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PRP for Degenerative Cartilage Disease: A Systematic Review of Clinical Studies

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Abstract

Objective: To explore the utilization of platelet-rich plasma (PRP) for degenerative cartilage processes and evaluate whether there is sufficient evidence to better define its potential effects. *Design*: Systematic literature reviews were conducted in PubMed/MEDLINE and Cochrane electronic databases till May 2015, using the keywords "platelet-rich plasma OR PRP OR autologous conditioned plasma OR ACP AND cartilage OR chondrocyte OR chondrogenesis OR osteoarthritis (OA) OR arthritis." *Results*: The final result yielded 29 articles. Twenty-six studies examined PRP administration for knee OA and 3 involved PRP administration for hip OA. The results included 9 prospective randomized controlled trials (RCTs) (8 knee and 1 hip), 4 prospective comparative studies, 14 case series, and 2 retrospective comparative studies. Hyaluronic acid (HA) was used as a control in 11 studies (7 RCTs, 2 prospective comparative studies, and 2 retrospective cohort). Overall, all RCTs reported on improved symptoms compared to baseline scores. Only 2 RCTs—one for knee and one for hip—did not report significant superiority of PRP compared to the control group (HA). Nine out of 11 HA controlled studies showed significant better results in the PRP groups. A trend toward better results for PRP injections in patients with early knee OA and young age was observed; however, lack of uniformity was evident in terms of indications, inclusion criteria, and pathology definitions in the different studies. *Conclusion*: Current clinical evidence supports the benefit in PRP treatment for knee and hip OA, proven to temporarily relieve pain and improve function of the involved joint with superior results compared with several alternative treatments. Further research to establish the optimal preparation protocol and characteristics of PRP injections for OA is needed.

Keywords

platelet-rich plasma, PRP, osteoarthritis, cartilage, hyaluronic acid, injections

Introduction

Background

Degenerative osteoarthritis (OA) is the most common form of arthritis and a major public health problem worldwide. It affects nearly 27 million adults in the United States alone.[1] Often causing pain, loss of function, and disability, it has a substantial social impact due to the rising mean age of the population, increasing rates of obesity, and a growing emphasis on physical activity in all age groups.[2] Attempts to analyze and understand the biology of this disease have not yet led to satisfactory results. OA is regarded as the result of a long chain of events; however, some parts in that chain are still a mystery and uncertainty exists regarding which part of this process should be targeted in order to inhibit and prevent disease progression. Cartilage possesses limited regeneration properties. Joint tissue damage and OA may result from loss of proper tissue homeostasis due to trauma or chronic repetitive overload, but could also be the result of metabolic and biological predispositions.[3] Numerous approaches have been proposed as noninvasive treatment options[4]; however, none has shown any distinct ability to change the natural history of the disease. The fact that current conservative OA therapies are unable to supply consistent satisfying results is attributed mainly to insufficient understanding of the molecular basis of

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disease development and progression, as well as the lack of dynamic biomarkers that might reflect specific biological or pathological processes. There are currently no disease modifying medical interventions for OA, and treatments are primarily aimed at symptom relief.[5] In recent years, research efforts have shifted toward identifying key biochemical pathways that can be targeted therapeutically through biological intervention. One of the major foci of research in the past decade has been platelet-rich plasma (PRP), drawing much attention as an innovative and promising therapeutic modality. PRP therapies are considered a major potential breakthrough in the treatment of many medical conditions and are currently one of the hottest topics in regenerative medicine. Among these, PRP has emerged as a biological therapy for the treatment of cartilage injuries and for intraarticular application to address knee pain. The purpose of this study was to systematically review the scientific evidence for utilization of PRP in pathologic processes of cartilage and as a potential addition to the management strategy algorithm for OA. Using the existing data, our aim was to explore the rationale behind the utilization of PRP in pathologic degenerative cartilage processes and evaluate whether there is sufficient evidence to better define its potential effects.

