SD)): PRGF:74.0(42.7) HA:78.3(48.1) *P=0.561* Normalized WOMAC Pain score 6 months (mean(SD)): PRGF:24.1(15.5) HA:26.9(15.8) *P=0.265* PRGF:25.2(15.4) HA:25.5(17.9) *P=0.901* PRGF:24.8(15.9) HA:25.9(17.2) *P=0.682* Lequesne index 6 months (mean(SD): PRGF: 5.2(3.4) HA: 5.4(3.3) *P=0.714* Adverse effects: No significant difference (*P=0.811*) between groups and most are not related to the type of treatment.

Risk of bias (Sánchez 2012)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "... the treatment assigned by randomization was delivered. A stratified randomization (1 stratum per center) was carried out". Randomization was carried out by using specific computer software. Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote: " ...keeping that relation in a sealed envelope". „This envelope was not opened until the moment before applying the treatment". Comment: Probably done

Blinding of participants (performance bias)	Low risk	No difference between the intervention and comparison group regarding dosage. The application area was hidden from view and blood was drawn for all patients. Comment: probably done
Blinding of personnel (performance bias)	High risk	Not reported. Reporting "double blinded" means participants and observers. Comment: Probably not done
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Response was assessed by researchers not involved in the application of treatment. The data report forms did not make any references to the treatment applied". Comment: Probably done
Incomplete outcome data (attrition bias)	Low risk	Analysis: Intention to treat. Number of patients randomized and analyzed was reported. The exclusion and withdrawal percentages did not differ significantly between groups
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes have been reported in the pre-specified way.
Other bias	Low risk	Power analysis has been calculated. (110 patients per treat arm to provide at least 90% power to detect differences in the proportions of patients achieving 50% pain improvement with PRGF vs HA at a 5 % level of significance).

Vaquerizo 2013	
Study type/Country/Treatment	Randomized, two arm, controlled trial Multicenter, Spain PRGF-Endoret versus Durolane Hyaluronic Acid
Participants	Mean age: 63.6, % Female: 60.4 Mean disease duration: NR Number Randomized: 96 Follow-up: 24 and 48 weeks <u>Inclusion:</u> Age: > 50 y Clinical symptoms: > 6 months OA of the knee according ACR criteria, radiological **Kellgren Lawrence** grade II to IV <u>Baseline values:</u> Kellgren Lawrence grade n(%): II PRGF: 14(29.2) HA: 18 (37.5) III PRGF: 26(54.2) HA: 21(43.8) IV PRGF: 8(16.7) HA: 9(18.8) WOMAC score (mean (SD)): Pain PRGF: 9.6(2.5) HA: 10.2(3.5) Stiffness: PRGF: 3.7(1.7) HA: 4.0(2.0) Physical function: PRGF: 32.6(9.9) HA: 36.7(13.7) Total: PRGF: 45.9(12.7) HA: 50.8(18.4) Lequesne Index: (mean(SD)) PRGF: 12.8(3.8) HA: 13.1(3.8)
Intervention	<u>Intervention (n=48):</u>

	3 PRP (type 4B, PRGF) intra articular injection (8mL) Interval: 2 weeks <u>Comparison (n=48)</u> Single HA (Durolane) intra-articular injection
Outcomes	<u>Primary outcome(s):</u> % of patients having a 30% decrease and 50% decrease in the summed WOMAC subscale scores –pain, stiffness and physical function and Lequesne index <u>Secondary outcome(s):</u> WOMAC subscales pain (0-20), stiffness (0-8), physical function (0-68) and total score (0-96) Lequesne scale (0-24) Adverse effects
Results	30% decrease WOMAC score 24 and 48 weeks resp. (N(%)): Pain: PRGF: 40(83), 28(58.3) HA: 7(17), 5(11.9) *P<0.001, P<0.001* Stiffness: PRGF: 24(52), 24(52.2) HA: 11(27), 5(12.2) *P<0.02, P<0.001* Physical function: PRGF:29(60), 26(54.2) HA: 7(17), 7(16.7) *P<0.001, P<0.001* 50% decrease WOMAC score (N(%)) Pain: PRGF: 26(54), 15(31) HA: 5(11), 1(2) *P<0.001, P<0.001* Stiffness: PRGF: 16(35), 16(33 HA: 7(16), 2(5) *P=0.035, P=0.001* Physical function: PRGF: 19(40), 15(31) HA: 5(11), 0(0) *P=0.001, P=0.001* 30% decrease Lequesne (N(%)): PRGF: 35(73), 23(47.9) HA: 7(17), 1(2.4) *P<0.001, P<0.001* 50% decrease Lequesne (N(%)): PRGF: 14(29), 9(19) HA: 2(4), 1(2) *P=0.002, P=0.017* WOMAC total score 24 and 48 weeks resp. (mean(SD)): PRGF: 27.2(15.1), 30.8(15.5) HA: 50.4(23.2), 54.2(19.2) *P*<0.001, *P*<0.001 Lequesne index 24 and 48 weeks resp. (mean(SD)): PRGF: 5.2(3.4), 8.9(3.7) HA: 5.4(3.3), 14.4 (3.8) *P=<0.001, P=0.001*

