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REVIEW ARTICLE

Effectiveness of platelet-rich plasma in the management of hip osteoarthritis: a systematic review and meta-analysis

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Abstract

The effectiveness of platelet-rich plasma (PRP) injections for osteoarthritis (OA) is still controversial. Previous research supports the use of intra-articular PRP injections to promote a favorable environment for joint tissue healing and to delay the progression of OA. The purpose of this review is to investigate the effectiveness of PRP in the management of hip osteoarthritis (HOA). Five electronic databases were searched from inception to May 2019: Medline (via PubMed), SportDiscus via EBSCO, ProQuest Health & Medical Complete, CINAHL, and Cochrane. Risk of bias was assessed with the Cochrane risk of bias tool. The GRADE method was used to assess the level of evidence for the studies included in this review. Clinical trials evaluate PRP injections among adult patients diagnosed with HOA according to the American College of Rheumatology criteria. At least one outcome measure for pain or function must have been reported. A total of 4 trials (334 participants, 340 hips) were included, all marked as "moderate risk of bias". Pain and function were assessed throughout the studies with visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Harris Hip Score (HHS) tools. Intra-articular PRP injections were more effective at stages earlier than 3 months for both treatment groups with the exception of WOMAC score in one study. The superiority of PRP against comparative treatments was only reported in one study; longer-term evaluations from 4 to 12 months showed diverse results, with only one study reporting significantly better results for PRP. PRP may be beneficial and safe for patients with HOA at mid-term follow-up. However, its superiority over other procedures such as hyaluronic acid remains unclear. Further researches with high-quality designs and larger samples become imperative.

Keywords Cartilage · Growth factors · Hip · Osteoarthritis · Platelet-rich plasma

Introduction

Osteoarthritis (OA) is a chronic musculoskeletal condition which typically affects the knee and hip joints. It responds to a syndrome characterized by joint pain, stiffness, and dysfunction, associated with joint degeneration and loss of articular cartilage [1]. OA prevalence is higher than any other joint disease, mostly affecting subjects over 60 years and female population. It is estimated that 27 million Americans, or 12.1% of the adult population, suffer from OA, numbers predicted to highly rise in the next decade [2]. Moreover, 80% of OA patients will complain of movement impairment, and 25% are unable to perform normal daily activities of life [3]. In fact, the OA-associated disability considerably burdens the economic sphere, entailing both direct costs, such as those related to treatments and joint replacement surgeries, and indirect costs, like loss of productivity [4].

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Knee and hip are the most common sites for OA suffering in developed countries [5, 6]. According to the European League Against Rheumatism (EULAR), a separation should be maintained between recommendations for knee and hip OA (HOA) mainly based on anatomical and physiological differences, and risk factors for development [7]. Etiologic and pathogenic factors in HOA rely on anatomic variability in most cases, such as femoroacetabular morphology, and excessively abnormal shearing forces which subsequently generate a chronic inflammatory process [8]. Among the different risk factors leading to HOA, both non-occupational and work-related causes can be found to have an implication on the development of the disease.

Although there is no cure for OA, different treatment modalities focus on alleviating pain, maintaining or improving joint mobility, and preventing functional decline. Pharmacologic interventions include glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or cartilage protective agents [9, 10], and non-pharmacological options include physical therapy, exercise, or patient education [9]. However, the benefit of these treatments is limited to short-term effects, and the evidence supporting their capacity of altering the biological progression of OA remains unclear [11].

Platelet-rich plasma (PRP) is one such biological therapy gaining increasing popularity for the management of OA. Being firstly reported for therapeutic use in the late 1980s [12], PRP has been traditionally known as a volume of plasma with higher platelet count. It is produced by the centrifugation of autologous whole blood, obtaining such blood derivate with richer platelet concentration than the baseline sample. PRP is reported to release cytokines and growth factors in the diseased area after a degranulation process, thus stimulating and promoting a favorable environment for soft tissue healing processes [13, 14], first with an initial pro-inflammatory action [15] and followed by decreasing inflammatory molecules [16]. Chondrocytes treated with PRP in vitro have shown to stimulate the matrix metabolism of articular cartilage and the synthesis of proteoglycans and collagen, presenting the resulting tissue histological and biomechanical similarities with the original tissue [17].

Regarding bioactivity of PRP, some studies have documented to contain more than 800 proteins which experiment reactions for several bioactive factors [18]. Apart from its coagulative and inflammation-regulatory effects, platelets also play a role in delivering active molecules (such as ascorbic acid, nucleotides, or chemokines) and a wide variety of growth factors (GFs) [19].

Hence, multifactorial actions can be expected from PRP in different fields, such as bone or vessel remodeling, inflammation, angiogenesis, synthesis of extracellular matrix proteins like collagen, or even cell differentiation [20]. Regarding effects on cartilage, TGF-β is considered to preserve and stimulate the synthesis of chondrocytes in vitro by improving cell proliferation and matrix production. It also promotes bone formation in vivo by cooperating with bFGF to induce the migration of specific bone marrow cells [21].

