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EFFECTIVENESS OF PLATELET-RICH PLASMA IN THE MANAGEMENT OF HIP OSTEOARTHRITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Context: Hip osteoarthritis (HOA) is a chronic condition whose pathogenic agents usually rely on anatomical variability, but the evidence regarding other risk factors potentially influencing the disease is not totally clear. Platelet-rich plasma (PRP) becomes popular as a viable intervention in confronting its symptoms. **Objective**: To conclude a previously published systematic review protocol focusing on the effectiveness of the isolated effect of PRP against other procedures in the management of HOA. **Methods**: A research in Pubmed, ProQuest Health & Medical Complete, CINAHL, SPORT Discus and Cochrane Central Register of Controlled Trials databases was performed. Risk of bias was assessed with the Cochrane Risk of Bias Tool. **Results**: The selected studies (n=4) were randomized controlled trials and marked as "low risk of bias". Pain and function were assessed throughout the studies with VAS, WOMAC and HHS scores, obtaining better results at stages earlier than 3 months for both treatment groups with the exception of WOMAC score in one study, but 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. **Conclusions**: The safety and early effects of PRP showed improvements in pain and function in HOA, but its dominance against other procedures, particularly in longer evaluations, remains unclear. Further researches with high-quality designs and larger samples become imperative.

RESUMEN

Contexto: La osteoartritis de cadera es una condición crónica cuyos desencadenantes suelen relacionarse con variantes anatómicas, aunque la evidencia acerca de otros factores de riesgo no es del todo clara. El plasma rico en plaquetas (PRP) se populariza como intervención viable en el tratamiento de sus síntomas. **Objetivo**: Concluir un protocolo de revisión sistemática previamente publicado sobre la efectividad del tratamiento aislado con PRP frente a otros procedimientos en el manejo de la osteoartritis de cadera. **Métodos**: Se realizaron búsquedas en las bases de datos de Pubmed, ProQuest Health & Medical Complete, CINAHL, SPORT Discus y Cochrane Central Register of Controlled Trials. El riesgo de sesgo fue evaluado con la Cochrane RIsk of Bias Tool. **Resultados**: Los estudios seleccionados (n=4) fueron ensayos clínicos aleatorizados y calificados de "bajo riesgo de sesgo". Dolor y funcionalidad fueron

variables evaluadas mediante las escalas VAS, WOMAC y HHS, arrojando mejores resultados en fases tempranas menores de 3 meses en ambos grupos con la excepción de WOMAC en un estudio, aunque la superioridad del PRP fue únicamente confirmada en un estudio; los resultados entre 4 y 12 fueron diversos, con un solo estudio reportando cambios significativamente mejores para el PRP. **Conclusiones:** La seguridad y efectos a corto plazo del PRP mostraron mejoras en el dolor y la función, pero su preponderancia frente a los tratamientos comparativos, especialmente a más largo plazo, permanece en cuestión. Se necesitan más investigaciones con diseños de alta calidad y mayores muestras que respondan a estos interrogantes.

INTRODUCTION

Osteoarthritis (OA) is a chronic musculoskeletal condition which typically affects the knee and/or hip joints. It responds to a syndrome characterized by joint pain, stiffness and dysfunction, associated with joint degeneration and loss of articular cartilage[1]. Its 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 those with OA will complain about any movement impairment, and 25% are unable to perform normal daily activities of life[3]. In fact, the disability associated with OA 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].

Hip osteoarthritis (HOA) slightly differs from other sites of osteoarthritis, generally remaining behind knee OA due to its lower prevalence and less easiness in which OA can be screened by image[5]. In most cases, etiologic and pathogenic factors rely on anatomic variability, such as femoroacetabular morphology, and excessively abnormal shearing forces which subsequently generate a chronic inflammatory process[6]. Among the different risk factors leading to hip OA, both non-occupational and work-related causes can be found to have an implication on the development of the disease. Established non-occupational risk factors are the following:

- Genetic predisposition: twin and family studies estimate that the heritable component could rise up to 50 and 65%, stablishing also associations between general joint hypermobility and a decrease of cartilage matrix protein levels[7].
- Age: one of the stronger risk factor in all joints, it entails a direct relation with OA, probably by accumulating risk factors and normal biologic changes that occur as people age, such as cartilage thinning, oxidative damage and fragility[8].
- Gender: women are more likely to develop OA and also in more severe degrees. As time around menopause has been observed to present a higher prevalence of OA, studies have hypothesized that hormonal factors may be quite relevant and something to consider, although results on estrogen on OA from some studies have generated conflicting evidence[7].
- Obesity: traditionally recognized as a strong risk factor for OA, there is a consistent evidence supporting the relation between obesity and risk of bilateral hip OA and

potential future hip replacement interventions, probably due to the overloading component and the subsequent synovial joint collapse and failure of ligaments and other supporting structures[9].

- Hip injury: some evidence tend to link consequences of traumatic hip injuries (such as structural deformity) with increasing risk of later OA, although this relation is weaker compared to knee OA[10].
- Body mass index (BMI): having common points with obesity, there is a tendency of developing hip OA as BMI increases but, as stated before, the relationship is weaker than for knee OA[11].
- Physical activity/sports: there is also conflicting evidence about the role of activity and subsequent OA. Some studies show that general levels of physical activity, in contrast to sedentarism, increase the risk of hip and knee OA by themselves, not only remaining risky for professional athletes[12]. On the other hand, other studies have shown that recreational/moderate long-distance running is not associated with increased risk of OA[13].

Given the alleged role of mechanical loading as one potential factor of developing OA, occupational activities that increase the stress on the hip could plausibly explain the risk behind this pathology. Overall, there seem to be a consistency among different studies and a direct relation with heavy manual work and farming or construction activities. However, some risks when interpreting these results must be considered, since physically demanding jobs could bring workers to earlier medical care, thus overestimating disability risks in comparison with studies handling cases of surgical processes[14].

Although there is no cure for OA up to date, different treatment modalities focus on alleviating pain, maintaining or improving joint mobility and preventing functional decline, and they involve both operative and conservative approaches. Pharmacologic interventions include glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) or cartilage protective agents[15,16], and non-pharmacological options include physical therapy, exercise or patient education[15]. 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[17].

Platelet-rich plasma (PRP) is one such biological therapy gaining increasing popularity for the management of OA. Firstly described in the early 1970s, 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 probably promoting a favorably environment for soft tissue healing processes[18,19], first with an initial pro-inflammatory action[20] and followed by decreasing inflammatory molecules[21]. 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[22].

Preparation techniques can vary, and different protocols are currently used. Some controversy exists about the separation and centrifugation processes, and the concentration obtained by each method still differs, which has led to the commercialization of different PRP kits. Thus, the term "PRP" has been expanded to include other terms also related to autologous conditioned plasma (ACP)[23].

Regarding bioactivity of PRP, some studies have documented to contain more than 800 proteins which experiment reactions, such as phosphorylation, for several bioactive factors[24]. Platelets, apart from its coagulative and inflammation-regulatory effects, they also play a role in delivering active molecules (such as ascorbic acid, nucleotides or chemokines) and a wide variety of growth factors (GFs) with diverse contributions, like the following[25]:

- Platelet-derived growth factor (PDGF).
- Endothelial growth factor (EGF).
- Transforming growth factor β-I (TGFβ-I).
- Vascular endothelial growth factor (VEGF).
- Hepatocyte growth factor.
- Basic fibroblast growth factor (bFGF).

Hence, multifactorial action 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 are some of its reported effects[26]. 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 and elevate bone mass along with elevating TGFβ-I activity[27].

Regarding safety of PRP treatment, it is important to mention its antimicrobial effects, uncommonly associated with adverse effects like infection, bleeding, allergic reactions or temporary stiffness/soreness, normally lasting from less than a week and not being different from other intra-articular or peri-articular injective treatments[28].

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.

AIMS AND OBJECTIVES

Aims

Several systematic reviews study the effects of PRP injections in a wide variety of pathologies and tissues. Due to the increasing relevance and prevalence of OA in the general population, many clinical trials with different experimental designs begin to arise trying to go one step further and explain the benefits of this procedure. To our knowledge, no previous systematic reviews have been previously developed in order to analyze the effects of PRP in the treatment of hip OA. In an attempt to conclude a previously published systematic review protocol addressing this topic, the aim of our study is to systematically and critically review the existent literature evaluating the isolated effects of PRP in the management of hip OA against other therapeutic procedures.