Rationale behind the Use of PRP for Degenerative Cartilage Disease

PRP is defined as a biological therapeutic modality consisting of preparations containing a supraphysiological concentration of platelet and plasma proteins that accelerate the repair process by direct and indirect mechanisms. The aim of this treatment is to improve the reparability of endogenous cells. It is based on the intraarticular delivery of autologous platelet-rich preparations containing a large pool of growth factors and proteins stored in the alpha-granules of platelets. These growth factors and proteins, which have been implicated in tissue repairing mechanisms and have been found to take part in the regulation of articular cartilage,[6] are aimed at stimulating repair and replacement of damaged cartilage. Numerous growth factors in PRP stimulate cartilage matrix synthesis and counteract the effects of catabolic cytokines such as interleukin-1 and tumor necrosis factor-α. Growth factors, as a pool, have been found to possess synergistic effects on cartilage matrix synthesis[7,8] and are known to induce further growth factor protein production by neighboring articular chondrocytes.[9] Basic science evidence supports the therapeutic potential of PRP. Chondrocytes treated *in vitro* with releasate from thrombin-clotted leukocyte-PRP (L-PRP)[10] resulted in significantly increased cell proliferation, synthesis rate, and accumulation of glycosaminoglycans and collagen type II (COL2) compared with controls.[11] In another study, human OA chondrocytes were removed from patients undergoing total hip arthroplasty, and PRP application induced the expression of proteins involved in chondrocytic differentiation compared with platelet poor plasma (PPP) and fetal bovine serum.[12] In this study, PRP was shown to be more effective than PPP or fetal bovine serum at increasing cell proliferation and inducing expression of genes associated with normal chondrocyte phenotype, including aggrecan and Sox-9 with sustained but not increased levels of COL2. Other basic science research demonstrated that PRP causes inhibition of the transactivating activity of nuclear factor-κB (NF-κB) and decreased expression of cyclooxygenase-2, which are important inflammatory regulators.[13] These findings suggest that PRP has the ability to stimulate local host cartilage and improve repair. Anitua *et al*. examined the effect of a platelet-derived preparation rich in growth factors (PRGFs) in OA synovial cell biology and revealed the ability of PRGF to stimulate HA synthesis, driving the secretion of HA by the synovial fibroblasts.[14] Synovial cells were isolated from 10 osteoarthritic patients and cultured in serum-free media (basal conditions) and exposed to either a platelet-poor preparation or PRGF (no or very low leukocyte penetration) for 72 hours. Cells activated with interleukin-1 for 48 hours were also exposed to PRGF. They found that PRGF significantly enhanced HA secretion compared with platelet-poor preparations. PRGF also significantly enhanced the secretion of HA induced by interleukin-1 activation, suggesting that pure platelet rich plasma could serve to induce chondroprotection and joint lubrication after intraarticular application even in the face of inflammation. These data support the therapeutic potential for PRP in the articular environment with anabolic effects on cartilage, mesenchymal stem cells, and synovial coverage.

Methods

Two independent reviewers performed a search using the PubMed/MEDLINE and Cochrane electronic databases till May 2015. Combinations of the terms "platelet-rich plasma OR PRP OR autologous conditioned plasma OR ACP AND cartilage OR chondrocyte OR chondrogenesis OR osteoarthritis OR arthritis" were used. Our inclusion criteria were studies evaluating the effect of PRP or any blood product with platelet concentration higher than baseline values published in peer-reviewed journals in the English language. We included different variations of PRP preparations in this study: activated and nonactivated PRP, PRP releasate, and PRP gels. Of all the articles, we selected only articles reporting on clinical studies which had utilized PRP, PRGF, or autologous conditioned plasma (ACP) for the treatment of degenerative cartilage pathology or OA of the knee or hip joint in humans and those articles that were published in the English language. Exclusion criteria were (1) animal studies; (2) patients with previous surgical intervention (i.e., total knee arthroplasty or anterior cruciate ligaments reconstruction); (3) articles involving nonosteoarthritic indications (osteonecrosis, osteochondral lesions, etc.); and (3) articles not published in English. In addition, articles that used PRP as

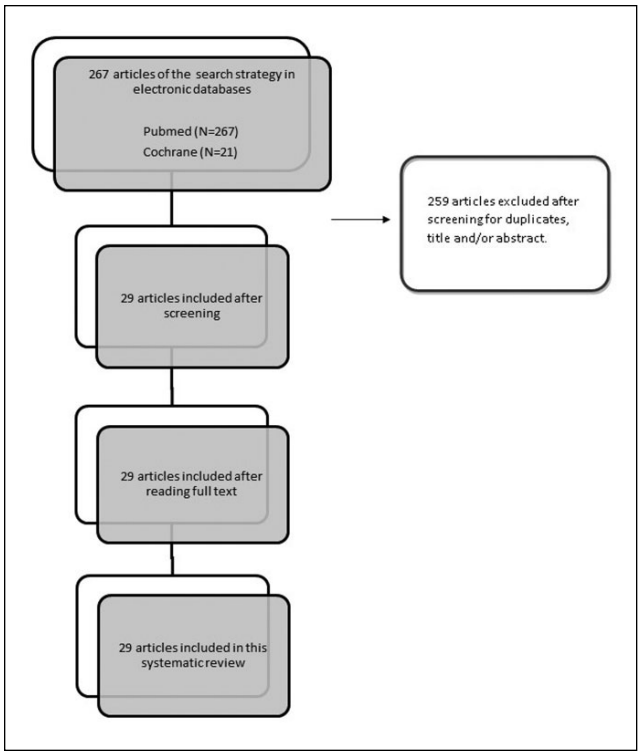

Figure 1. Study flow diagram.