Several systematic reviews study the effects of PRP injections in a broad array of pathologies and tissues [22–26]. Due to the increasing relevance and prevalence of OA in the general population, many clinical trials with different experimental designs begin to arise to explain the benefits of this procedure. Research on intra-articular approach for HOA has been recently published, either in a general context focusing on large joints [27, 28] and cartilage pathology [29], or in the HOA-specific context and confronting two different treatment modalities [30]. However, at the time this study was performed, no previous published literature analyzing specifically outcomes for patients treated with PRP for HOA existed. Therefore, in an attempt to conclude a previously published systematic review protocol addressing this topic, the purpose of the present study is to systematically review the available literature to determine the effectiveness of PRP injections and its in-isolation influence against other approaches for the treatment of HOA.

Methods

This review was carried out following recommended advice from the Cochrane Handbook [31], reported according to the PRISMA statement [32] and registered in advance with PROSPERO (reference number: CRD42014010210) [33].

Literature search

Electronic resources were independently analyzed by two researchers (IM-P, MO-C) using the Medical Subject Headings (MeSH) according to each database. A primary search in five electronic databases (PubMed, ProQuest Health & Medical Complete, CINAHL, SPORT Discus, and Cochrane Central Register of Controlled Trials) was performed to retrieve primary studies published prior to May 2019. A secondary hand search was performed in gray literature and references to include additional records. The search strategy was based on three broad concepts: (i) osteoarthritis, (ii) hip, and (iii) platelet-rich plasma. In addition, systematic reviews and other reviews were thoroughly examined so that potential eligible articles were not missed. A recognized expert in this field was consulted in attempt to identify any further published or unpublished studies.

Study selection

Inclusion criteria

The following inclusion criteria for relevant articles were used during the initial screening of titles and abstracts: clinical reports of any level of evidence, written in both English and Spanish languages, with no time limitation, on the use of PRP or any equivalent product (i.e., platelet-leucocyte gel, platelet concentrate, or platelet gel) to treat conservatively

adult patients (> 18 years) diagnosed with mild, moderate, or severe HOA according to the American College of Rheumatology criteria [34]. PRP injections had to be applied in isolation in at least one of the treatment arms, with pain or function being reported as outcome measures both in public and private practice intervention settings. Title and abstract of all identified studies were independently screened for inclusion by two authors (IM-P, MO-C) during first selection phase. Study selection discrepancies between the two researchers were resolved by discussion.

Exclusion criteria

Studies accomplishing at least one of the following statements were not included: (i) studies involving only children or animal subjects; (ii) non-OA injuries; (iii) OA affecting other joints; and (iv) history of previous operative treatment for HOA.

Data extraction

A qualitative synthesis comparing the results of the different articles was conducted. Data from studies was extracted from the studies regarding the following: (i) general information (authors and year of publication); (ii) participants' characteristics; (iii) main intervention—PRP injection; (iv) outcomes; and (v) related results, and any other important aspect related to each research question of interest, using a standardized form. Summary tables were created showing key study characteristics. When data were not available from tables or the results section, the authors of the studies were contacted. Disagreements between the reviewers were resolved by discussion and consensus. A meta-analysis regarding pain (VAS) was conducted according to the DerSimonian and Laird random effects method [35] (Fig. 2).

Methodological quality assessment

Risk of bias of the included studies was independently appraised by two authors (MO-C and IM-P), using the Cochrane risk of bias tool [31]. High-quality studies were defined as those with a low risk of bias in four or more of the Cochrane Tool's domains. These domains were based on randomization method, allocation concealment, blinding of participants, blinding of outcome assessment, completeness of outcome data, selection data, and other perceived bias. For each domain, the reviewers qualified the risk of bias as "low" (v), "high" (^), or "unclear (?)". Studies were considered as "low risk of bias" when all items were scored as "v". When studies scored "^" or "?" on one/two items, a "moderate bias" was considered. Trials with more than two "v" or "?" were categorized as "high risk of bias." Any disagreement was discussed until consensus was reached.

The overall quality of the evidence was assessed using the Grades of Recommendations Assessment, Development and Evaluation (GRADE) instrument. Overall quality was classified as either very low, low, moderate, or high [36].

Results

Study identification

The electronic databases search in May 2019 resulted in 197 articles. No additional papers were included from other sources. Of the initial 197 citations, 6 underwent full-text review. After excluding further 2 studies, a total of 4 articles met inclusion criteria in qualitative synthesis [37–40]. Figure 1 includes a PRISMA flow diagram of study identification and selection.

Treatment modalities

One of the studies compared PRP with hyaluronic acid (HA) in isolation and in combination with PRP [38], whereas other 3 studies compared PRP with HA [37, 39, 40].

Sample sizes

The average number of recruited patients was 83.5 and ranged from 43 to 111. The total follow-up of three studies [37, 38, 40] was 12 months and only one reduced that duration to 4 months [39].

Subjects

The mean age in the selected trials was 59.8 years (range 20 to 80). Eligibility criteria were based both on clinical and radiological features. The severity of Hip OA was graded with Kellgren and Lawrence (K&L) radiological grading scale/classification system. Table 1 gathers the distribution of hip OA grade. The most prevalent OA grade for hips receiving PRP treatment was reported to be grade III.