Objectives

- Completing and concluding the previously published systematic review protocol addressing the management of hip OA with PRP treatment.
- Briefly summarizing the current background knowledge surrounding PRP and OA.
- Critically identifying up-to-date randomized controlled trials addressing hip OA with isolated PRP in at least one of the treatment arms.
- Evaluating internal validity by assessing risk of bias of the final selected articles.

- Organizing the extracted data regarding population's characteristics, PRP procedures and obtained results in the corresponding tables.
- Comparing the reported results, extracting general and specific conclusions about the use of PRP injections on hip OA, and developing, whether possible, a meta-analysis of any given outcome.
- Finding strength and limitations of the selected studies in order to guide and orient future investigations.

METHODS

This review has conformed to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[29]. The methodology was specified a priori through protocol registration with the PROSPERO International Prospective Register of Systematic Reviews[30], registration number CRD 42014010210.

Literature Search

Electronic resources were analyzed by the researchers using the Medical Subject Headings (MeSH) according to each database, which in detail classify and describe everything related to biomedicine. 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, followed by a secondary search to include additional records through hand search. Key terms used and combined in our search strategy was "osteoarthritis", "hip" and "platelet-rich plasma". In addition, systematic reviews and other reviews were thoroughly examined so no potential eligible articles were missed. A recognized expert in this field was consulted in attempt to identify any further published or unpublished studies.

Study Selection

Papers examining interventions based on PRP injections or any equivalent product (i.e., platelet-leucocyte gel, platelet concentrate or platelet gel) on patients with HOA and published after January 1973 were considered. In a first selection phase, title and abstract of all identified studies were independently screened for inclusion against the eligibility criteria.