a supplemental treatment to alternative modalities like bone marrow aspirate concentrate, scaffold-based cartilage repair, and mesenchymal stem cells were also excluded, as well as articles that included PRP as augmentation for different cartilage-related procedures (microfractures, cartilage implantation). Reference lists of included studies were also reviewed to ensure that no relevant articles were overlooked/missed. Review articles, expert opinions, case reports, and letters to editors were excluded from this review. Two authors performed the literature search, and 4 authors independently reviewed the search results. For the search results, articles titles and abstracts were reviewed, and potentially eligible studies received full-text review. Final agreement on inclusion was discussed among all authors, and the main author had the definitive decision vote in controversial cases. The initial search included 288 articles, from which 259 were excluded after screening for duplicates, title, and/or abstract. The final result yielded 29 articles (**Fig. 1**) in which PRP was a prime treatment and are described in brief in **Tables 1** and **2**.

Results

The results of our systematic review yielded 29 clinical studies (**Tables 1** and **2**). The majority of these studies (26) examined PRP administration for knee OA, while only 3 of the studies involved PRP administration for hip OA. The results included 9 prospective randomized controlled trials (RCTs), 4 prospective comparative studies, 14 case series, and 2 retrospective comparative studies. One of the studies, by Hart *et al*., was not clear with regard to whether a randomization process was involved and was therefore regarded as a prospective comparative study. Eight of the RCTs were conducted for knee OA and 1 for hip OA. Hyaluronic acid was used for the control groups in 7 RCTs, saline was used in 1 study, and an exercise program was used in 1 study. In the prospective comparative studies, HA was used for the control group in 2 studies, mesocaine was used in 1 study,[24] and in another study[19] the control group consisted of knees not receiving a second cycle of PRP injection at the completion of 1 year from first cycle. In the retrospective comparative studies group HA was used for the control group.

Age range in the studies was wide and not uniform. Various studies included patients as young as 18 years and as old as 85 years, with different age ranges. Four studies did not report age range.

Nineteen studies used the Kellgren Lawrence scale for the quantification of OA changes of which 7 studies included patients with Kellgren Lawrence grades 0 to 4, and 6 studies included patients with Kellgren Lawrence grades 0 to 3. Three studies used the Outerbridge condromalacia scale, while 1 study used the Ahlback scale, and 5 studies did not report the OA scale used. Within the RCTs group, 4 used the Kellgren Lawrence scale, 1 used the Ahlback scale, and the rest did not report the usage of any scale.

The follow-up period in the different studies ranged from 5 weeks to 24 months, with the majority of studies reporting outcomes with a follow-up period of 12 months (13 studies) and 6 months (12 studies). Only 2 studies reported a follow-up of 24 months.

The studies included in this review vary in the PRP preparation method and different production techniques yielding different resulting preparations. Twelve different preparation techniques—commercial and independent noncommercial methods—were used in the different studies. Table 3 summarizes the different types of solutions used in the studies included in this systematic review according to currently used classification systems.

Platelet concentration in these studies ranged between 1.3 times to 8 times the blood concentration, with the majority ranging between 2 and 4 times the blood concentration. Sixteen studies reported use of an activator prior to injection, and 14 of these studies used calcium chloride 10%. Fourteen studies used white blood cell (WBC)–containing preparations, 5 of which studies reported the use of PRP preparations with WBC content above blood concentration (1.2 to 4.7 times the blood concentration). Thirteen studies used WBC-free or minimal WBC preparations. Two studies did not report on WBC content.

Table 1. Clinical Studies.