Methodological quality assessment

The mean number of "low risk of bias" domains in Cochrane Tool was 5/7, obtaining each one of them a total of 5/7, and therefore designated as moderate/high-quality studies. Overall, these scores are relatively good, considering that injection therapy does not allow for blinding of the participants or therapists. Blinding of outcome assessment was only accomplished in half of the studies; however, no other perceived bias was noticed in any of the studies (Table 2). Using the GRADE instrument, the overall quality of evidence ranged from low to moderate. The two reviewers had initial agreement and reached consensus on all criteria.

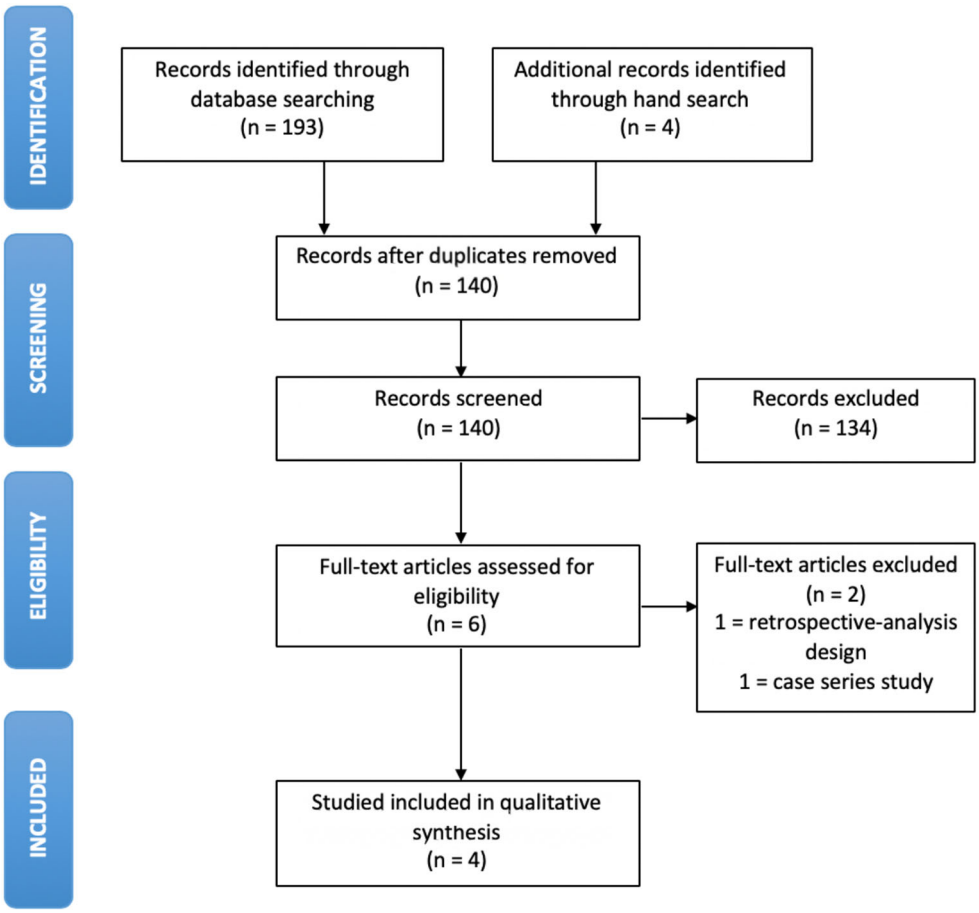

Fig. 1 Flowchart of the selection process according to PRISMA statement

Table 1 Baseline characteristics of the selected studies

Authors, year	Type of study	Geographic location	Sample size	Age (years)	Intervention arms	Measured outcomes	Hip OA KLG in PRP group (%)			
							I	II	III	IV
Battaglia et al., 2013	RCT	Italy	$n = 100$ at baseline, $n = 96$ at the end of the study	53 ± 12	PRP group ($n = 50$) and HA group ($n = 50$)	VAS and HHS	0	32	42	26
Dallari et al., 2016	RCT	Italy	$n = 111$	Between 20 and 65	PRP group ($n = 44$), PRP + HA group ($n = 31$) and HA group ($n = 36$)	VAS, HHS, WOMAC, measurements of the concentration of GFs	31	22	22	25
Di Sante et al., 2016	RCT	Italy	$n = 43$	73 ± 7	PRP group ($n = 21$) and HA group ($n = 22$)	VAS and WOMAC	excluded	24	76	excluded
Doria et al., 2017	RCT	Italy	$n = 80$	68 ± 5	PRP group ($n = 40$) and HA group (n = 40)	VAS, HHS, and WOMAC	NS	NS	excluded	excluded

Values are mean ± SD or as otherwise indicated

RCT, randomized controlled trial; *PRP*, platelet-rich plasma; *HA*, hyaluronic acid; *VAS*, visual analogic scale; *HHS*, Harris Hip Score; *WOMAC*, Western Ontario and McMaster Universities Osteoarthritis Index; *GF*, growth factors; *OA*, osteoarthritis; *KLG*, Kellgren-Lawrence Grade; *NS*, non-specified

Table 2 Risk of bias assessment: Cochrane tool for risk of bias assessment of randomized trials

Authors, Year	*Random sequence generation*	*Allocation concealed*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
Battaglia et al., 2013[25]	LRB	LRB	HRB	HRB	LRB	LRB	LRB
Dallari et al., 2016[26]	LRB	LRB	HRB	LRB	LRB	HRB	LRB
Di Sante et al., 2016[27]	LRB	LRB	HRB	HRB	LRB	LRB	LRB
Doria et al., 2017[28]	LRB	URB	HRB	LRB	LRB	LRB	LRB

LRB, low risk of bias; *HRB*, high risk of bias; *URB*, unclear risk of bias. Green color indicates low risk of bias; red color indicates high risk of bias, and yellow color indicates uncertain risk of bias

Baseline demographic data

All studies included only adults and recruited patients to have symptomatic hip OA. A total of 334 patients were included (340 hips) in the 4 studies. Sample size for the PRP arm varied substantially, ranging from 21 to 50 hips. Curiously, all included studies were developed in the same country, Italy. Table 1 summarizes baseline features from the included studies.