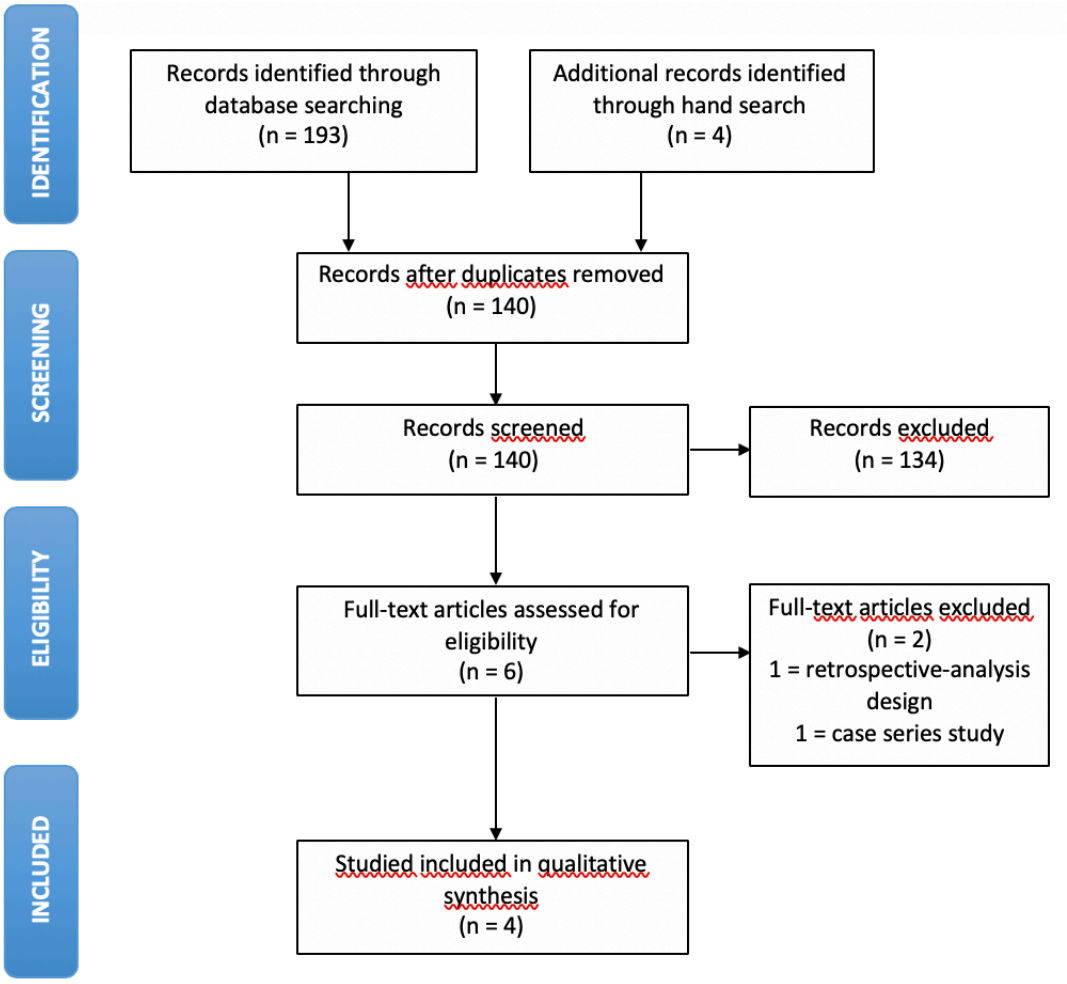
Inclusion Criteria

The articles finally included in this systematic revision were filtered depending on the following criteria: (1) studies written in English or Spanish; (2) studies design was RCT; (3) adult patients (>18 years) diagnosed with mild, moderate or severe HOA according to the American College of Rheumatology criteria [Altman et al., 1991]; (4) isolated PRP injections in at least one of the treatment arms; and (5) public and private practice as intervention settings.

Exclusion Criteria

Studies accomplishing at least one of the following statements were not included: (1) non-RCT design; (2) studies involving animal subjects, non-OA injuries, OA affecting other joints, children only; (3) intervention settings of acute rehabilitation, outpatient rehabilitation, and community integration; (4) non-isolated PRP treatment in any of the intervention groups; and (5) history of previous operative treatment for hip OA.

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



Data extraction

A qualitative synthesis comparing the results of the different articles was conducted. Data from studies was extracted from the studies regarding: 1) general information (authors and year of publication); 2) participants' characteristics; 3) main intervention -PRP injection-; 4) outcomes; and (5) 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. Disagreements between the reviewers were resolved by discussion and consensus. A meta-analysis of different VAS follow-ups was conducted according to the DerSimonian and Laird random-effects method[31] (Figure 2).

Risk of Bias Assessment

The risk of bias in the included randomized studies was independently undertaken by using the Cochrane Risk of Bias Tool[32]. High quality studies were defined as those which had a low risk of bias for four or more of the Cochrane Tool's domains. These domains based on: randomization method, allocation concealment, blinding of participants, blinding of outcome assessment, completeness of outcome data, selection data and other perceived bias, and each of the domains was marked as "low risk of bias" (LRB), "unclear risk of bias" (URB), and "high risk of bias" (HRB).

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 a further 2 studies, a total of 4 articles met inclusion criteria in qualitative synthesis[33–36].

Treatment Modalities

One of the studies compared PRP with hyaluronic acid (HA) in isolation and in combination with PRP[34], whereas other 3 studies compared PRP with HA[33,35,36].

Sample sizes

The average number of recruited patients was 83.5 and ranged from 43 to 111. The total follow-up of three studies[33,34,36] was 12 months and only one reduced that duration to 4 months[35].

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 Kellgreen and Lawrence (K&L) radiological grading scale/classification system by all authors. Table 2 gathers the distribution of hip OA grade. The most prevalent OA grade for hips receiving PRP treatment were reported to be grade III.

Risk of Bias 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 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. The two reviewers had initial agreement and reached consensus on all criteria.

Table 1. 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	LRB	LRB	HRB	HRB	LRB	LRB	LRB
Dallari et al., 2016	LRB	LRB	HRB	LRB	LRB	HRB	LRB
Di Sante et al., 2016	LRB	LRB	HRB	HRB	LRB	LRB	LRB
Doria et al., 2017	LRB	URB	HRB	LRB	LRB	LRB	LRB
Abbreviations: LRB, low risk of bias; HRB, high risk of bias; URB, unclear 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.

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.

Table 2. 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[33]	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[34]	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[35]	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[36]	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
Abbreviations: 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, Kellgreen-Lawrence Grade; NS, Non-Specified.