Authors	Diagnosis	Study Design	Age Group	PRP Preparation (Number of Injections and Intervals)	Control Group (Number of Injections and Intervals)	Leucocytes	Activator	Follow-Up	Outcome Measures	Adverse Effects
Raeissadat *et al.*[15] (2015)	Knee OA, Kellgren-Lawrence grades 1-4	Randomized controlled clinical trial (160 patients)	40-70 years	Rooyagen Kit for PRP—concentrations of 4 to 6 times (n = 87), 2 intraarticular injections at 4-week interval	HA group. Hyalgan (n = 73), 3 doses of intraarticular injection at 1-week interval	PRP containing leukocytes	No activator	12 months after treatment	WOMAC and SF-36 questionnaires	No adverse reactions
Raeissadat *et al.*[16] (2014)	Knee OA, Kellgren-Lawrence grades 1-4	Randomized controlled clinical trial. Not blinded. 31 patients in the PRP group and 31 patients in the control group.	44-67 years	Rooyagen Kit for PRP - concentrations of x 4-6. Two intra-articular injections at 4-week interval. + Exercise.	Exercise and acetaminophen 500 mg (without codeine). No injections.	PRP containing leukocytes	No activator.	6m after treatment	WOMAC and SF-36 questionnaires	No adverse reactions
Guler *et al.*[17] (2014)	Knee OA, Kellgren-Lawrence grades 1-2	Retrospective case series; 132 patients; 63 patients (86 knees) were in the HA group and 69 patients (89 knees) were in the PRP group	46-63 years	Independent technique; 3 intraarticular injections at 1-week intervals	HA group. Ostenil plus 40 mg/2.0 mL (Bio-gen, TRB Chemedica SA, Switzerland); 3 intraarticular injections at 1-week intervals	Leucocyte rich PRP	NA	2, 6 months after treatment	Knee Society's Knee Scoring System (KSS) and the visual analog scale (VAS) scoring system	No adverse reactions
Mangone *et al.*[18] (2014)	Knee OA, Kellgren-Lawrence grades 2-3	Prospective case Series; 72 patients	50-85 years	Regen Kit Athena for PRP; 3 injections; 3-week interval	None	Leucocyte rich PRP	Calcium gluconate	Baseline, 1, 3, 6, 12 months after last injection	WOMAC scale for the knee, VAS at rest and VAS in movement	No adverse reactions
Gobbi *et al.*[19] (2014)	Early knee OA. Kellgren-Lawrence grades 1-2	Prospective, randomized study initiated in 2009; 50 knees were randomly selected from 119 knees and received a second cycle of PRP injection at the completion of 1 year from first cycle	40 and 65 years	Regen ACR-C. A cycle consisted of 3 injections, each given at a monthly interval	Knees received only first cycle of PRP	Leucocyte poor PRP	NA	Baseline, 12, 18, and 24 months after treatment	KOOS,VAS, Tegner and Marx scoring systems	No adverse reactions
Filardo *et al.*[20] (2014)	Knee OA, Kellgren-Lawrence grades 0-4	Therapeutic case series of 51 knees; 2 interventional groups; early-moderate OA (K-L 0-3) in 41 knees vs. severe OA (K-L 4) in 10 knees; both groups received 3 injections of PRP	Mean age 59 years, range: 20-87 years	ACP Kit (Arthrex Inc). 3 weekly intraarticular injections of PRP	2 interventional groups: early-moderate OA (K-L 0-3) vs. severe OA (K-L 4); both received the same PRP protocol	Leucocyte poor PRP	NA	Mean follow-up of 14.5 months (range: 6-24 months)	IKDC-Subjective, EQ-VAS, Tegner, and KOOS scores	Mild pain and/or slight swelling were reported which resolved spontaneously within 24-48 hours
Battaglia *et al.*[21]	Hip OA	Randomized controlled clinical trial (100 patients)	Mean age: 53 ± 12, range: 25-76 years	Independent technique	HA (Hyalubrix) administered via intraarticular ultrasound-guided injections	PRP containing leukocytes	Calcium chloride	Baseline, 1, 3, 6, and 12 months after treatment	the Harris Hip Score (HHS) and VAS	

(continued)

Table 1. (continued)