The mean/median age of the studies was relatively comparable (between 53 and 73 years), although the age range varied across studies. The mean age of included patients who received PRP injections was 59.1 years, and 48% were female patients. The mean age of the control patients (HA or HA + PRP) was 62.3 years, and 46.6% were female patients. Mean body mass index (BMI) was also reported in two studies, with a mean of 25.6 and ranging from 24.3 to 27.

Figure 1 outlines search strategy results. After the searching, reviewing and assessing processes, 4 RCTs were included. All of them were published in peer-reviewed journal and were conducted in Italy.

PRP preparation technique

PRP preparation protocols varied among studies. PRP preparation techniques for every study are summarized in Table 3, including extracted volume, centrifugation parameters (i.e., time, frequency), platelet concentration, white blood cell presence, and activator administration (i.e., calcium chloride).

Injection procedure

Although the application of PRP may vary in terms of frequency and treatment intervals, all included studies in our systematic review involved multiple PRP injections. A total of 3 injections was the number of PRP applications each hip received, and the sequence of injections ranged from 1 to 2 weeks. Location of injections and volume injected were also diverse (Table 4).

Patient-reported outcomes

All included studies reported function and pain measures (Table 5), which means at least one of the OMERACT III core set of outcome measures, whereas three of them also included quality of life outcomes. Primary outcome measures assessing function and pain were the visual analogic scale (VAS) for pain, and Harris Hip Score (HHS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for evaluating function. Secondary outcome measurements were estimation of the growth factors' concentration, adverse effects, and imaging evaluations.

Main outcomes

PRP on pain and function

Painful sensation and functional measures were assessed by different evaluation procedures using validated scores such as VAS [37–40], HHS [37, 38, 40], and WOMAC (A—pain, B—stiffness, C—function) scales [38–40]. Three studies compared PRP versus HA [37, 39, 40], and one study included two control groups with subjects receiving HA and HA + PRP respectively [38]. Figure 2 shows the summarized effect of PRP on hip OA at various times among all selected studies.

Battaglia et al. [37] evaluated the effects of PRP in pain using VAS and HHS scores. Subjects were randomly allocated in PRP group and HA group, and measures were taken at baseline, 1, 3, 6, and 12 months after last injection. Results showed significant but time-variable improvements in both groups, reporting the best results between 1- and 3-month follow-up ($p < 0.0005$), following a slightly progressive worsening from 6- to 12-month follow-up ($p = 0.005$). However,

Table 3 PRP procedures: type and preparation techniques

Authors, year	Extracted blood-volume	Centrifugation parameters	Aliquots obtained	Storage temperature	Platelet concentration (%)	White cells/red cells count	Activator administration	Source for each Injection	PRP system (ACP, custom…)
Battaglia et al, 2013	150 mL	2 centrifugations: -First at 1800 rpm (15 min) -Second at 3500 rpm (10 min)	4 units of 5 mL each	− 30 °C	600	Leukocytes: ≅ 8300/μL Erythrocytes: 0	10% calcium chloride	Frozen sample	NR
Dallari et al, 2016	150 mL (unilateral disease) or 300 mL (bilateral disease	2 centrifugations: -First at 1480 rpm (6 min) -Second at 3400 rpm (15 min)	Units of 5 mL: −4 units in unilateral disease − 7 units in bilateral disease	− 30 °C	NR	NR	10% calcium chloride	Frozen sample	NR
Di Sante et al, 2016	8 mL for each hip treated	2 centrifugations, both at 3100 rpm (9 min each)	4 mL of PRP	NR	100–150	Leukocytes: 0 Erythrocytes: NR	NR	Fresh sample	Autologous Platelet Gel
Doria et al, 2017	150 mL	2 centrifugations: -First at 1480 rpm (6 min) -Second at 3400 rpm (15 min)	4 units of 5 mL each	− 30 °C	NR	NR	NR	Frozen sample	NR

US, ultrasound; *NR*, non-reported; *ACP*, autologous conditioned plasma (Biocore; Arthrex, Karlsfeld, Germany)

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)

final scores remained similar between groups. Additionally, temporal variation of VAS seemed to be more significantly influenced by OA grade, being OA grade IV at 1-month follow-up which experienced an immediate but short-term pain reduction in comparison with OA grades II and III ($p < 0.0005$).