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 were variable among studies. PRP preparation techniques for every study are summarize 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 studied 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 Visual Analogic Scale (VAS)[33–36], Harris Hip Score (HHS)[33,34,36] and Western Ontario and McMaster Universities Arthritis Index (WOMAC) subscales (A-pain, B-stiffness, C-function)[34–36]. Three studies compared PRP versus HA[33,35,36], and one study included two control groups with subjects receiving HA and HA+PRP respectively[34].

Battaglia et al.[33] evaluated the effects of PRP in pain using VAS and HHS scores. Subjects were randomly allocated in PRP group and HA group, and all 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, 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.[34] 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.[35], 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.[36] 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-up 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-up 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-up in both groups.

Summarizing, early follow-up evaluations (at 1-[33,35], 2-[34] and 3-month[33] 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[35], where only VAS showed a significant improvement. These early evaluations were also the point when subjects improved the most in two studies[33,36]; however, the superiority of PRP against comparative treatments differed between studies: two articles[34,35] showed significantly better results than those reported in control groups ($p<0.05$); one study[33], 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-[35], 6- and 12-month[33,34,36] follow-ups after last injection) also revealed diverse results. One study[35] found that all WOMAC subscales and VAS score significantly improved only in HA group at 4-month follow-up ($p<0.01$); two studies[33,36] reported significant results for every outcome at 6- and 12-month follow-up in both treatment groups ($p<0.05$), without significant differences between them; and one study[34] showed significant improvements in favor of PRP group both in VAS score at 6- and 12-month follow-up ($p<0.01$) and in WOMAC score at 6-month follow-up against comparative treatments ($p<0.05$).

Secondary Outcomes

Growth Factors (GFs) and Outcomes

Influence of GFs and their relationship with outcomes over time was only evaluated by one study. Dallari et al.[34] 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

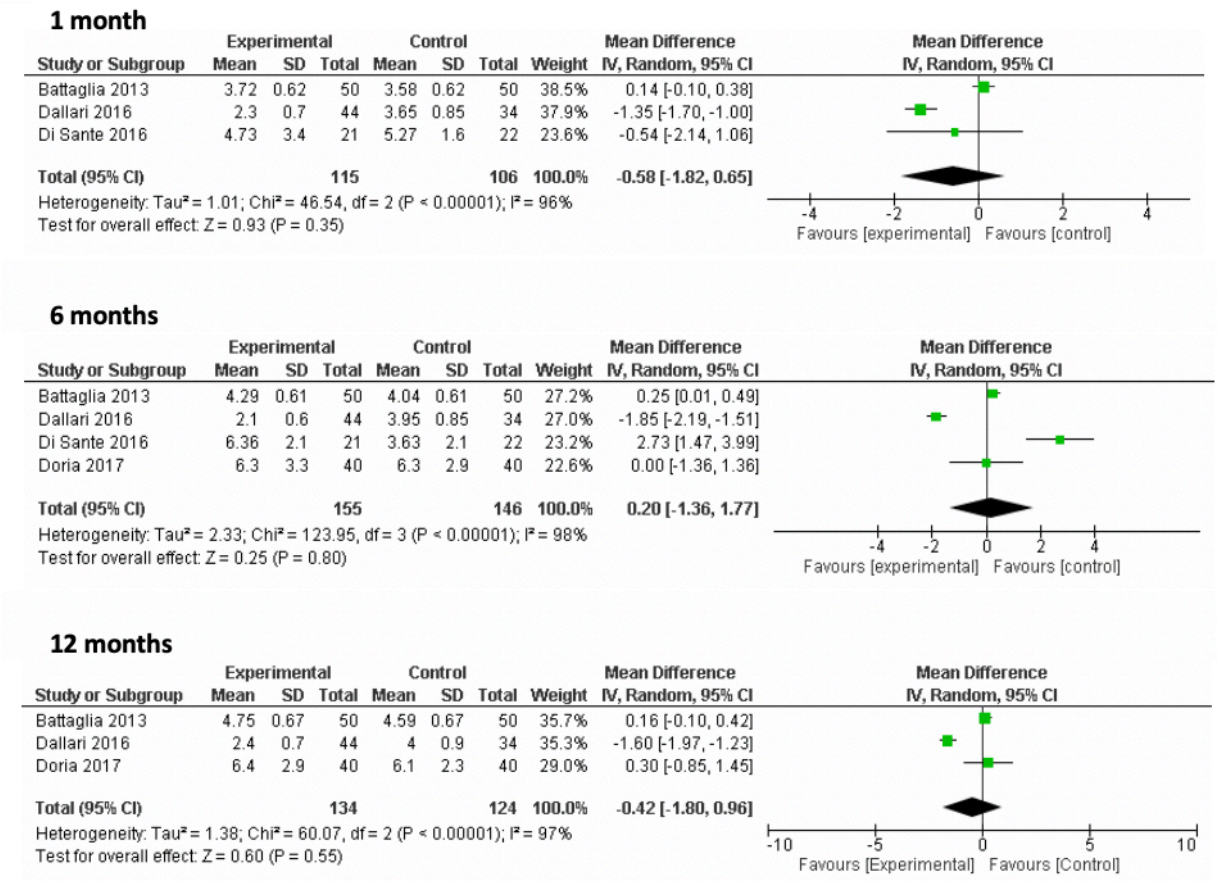
Safety of the injection technique, although generally mentioned in the included literature, was only statistically measured in one of the studies[36]. In this study, adverse events were also compared between PRP and HA treatments, showing the PRP group a significantly higher post-injective pain reaction ($p=0.043$). However, it ceased within few weeks without affecting the