Authors	Diagnosis	Study Design	Age Group	PRP Preparation (Number of Injections and Intervals)	Control Group (Number of Injections and Intervals)	Leucocytes	Activator	Follow-Up	Outcome Measures	Adverse Effects
Vaquerizo *et al.*[22] (2013)	Knee OA, Kellgren-Lawrence grades 2-4	Multicenter, randomized controlled, clinical trial (96 patients: 48 in each group)	>50 years	PRGF-Endornet (3 injections of 8 mL at 1-week intervals)	Durolane HA 48 patients (1 injection)	Avoided leucocyte pick up	Calcium chloride	Baseline, 6 months, and 12 months after treatment	WOMAC and Lesquene scores; OMERACT-OARSI responders	Mild postinjection pain after PRGF (8 patients); mild postinjection pain after Duralane (6 patients); Pseudo-septic reaction after Duralane (2 patients)
Patel *et al.*[23] (2013)	Early OA	Randomized, controlled trial (148 knees)	Range: 33-80 years	Independent technique: single injection—52 knees; 2 injections (3 weeks apart)—50 knees	Saline injections (46 knees)	WBC filtered PRP	NA	6 weeks, 3 months, and 6 months after treatment	WOMAC and VAS scores	Nausea and dizziness in 22.2% and 44% patients in single and double injection groups, respectively
Hart *et al.*[24] (2013)	Grade 2 and 3 chondromalacia	Prospective case series (50 patients)	Range: 31-75 years	Independent technique: (2-2.5 fold platelet conc.) 9 injections in 1 year	None	NA	NA	Baseline and 12 months	Lysholm, Tegner, IKDC, Cincinnati scores, and MRI with a 12-month follow-up	No adverse effects
Torrero *et al.*[25] (2013)	Grade 1-3 Outerbridge chondropathy	Prospective case series (30 patients)	18-65 years	GPS mini set (BIOMET) 1 intraarticular injection	None	NA	Calcium chloride	Baseline, 1, 3, and 6 months after treatment	KOOS and VAS scores	No severe adverse reactions
Jang *et al.*[26] (2013)	Degenerative OA	Prospective case series (65 patients)	NA	Independent technique; 1 intraarticular injection	None	NA	NA	Baseline, 1, 3, 6, 9, and 12 months after treatment	IKDC and VAS scores	No severe adverse reactions
Say *et al.*[27] (2013)	Symptomatic (pain) mild to moderate osteoarthritis (Kellgren-Lawrence grades 1-3)	Prospective study,90 patients	47-63 years	(PRGF)[a]: a single 2.5-mL PRP injection	3 Injections of LMW hyaluronic acid at weekly intervals	Leucocyte poor PRP	Calcium chloride	Baseline, 3 and 6 months after treatment	KOOS and VAS scores	No adverse reactions
Halpern *et al.*[28] (2013)	Symptomatic early knee OA (Kellgren-Lawrence grades 0-2)	Prospective case series (22 patients)	30-70 years	MTF Cascade system; a single 6-mL PRP injection	None	NA	Calcium chloride	Baseline, 1 week, 1, 3, 6, 12 months after treatment; MRI follow-up at 12 months	WOMAC and VAS scores, and MRI at 1 year	No adverse reactions

(continued)

Table 1. (continued)

Authors	Diagnosis	Study Design	Age Group	PRP Preparation (Number of Injections and Intervals)	Control Group (Number of Injections and Intervals)	Leucocytes	Activator	Follow-Up	Outcome Measures	Adverse Effects
Gobbi *et al.*[29] (2012)	Symptomatic knee OA (Kellgren-Lawrence grades 1-3)	Prospective case series (50 patients)	40-70 years	Regenlab-ACR C (2 intraarticular injections at monthly intervals)	None	Leucocyte poor PRP	None	Baseline, 6 and 12 months after treatment	VAS, IKDC Subjective, KOOS, and Tegner scores	No adverse reactions
Filardo *et al.*[30] (2012)	Symptomatic knee degenerative lesions and OA (Kellgren-Lawrence grades 0-4)	Prospective clinical study (144 patients)	30-80 years	Independent technique: single spin preparation (PRGF): 72 patients (3 injections); double-spinning preparation: 72 patients (3 injections)	None	PRP with leucocytes	NA	Baseline, 2, 6, and 12 months after treatment	IKDC, EQ-VAS, and Tegner scores	More pain reaction and swelling following PRP injection compared to PRGF
Napilitano *et al.*[31] (2012)	Knee OA (Kellgren-Lawrence grades 1-3 and Outerbridge grades 1-2)	Prospective case series (27 patients)	(18-81 years)	RegenLab 3 injections of PRP at weekly intervals	None	Leucocyte poor PRP	Calcium gluconate	1 week and at 6m after treatment	NRS and WOMAC scores	No adverse effects
Spakova *et al.*[32] (2012)	Knee OA (Kellgren-Lawrence grades 1-3)	Prospective, comparative study	19-77 years	Independent technique: 3 injections of PRP at weekly intervals (4.5-times increase in platelet concentration)	3 injections of HA at weekly intervals	Leucocyte rich PRP	NA	3 and 6 months after treatment	WOMAC and the 11-point pain intensity Numeric Rating Scale	No severe adverse events
Cerza *et al.*[33] (2012)	Knee gonarthrosis	Randomized, controlled clinical trial (120 patients)	NA	PRP (Arthrex ACP): 60 patients, 4 PRP injections at weekly intervals	HA: 60 patients, 4 injections at weekly intervals	NA	NA	1, 2, and 6 months after treatment	WOMAC score	No adverse reactions
Filardo *et al.*[34] (2012)	Knee OA (Kellgren-Lawrence grades 1-3)	Prospective, randomized trial	NA (exclusion beyond 80 years); mean age 55 and 58 years in each group	Independent technique: 54 PRP injections weekly for 3 weeks	55 HA injections weekly for 3 weeks	PRP with leucocytes	10% Calcium chloride	2, 6, and 12 months after treatment	IKDC, EQ-VAS, Tegner, and KOOS scores	No major adverse effects
Sanchez *et al.*[35] (2012)	Symptomatic knee OA (Ahlback grades 1-3)	Prospective, randomized, controlled, multicenter trial (176 patients)	41-74 years	PRGF-Endoret 3 injections at weekly intervals	3 HA injections; each at a weekly interval	Leucocyte poor plasma	Calcium chloride 400µL	6 months after treatment	WOMAC and VAS pain subscale	1 patient who received HA felt numbness in the infiltration area, and another patient had itching on the outside area of both thighs; 1 treated with PRGF-Endoret had pain after the third infiltration