Dallari et al. [38] assessed the therapeutic effects of PRP using VAS, WOMAC, and HHS scores. Subjects were randomly allocated in PRP group, HA group, and HA + PRP group, and measures were taken at baseline, 2, 6, and 12 months after last injection. Results showed the same significant improvement in VAS, HHS, and WOMAC scores during time ($p < 0.0005$), with significant interactions for VAS ($p = 0.003$) and WOMAC ($p = 0.002$) scores regarding treatment type. At 2-month follow-up, PRP group showed significantly better between-group results in VAS (versus HA group, $p = 0.026$; versus HA + PRP group, $p = 0.010$) and WOMAC scores (versus HA group, $p = 0.009$; versus HA + PRP group, $p = 0.002$). At 6-month follow-up, the trend was similar in favor of PRP group for VAS and WOMAC scores in comparison with HA and HA + PRP groups ($p < 0.01$). At 12-month follow-up, only VAS showed a significant trend among groups (versus HA group, $p = 0.002$; versus HA + PRP group, $p = 0.017$).

Di Sante et al. [39], by their part, used WOMAC subscales and VAS score to measure pain and functionality. Subjects were randomly distributed to PRP group and HA group, and measures were registered at baseline, 1, and 4 months after last injection. Regarding pain, VAS scores in PRP group showed significant changes only at 1-month follow-up ($p < 0.01$), afterward lost and not statistically significant at 4-month follow-up, where HA group, on the other hand, showed significant improvements ($p < 0.01$), being the differences significant between groups ($p = 0.0004$). With respect to WOMAC-A scores, differences were only significant in HA group at 4-month follow-up ($p < 0.01$). Concerning functionality, significant changes in WOMAC-B and WOMAC-C scores were only found at 4-month follow-up in HA group ($p < 0.01$).

Doria et al. [40] aimed to evaluate pain and functionality after PRP treatment by using VAS, HHS, and WOMAC scores. Subjects were randomly allocated to PRP group and HA group, and results were measured at baseline, 6, and 12 months after last injection. Regarding pain, significant changes were observed in VAS, HHS, and WOMAC subscores at 6- and 12-month follow-ups in both groups ($p < 0.01$). Concerning disability, significant improvements were also found in WOMAC subscale at 6- (PRP group, $p = 0.0142$; HA group, $p = 0.0158$) and 12-month (PRP group, $p = 0.0306$; HA group, $p = 0.0402$) follow-ups in both groups. Function changes in HHS score followed a significant and similar trend at 6- (PRP group, $p = 0.0005$; HA group, $p = 0.0003$) and 12-month (PRP group, $p = 0.0031$; HA group, $p = 0.0037$) follow-ups in both groups.

Table 4 PRP treatment proceeding features in selected studies

Authors, year	Number of injections	Volume injected (mL)	Injected sites	Sequence of injections (N)/interval (weeks)	Image guidance	Post PRP intervention	Follow-up
Battaglia et al., 2013	3	5	Anterior approach at the base of the femoral head-neck junction	Once every 2 weeks	US	NSAIDs forbidden for 48 h after treatment, allowed thereafter	Baseline, 1, 3, 6, and 12 months after last injection
Dallari et al., 2016	3	5	Anterolateral region of the hip, at the base of the femoral neck	Once per week	US	Only ice application was allowed	Baseline, 2, 6, and 12 months after last injection
Di Sante et al., 2016	3	3	Anterior synovial recess at the junction of the femoral head and neck	Once per week	US	Not allowed	Baseline, 1 and 4 months after last injection
Doria et al., 2017	3	5	Anterosuperior, parasagittal approach over the base of the femoral neck	Once per week	US	NR	Baseline, 6 and 12 months after last injection

US, ultrasound; *NR*, non-reported; *NSAIDs*, non-steroidal anti-inflammatory drugs

Summarizing, early evaluations (at 1-[37, 39], 2-[38], and 3-month [37] follow-ups after last injection) showed a consistent significant improvement of every outcome in all PRP groups ($p < 0.01$), with the exception of WOMAC score in one study [39], where only VAS showed a significant improvement. These early assessments were also the points when subjects improved the most in two studies [37, 40]; however, the superiority of PRP against comparative treatments differed between studies: two articles [38, 39] showed significantly better results than those reported in control groups ($p < 0.05$); one study [37], on the other hand, showed equally significant changes in both PRP and HA groups with no significant differences between them. Longer-term assessments (at 4-[39], 6-, and 12-month [37, 38, 40] follow-ups after last injection) also revealed diverse results. One study [39] found that all WOMAC subscales and VAS score significantly improved only in HA group at 4-month follow-up ($p < 0.01$); two studies [37, 40] reported significant results for every outcome at 6- and 12-month follow-ups in both treatment groups ($p < 0.05$), without significant differences between them; and one study [38] showed significant improvements in favor of PRP group both in VAS score at 6- and 12-month follow-ups ($p < 0.01$) and in WOMAC score at 6-month follow-up against comparative treatments ($p < 0.05$).

Secondary outcomes

Growth factors and outcomes

Influence of GFs and their relationship with outcomes over time were only evaluated by one study. Dallari et al. [38] showed that, in a limited group of patients whose PRP aliquots were analyzed for proinflammatory and anti-inflammatory markers, a significant moderate correlation between the anti-inflammatory IL-10 marker and VAS score improvements during time was found ($p = 0.040$).