		Adverse effects: PRGF: 14.6% HA: 18.8% PRGF vs. HA: *P=.610* Withdrawals: PRGF: 0 HA: 1

Risk of bias (Vaquerizo 2013)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A simple randomization was carried out" Comment: Probably done. The use of specific software for randomization as a random component in the sequence generation process was described.
Allocation concealment (selection bias)	Low risk	Quote: "..keeping that relation in a sealed envelope" Comment: Probably done. The envelope was not opened until the moment before the treatment was applied.
Blinding of participants (performance bias)	High risk	Different dosage used in both treatment groups makes it impossible to blind the patients. Comment: Probably not done
Blinding of personnel (performance bias)	High risk	Different dosage, preparation of PRGF at each treatment visit and insufficient information about blinding personnel makes blinding of personnel dubious. Comment: Probably not done
Blinding of outcome assessment (detection bias)	Low risk	Quote: „The response was assessed by researchers not involved in the application of treatment. In the data report forms, there was no reference to the treatment that had been applied. The evaluation of the patients´ status and disease progression was performed by physicians in a blinded way".

		Comment: Probably done
Incomplete outcome data (attrition bias)	High risk	Number of allocated and analyzed participants was reported. 6 months follow up: No missing data in both groups. 12 months follow up: No missing in intervention group and 6/48 missing from comparison group Comment: Differ across groups at longer term outcome (> 6 months)
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes have been reported in the pre-specified way.
Other bias	Unclear risk	Power analysis has been calculated. (48 patients per group to provide at least 80% power to detect differences in the WOMAC pain scale superior to 1.2 for PGRF vs HA at a 5 %level of significance taking into account 10% losses). Per protocol analysis

Characteristics of excluded studies

Study	Reason for exclusion
Yang 2008	Intervention of interest: Autologous conditioned serum (Orthokine)
Baltzer 2009	Intervention of interest: Autologous conditioned serum (Orthokine)
Klatt 2011	Point/counterpoint discussion: Total knee arthroplasty versus PRP
ClinicalTrail.gov identifier NCT00728611	Study has been completed. Unfortunately, no additional information was available.

Characteristics of ongoing studies

Laver 2011	
Study name	Platelet Rich Plasma (PRP) as a Treatment for Knee Osteoarthritis - A Randomized-Double-Blind Trail
Methods	Randomized, two arm, controlled trial
Participants	Patients with knee osteoarthritis, age between 40 and 75 years old. Inclusion: diagnosed osteoarthritis of the knee more than 1 year, no knee deformation. Exclusion: mental or physical disabilities, pregnancy, deformities of the knee.
Intervention	Biological: Platelet rich plasma (PRGF) Drug: Hyaluronic acid (HA)
Outcomes	Primary outcome: Improvement in pain, function, quality of life and activity level in OA of the knee

	1-2 years
Starting date	September 2011
Contact information	Lior Laver tel: +972-50-8464466 laver17@gmail.com
Notes	Study not yet open for participant recruitment
ClinicalTrails.gov identifier	NCT01270412

Nayana 2011	
Study name	A prospective, Randomized, Double-blinded, Clinical Trail, Comparing Platelet-rich Plasma Intra articular Knee Injections Versus Corticosteroid Intra-articular Knee injections for Knee Osteoarthritis
Methods	Randomized, two arm, controlled trial
Participants	Patients with knee osteoarthritis, age between 40 and 80 years old. Inclusion: degenerative OA of the knee confirmed radiologically, degenerative osteoarthritis of the knee replacement candidate, walking ability in patients with or without external support and baseline in pain VAS greater than 60 Exclusion: neoplastic disease, immunosuppressive states, received IA injections of steroids, anesthetic and/or HA in the last 3 months, patients who have undergone arthroscopic surgery on the last 3 months, patients with involvement of bone metabolism except osteoporosis, fibromyalgia, liver disease, deficit coagulation, thrombocytopenia, anticoagulant treatment
Intervention	Biological: platelet-rich plasma Drug: Corticosteroid
Outcomes	Primary outcome: Visual analogue pain scale (VAS) one moment after treatment. Secondary outcome: Visual analogue pain scale (VAS) one, three and six months after treatment, adverse events, scale of the SF 36 quality of life one, three and six months after treatment.
Starting date	July 2011
Contact information	Nayana Joshi tel: 0034934893481 njoshijubert@gmail.com
Notes	Study is ongoing, but not recruiting participants
ClinicalTrails.gov identifier	NCT01381081