long-term results and not reporting major complications neither at 6- or 12-month follow-up. Other studies, despite not being statistically analyzed, also reported some side effects. Battaglia et al.[33] found that one patient developed a superficial hematoma during the first infiltration due to transitional venous damage, but spontaneously resolved in two weeks.

OA Grade and Outcomes

Influence of OA grade in temporal variations of the outcomes was also considered in two studies. Battaglia et al.[33] 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.[34] claimed that OA grade was also considered to partially play a role in the effects of treatment type ($p=0.014$).

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



DISCUSSION

Strengths

This review has several methodological strengths. Ours is possibly the first attempt to systematically review the available literature for evaluating the effectiveness of PRP on hip OA. Moreover, an a priori research design was employed since our protocol was previously published on PROSPERO repository.

A systematic and transparent approach have 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 were replaced by 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.

This review has some major limitations. 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.

Beyond the methodologic quality, another possible limitation is the heterogeneity of the studies in terms of primary outcomes or treatment times. Moreover, we did not contact individual study authors, being results reported in the review based uniquely on published data. Grey literature such as conference abstracts and dissertations were discarded for not containing enough data to evaluate study quality.

The superiority of PRP against included comparative interventions (HA or HA+PRP) remains questionable. Two studies[33,36] showed no significant differences between groups, one study[34] reported better results for PRP treatment and other article[35] 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[33] found their peak-improvements in VAS at 1- and 3-month follow-ups, similarly to Di Sante et al.[35] who, in fact, only found significant changes at 1-month follow-up.

Only two studies[33,35] 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 study[34] 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[37–39]. However, several reasons were suggested to justify the study designs: Battaglia et al.[33] stated that intra-articular injections of either lidocaine or saline may only act as partial placebo interventions as intracapsular bleeding could lead to unavoidable biologic changes, thus reducing the possibilities of a pure sham effect; Dallari et al.[34], 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.[35] 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 allowed for any anti-inflammatory/analgesic drugs intake[35] and another did not clarify such information[36], two studies indeed varied in their a posteriori recommendations. NSAIDs consumption 48 hours after last injection was permitted by one study[33], and local application of ice was allowed by another[34]. 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[35,36] 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.

CONCLUSIONS

This study has shown that PRP injections constitute a safe treatment procedure which has remarkable and significant effect on improving pain and function at early stages of 3 months or less, although one study did not report significant differences between PRP and HA. Longer-term assessments showed diverse results, and despite being one study with significant results in favor of PRP, such improvements tended to be significantly comparable between groups or better for HA.