Adverse effects

Safety of the injection technique, although generally mentioned, was only statistically measured in one of the studies [40]. In this study, adverse events were also compared between PRP and HA treatments, showing the PRP group a significantly higher post-injective pain reaction ($p = 0.043$). However, it ceased within few weeks without affecting the long-term results. Other studies, despite not being statistically analyzed, also reported some side effects. Battaglia et al. [37] found that one patient developed a superficial hematoma after first infiltration due to transitional venous damage, but spontaneously resolved in 2 weeks.

OA grade and outcomes

Influence of OA grade in temporal variations of the outcomes was also considered in two studies. Battaglia et al. [37] found that VAS score seemed to be more significantly influenced by OA grade, being OA grade IV at 1-month follow-up which experienced an immediate but short-term pain reduction in comparison with OA grades II and III ($p < 0.0005$). Dallari et al. [38] claimed that OA grade was also considered to partially play a role in the effects of treatment type ($p = 0.014$).

Table 5 Outcomes and results among included studies

Authors, year	Intervention groups	Outcomes	Follow-ups (months)						
			Baseline	1	2	3	4	6	12
Battaglia et al., 2013	EG: PRP	VAS	5.47 ± 0.50	3.72 ± 0.62‡,§	-	3.80 ± 0.61‡,§	-	4.29 ± 0.61‡,§	4.75 ± 0.67‡,§
		HHS	58.11 ± 3.93	73.72 ± 4.57‡,§		72.90 ± 4.36‡,§		70.23 ± 4.53‡,§	65.73 ± 5.13‡,§
	CG: HA	VAS	5.97 ± 0.49	3.58 ± 0.61‡	-	3.80 ± 0.60‡	-	4.04 ± 0.61‡	4.59 ± 0.67‡
		HHS	62.90 ± 3.92	78.02 ± 4.57‡		77.23 ± 4.37 ‡		75.79 ± 4.53‡	72.55 ± 5.13‡
Dallari et al., 2016	EG: PRP	VAS	NR	-	2.30 ± 0.60$^{‡,¥}$	-	-	2.10 ± 0.60$^{‡,¥}$	2.40 ± 0.70$^{‡,¥}$
		HHS	NR		NR‡,§			NR‡,§	NR‡,§
		WOMAC	NR		73 ± 5$^{‡,¥}$			72 ± 5$^{‡,¥}$	NR‡,§
	CG1: PRP + HA	VAS	NR	-	3.50 ± 0.90‡	-	-	3.50 ± 0.90‡	3.80 ± 0.90‡
		HHS	NR		NR‡			NR‡	NR‡
		WOMAC	NR		59 ± 0.60‡			59 ± 6‡	NR‡
	CG2: HA	VAS	NR	-	3.80 ± 0.80‡	-	-	4.40 ± 0.80‡	4.20 ± 0.80‡
		HHS	NR		NR‡			NR‡	NR‡
		WOMAC	NR		59 ± 0.60‡			59 ± 0.50‡	NR‡
Di Sante et al., 2016	EG: PRP	VAS	7.08 ± 2	4.73 ± 3.40$^{‡,¥}$	-	-	6.36 ± 2.10†	-	-
		WOMAC-A	58.89 ± 22	44.27 ± 28.80			53.47 ± 22.30†		
		WOMAC-B	53.72 ± 22.7	46.42 ± 27.50			47.22 ± 22.70†		
		WOMAC-C	59.87 ± 22.5	49.13 ± 29.10			50.80 ± 22.80†		
	CG: HA	VAS	6.32 ± 1.70	5.27 ± 1.60	-	-	3.63 ± 2.10‡	-	—
		WOMAC-A	42.36 ± 20.50	29.60 ± 13.40			19.90 ± 11.40‡		
		WOMAC-B	57.65 ± 26.20	47.69 ± 21.20			32.91 ± 20.60‡		
		WOMAC-C	45.83 ± 21.70	39.13 ± 17.20			28.39 ± 17.20‡		
Doria et al., 2017	EG: PRP	VAS	7.50 ± 2.10	-	-	-	-	6.30 ± 3.30‡,§	6.40 ± 2.90‡,§
		HHS	64 ± 10.30					75 ± 11.50‡,§	78 ± 11.30‡,§
		WOMAC-A	23.70 ± 2.10					7.80 ± 3.80‡,§	7.40 ± 2.50‡,§
		WOMAC-B	3.80 ± 4.10					2.10 ± 3.60‡,§	2 ± 4.20‡,§
		WOMAC-C	29.40 ± 2.60					12.30 ± 3.60‡,§	12 ± 3.80‡,§
	CG: HA	VAS	7.80 ± 1.90	-	-	-	-	6.30 ± 2.90‡	6.10 ± 2.30‡
		HHS	62 ± 9.80					74 ± 12.30‡	75 ± 11.40‡
		WOMAC-A	24 ± 1.90					9.70 ± 4.50‡	9 ± 5.60‡
		WOMAC-B	4.30 ± 5.30					3.10 ± 3.20‡	3.10 ± 4.30‡
		WOMAC-C	28.50 ± 2.50					11.30 ± 4.50‡	10.90 ± 4.20‡

Values are mean ± SD or as otherwise indicated

EG, experimental group; *CG*, control group; *PRP*, platelet-rich plasma; *HA*, hyaluronic acid; *VAS*, visual analogue scale; *WOMAC*, Western Ontario and McMaster Universities Osteoarthritis Index; *HHS*, Harris Hip Score; *NR*, non-reported

‡ Significant changes intra-group ($p < 0.05$)

$^{¥}$ Significant changes favoring EG

† Significant changes favoring CG

§ Non-significant changes between groups

Symbols of between-group comparisons are placed in EG rows

Discussion

This systematic review and meta-analysis examined the effectiveness of PRP in HOA patients in terms of pain and function at both mid- and long-term. Findings were limited by small sample size and the scarce number of trials. The superiority of PRP against included comparative interventions (HA or HA + PRP) remains questionable. Two studies [37, 40] showed no significant differences between groups, one study [38] reported better results for PRP treatment, and another article [39] found a better global effect of HA against PRP. However, the short-term effect of PRP on relieving pain may be remarkable. Although all of the studies showed early significant improvements in pain for both groups, PRP seemed to play an important role at early follow-ups; for instance, Battaglia et al. [37] found their peak improvements in VAS at 1- and 3-month follow-ups, similarly to Di Sante et al. [39] who, in fact, only found significant changes at 1-month follow-up.

Only two studies [37, 39] reported data regarding concentration of the PRP preparation, reaching concentrations of 600 and 100–150% respectively. Although potential therapeutic effect can be previously estimated to be greater as concentrations of PRP become higher, results did not support such statement.

As PRP injections are meant to interfere with catabolic and inflammatory events by releasing GFs and inflammation mediators, analysis of such markers may become relevant when correlating those properties with clinical outcomes. Only one

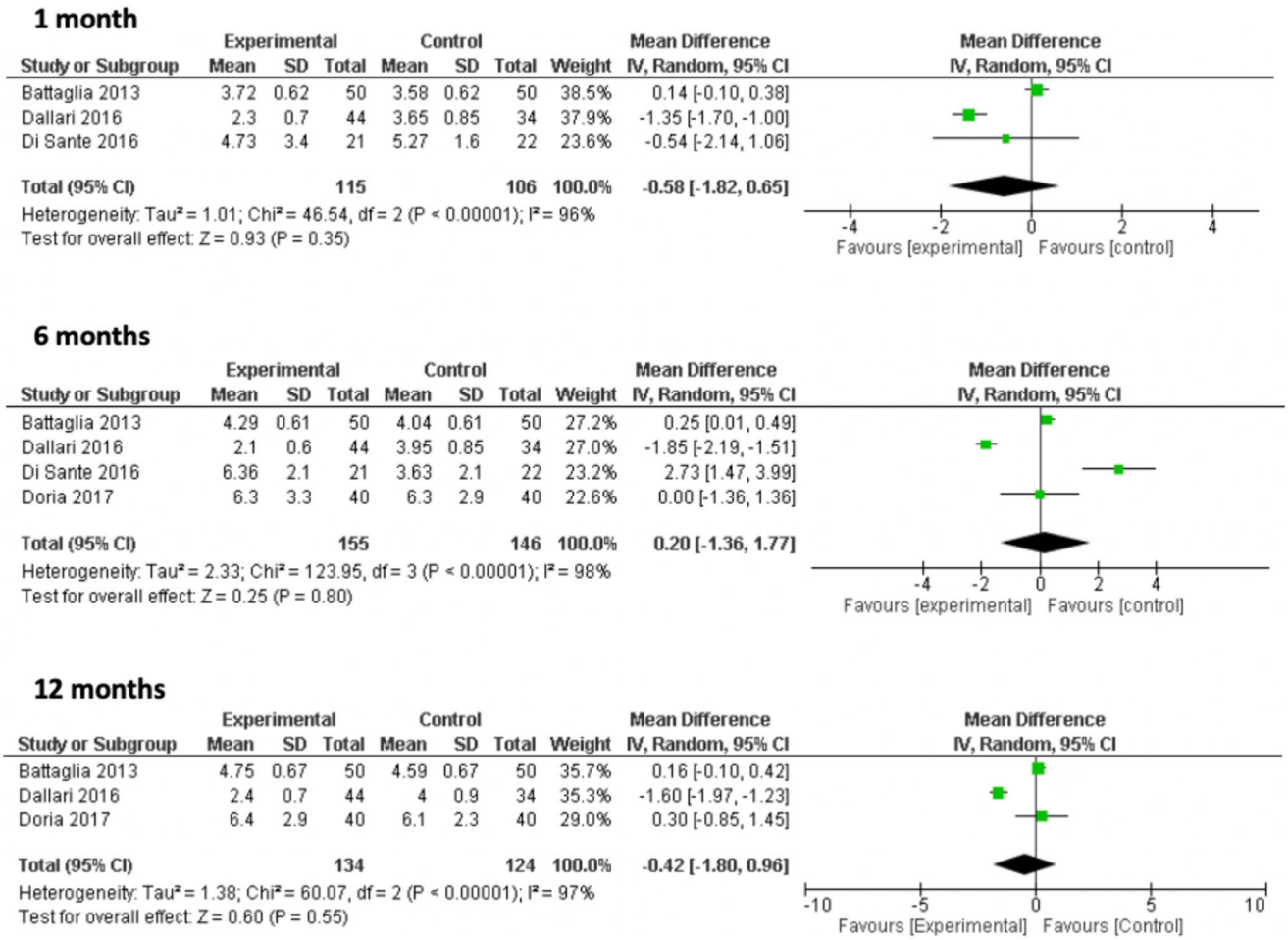

Fig. 2 Forest plot of VAS scores at 1-, 6-, and 12-month follow-ups

study [38] investigated such relation but in a reduced number of patients, finding relations between IL-10 and variations of the VAS score and quality of life. Although discrepancies found in patients' responses in other studies are related to different PRP procedures, the limited evaluated sample may have raised some difficulties when extrapolating the results to the general population.