Further studies analyzing proinflammatory and anti-inflammatory markers are needed, as well as studies comparing the results with a true placebo group and avoiding post-intervention anti-inflammatory procedures such as NSAIDs or ice, which could be relevant in order to prevent parallel effects lessening the reliability of the obtained results. In addition, detailed and more specific report of the scores related to the different scales/subscales (i.e., WOMAC-A, WOMAC-B and WOMAC-C) would be beneficial for deeper and more comprehensive meta-analysis and comparison purposes.

Large randomized, high-quality studies become imperative to test whether injections should be a routine part of management of patients with HOA.

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APPENDIX

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 minutes) -second at 3500 rpm (10 minutes)	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 minutes) -second at 3400 rpm (15 minutes)	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 minutes 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 minutes) -second at 3400 rpm (15 minutes)	4 units of 5 mL each	-30°C	NR	NR	NR	Frozen sample	NR

Abbreviations: 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).

Table 4. PRP treatment proceedings/features

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 hours 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
Abbreviations: US, Ultrasound; NR, Non-Reported; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs							

Table 5. Outcomes and results

Authors, Year	***Intervention Groups***	***Outcomes***	***Follow-ups (months)***						
			Baseline	***1***	***2***	***3***	***4***	***6***	***12***
Battaglia et al., 2013	EG: PRP	VAS HHS	5.47±0.50 58.11±3.93	3.72 ± 0.62 ‡ § 73.72±4.57 ‡ §	-	3.80 ± 0.61 ‡ § 72.90±4.36 ‡ §	-	4.29 ± 0.61 ‡ § 70.23±4.53 ‡ §	4.75 ± 0.67 ‡ § 65.73±5.13 ‡ §
	CG: HA	VAS HHS	5.97±0.49 62.90±3.92	3.58±0.61 ‡ 78.02±4.57 ‡	-	3.80±0.60 ‡ 77.23±4.37 ‡	-	4.04±0.61 ‡ 75.79±4.53 ‡	4.59±0.67 ‡ 72.55±5.13 ‡
Dallari et al., 2016	EG: PRP	VAS HHS WOMAC	NR NR NR	-	2.30±0.60 ‡ ¥ NR ‡ § 73±5 ‡ ¥	-	-	2.10±0.60 ‡ ¥ NR ‡ § 72±5 ‡ ¥	2.40±0.70 ‡ ¥ NR ‡ § NR ‡ §
	CG1: PRP+HA	VAS HHS WOMAC	NR NR NR	-	3.50±0.90 ‡ NR ‡ 59±0.60 ‡	-	-	3.50±0.90 ‡ NR ‡ 59±6 ‡	3.80±0.90 ‡ NR ‡ NR ‡
	CG2: HA	VAS HHS WOMAC	NR NR NR	-	3.80±0.80 ‡ NR ‡ 59±0.60 ‡	-	-	4.40±0.80 ‡ NR ‡ 59±0.50 ‡	4.20±0.80 ‡ NR ‡ NR ‡
Di Sante et al., 2016	EG: PRP	VAS WOMAC-A WOMAC-B WOMAC-C	7.08±2 58.89±22 53.72±22.7 59.87±22.5	4.73±3.40 ‡ 44.27±28.80 46.42±27.50 49.13±29.10	-	-	6.36±2.10 † 53.47±22.30 † 47.22±22.70 † 50.80±22.80 †	-	-
	CG: HA	VAS WOMAC-A WOMAC-B WOMAC-C	6.32±1.70 42.36±20.50 57.65±26.20 45.83±21.70	5.27±1.60 29.60±13.40 47.69±21.20 39.13±17.20	-	-	3.63±2.10 ‡ 19.90±11.40 ‡ 32.91±20.60 ‡ 28.39±17.20 ‡	-	-

Doria et al., 2017	EG: PRP	VAS HHS WOMAC-A WOMAC-B WOMAC-C	7.50±2.10 64±10.30 23.70±2.10 3.80±4.10 29.40±2.60	-	-	-	-	6.30±3.30 ‡ § 75±11.50 ‡ § 7.80±3.80 ‡ § 2.10±3.60 ‡ § 12.30±3.60 ‡ §	6.40±2.90 ‡ § 78±11.30 ‡ § 7.40±2.50 ‡ § 2±4.20 ‡ § 12±3.80 ‡ §
	CG: HA	VAS HHS WOMAC-A WOMAC-B WOMAC-C	7.80±1.90 62±9.80 24±1.90 4.30±5.30 28.50±2.50	-	-	-	-	6.30±2.90 ‡ 74±12.30 ‡ 9.70±4.50 ‡ 3.10±3.20 ‡ 11.30±4.50 ‡	6.10±2.30 ‡ 75±11.40 ‡ 9±5.60 ‡ 3.10±4.30 ‡ 10.90±4.20 ‡

Values are mean ± SD or as otherwise indicated.
Abbreviations: EG, Experimental Group; CG, Control Group; PRP, Platelet-Rich Plasma; HA, Hyaluronic Acid; NR, 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.