Another commonly reported limitation was the absence of a true control group based on placebo or gold standard interventions, such as acetaminophen/paracetamol or NSAIDs combined with physical therapy and/or exercise, according to literature's current recommendations [41–43]. However, several reasons were suggested to justify the study designs: Battaglia et al. [37] stated that intra-articular injections of either lidocaine or saline may only act as partial placebo interventions as intra-capsular bleeding could lead to unavoidable biologic changes, thus reducing the possibilities of a pure sham effect; Dallari et al. [38], by their part, opted to provide subjects with a more clinically accepted treatment due to the invasive nature of injective procedures; and Di Sante et al. [39] considered HA injection as the "gold standard" therapy.

Subsequent follow-up interventions at the conclusion of the procedures also differed among studies. Although one study did not allow for any anti-inflammatory/analgesic drug intake [39] and another did not clarify such information [40], two studies indeed varied in their a posteriori recommendations. NSAID consumption 48 h after last injection was permitted by one study [37], and local application of ice was allowed by another [38]. Therefore, some reported outcomes may have been mistakenly interpreted as these anti-inflammatory effects could disguise those deriving from the main intervention.

Clarity and accuracy through the process of reporting results can lead to a better understanding of the issue under consideration. Given that the different scales (WOMAC and HHS) measure multiple outcome spheres (such as pain, function, or quality of life), more specific information from the general score could be extracted and separately analyzed in relation to these dimensions. Only two studies [39, 40] provided detailed data about each tool and its corresponding measured outcome, for instance, mentioning WOMAC subscales and differentiating pain and function domains in HHS scores.

Regarding gender, percentage of women in both experimental and control groups was reported to be under 50%. Since women are more likely to develop HOA, representative and heterogeneous recruitments of female subjects reflecting the epidemiologic reality and considering potential factors triggering HOA could be beneficial for a deeper understanding of the condition. However, samples of the included studies, although sufficient, were not probably high enough to signify a bias on this matter.

Strengths

This review has several methodological strengths. An a priori research design was employed since our protocol was previously published on PROSPERO repository. A systematic and transparent approach has been used to review the question due to this systematic review was adhered to PRISMA guidelines. A comprehensive, systematic literature search was implemented involving main electronic databases, with clear inclusion and exclusion criteria. Each reference has been independently considered by two of the authors according to these criteria, and so the quality of the included studies has been assessed. These independent approaches tend to reduce the risk of bias. Finally, quality of evidence assessments used to formulate review conclusions and the availability of studies that focused exclusively on HIP-OA-diagnosed patients should be considered as strong points. Although we have conducted a thorough literature search, potentially relevant studies might not have been identified. A built-in weakness with systematic reviews is that they may become outdated when new studies are published. This systematic review is up-to-date as of May 2019.

Limitations

We should recognize several modifications from the initial protocol registered in PROSPERO (CRD 42016042641), as follows: (1) we decided to clarify the isolation aspect of the PRP injection in at least one of the treatment arms; (2) PEDro scale for risk of bias assessment was replaced by the Cochrane risk of bias tool. Our search strategy was developed focusing specific keywords related to hip OA (i.e., "hip osteoarthritis," "hip joint," "platelet-rich plasma") and did not include any cartilage-related term alone, so some useful studies may have been missed.

Moreover, we note several limitations of this review. First, the number of included studies and the number of patients in those studies (4 and 334, respectively,) are relatively small. Second, the quality of a systematic review is affected by the quality of the primary data from the included studies. Considerable heterogeneity remains among included papers in quantitative analysis in terms of primary outcomes, doses and frequency of injections, used method to produce PRP, and control group. In spite of performing subgroup analysis at follow-up and unifying hip function scores, heterogeneity was ineffectively reduced, which is consistent with previous systematic reviews [27, 29, 44, 45]. Additionally, no PRP subdivision into different types was made, so that efficacy and safety of different modes of PRP interventions for HOA could not be emphasized. The overall quality of the evidence was found to be moderate to low in the included studies.

Finally, individual study authors were not contacted, being results reported in the review based uniquely on published data. Gray literature such as conference abstracts and dissertations was discarded for not containing enough data to evaluate study quality.

Conclusions

The results of this review suggest that PRP may be beneficial and safe for patients with HOA. PRP has been demonstrated to contribute to HOA symptoms at mid-term follow-up with moderate to significant improvements in pain and function when compared with other similar procedures. However, due to the scarce number of trials and the lack of homogeneity across studies, large randomized, high-quality studies become imperative to test whether PRP injections should be a routine part of management of patients with HOA.

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Data availability Not applicable.

Code availability Not applicable.

Compliance with ethical standards

Disclosures None.

Ethics approval and consent to participate Not applicable.

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