SEARCH STRATEGIES OF THE DIFFERENT DATABASES:

PUBMED (n=80)

1. "Osteoarthritis"[Mesh]
2. "Osteoarthritis, Hip/etiology"[Mesh] OR "Osteoarthritis, Hip/etiology"[Mesh] OR "Osteoarthritis, Hip/pathology"[Mesh] OR "Osteoarthritis, Hip/rehabilitation"[Mesh] OR "Osteoarthritis, Hip/therapy"[Mesh]
3. #1 OR #2
4. "Hip"[Mesh]
5. "Hip Joint"[Mesh]
6. #4 OR #5
7. "Platelet-Rich Plasma"[Mesh]
8. "Injections, Intra-Articular"[Mesh]
9. "PRP"[mp]
10. #7 OR #8 OR #9
11. #3 AND #6 AND #10

Filters: Humans

PROQUEST HEALTH & MEDICAL COMPLETE (n=85)

1. MESH.EXACT.EXPLODE("Osteoarthritis:C.05.799.613") OR MESH.EXACT.EXPLODE("Osteoarthritis:C.05.550.114.606") OR MESH.EXACT("Osteoarthritis, Hip -- epidemiology") OR MESH.EXACT("Osteoarthritis, Hip -- etiology") OR MESH.EXACT("Osteoarthritis, Hip -- pathology") OR MESH.EXACT("Osteoarthritis, Hip -- rehabilitation") OR MESH.EXACT("Osteoarthritis, Hip -- therapy") OR MESH.EXACT("Osteoarthritis, Hip -- diagnosis")
2. MESH.EXACT("Hip Injuries") OR MESH.EXACT("Hip") OR MESH.EXACT("Hip Joint")
3. (MESH.EXACT("Platelet-Rich Fibrin") OR MESH.EXACT("Injections, Intra-Articular") OR MESH.EXACT("Injections") OR MESH.EXACT("Platelet-Rich Plasma")) OR PRP
4. #1 AND #2 AND #3

Filters: Humans

CINAHL (n=20)

1. MH "Osteoarthritis, Hip"
2. MH "Arthritis"

3. “Hip osteoarthritis”
4. #1 OR #2 OR #3
5. MH “Hip”
6. MH “Hip Joint”
7. #5 OR #6
8. MH “Platelet-Rich Plasma”
9. MH “Platelet-Derived Growth Factor”
10. “PRP”
11. MH “Injections, Intraarticular”
12. #8 OR #9 OR #10 OR #11
13. #4 AND #7 AND #12

SPORT DISCUS (n=7)

1. DE “Osteoarthritis”
2. “Hip osteoarthritis”
3. DE “Arthritis”
4. #1 OR #2 OR #3
5. DE “HIP joint”
6. DE “HIP joint injuries”
7. DE “HIP joint diseases”
8. #5 OR #6 OR #7
9. DE “PLATELET-derived growth factor”
10. DE “PLATELET-rich plasma”
11. “PRP”
12. DE “Injections”
13. #9 OR #10 OR #11 OR #12
14. #4 AND #8 AND #13

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS (n=1)

1. MeSH descriptor: [Osteoarthritis, Hip] explode all trees
2. MeSH descriptor: [Hip Joint] explode all trees
3. MeSH descriptor: [Hip] explode all trees
4. MeSH descriptor: [Platelet-Rich Plasma] explode all trees
5. MeSH descriptor: [Platelet-Derived Growth Factor] explode all trees

6. MeSH descriptor: [Injections, Intra-Articular] explode all trees
7. "PRP"
8. #1 AND (#2 OR #3) AND (#4 OR #5 OR #6 OR #7)