(continued)

Table 1. (continued)

Authors	Diagnosis	Study Design	Age Group	PRP Preparation (Number of Injections and Intervals)	Control Group (Number of Injections and Intervals)	Leucocytes	Activator	Follow-Up	Outcome Measures	Adverse Effects
Sanchez *et al.*[36] (2012)	Monolateral severe hip OA	Prospective case series (40 patients)	33-84 years	PRGF, Vitoria, Spain; 3 intra articular PRP injections, administered weekly	None	NA	Calcium chloride	7 weeks and 6 months after treatment	WOMAC, VAS, and Harris hip score	1 case of mild rash; transient sensation of heaviness in few
Battaglia *et al.*[37] (2011)	Hip OA (Kellgren-Lawrence grades 2-4)	Prospective case series (20 patients)	28-69 years	Independent technique: 3 US-guided PRP injections	None	NA	NA	Baseline, 1, 3, 6, and 12 months after treatment	Harris Hip Score and WOMAC scores	No severe adverse reactions
Kon *et al.*[38] (2011)	Cartilage degenerative knees and mild to severe knee OA (Kellgren-Lawrence grades 0-4)	Prospective, randomized study (150 patients)	30-81 years	50 patients: 3 autologous PRP injections	50 patients high molecular weight HA; 50 patients low molecular weight HA	PRP with leucocytes	10% Calcium chloride	2 and 6 months after treatment	IKDC and EQ-VAS scores	No adverse reactions
Wang-Saegusa *et al.*[39] (2011)	Knee OA (Outerbridge grades 1-4)	Prospective case series study (261 patients)	48.39 ± 16.65 years	PRGF (BTI, Vitoria, Spain): 3 intraarticular injections at 2-week intervals	None	NA	NA	6 months after treatment	VAS, SF-36, WOMAC Index and Lequesne Index	No adverse reactions
Kon *et al.*[40] (2010)	Degenerative cartilage lesions and OA knee (Kellgren-Lawrence grade 0-4)	Prospective case series (91 patients) 3 PRP injections	24-82 years	Independent technique: 3 injections at 3-week intervals	None	NA	10% Calcium chloride	6, 12 months after treatment	IKDC Objective and Subjective, EQ-VAS scores	No adverse reactions
Filardo *et al.*[41] (2011)[b]	Degenerative cartilage lesions and OA knee (Kellgren-Lawrence grades 0-4)	Prospective case series (91 patients) 3 PRP injections, 90 patients available at 2 years follow-up	24-82 years	Independent technique: 3 injections at 3-week intervals	None	NA	10% Calcium chloride	24 months	IKDC Objective and Subjective, EQ-VAS scores	No adverse reactions
Sampson *et al.*[42] (2009)	Primary and secondary knee OA	Prospective case series (14 patients)	18-87 years	GPS system (BIOMET); 3 PRP injections at 4 weekly intervals	None	NA	10% Calcium chloride	2, 5, 11, 18, and 52 weeks after treatment	VAS, KOOS, and cartilage ultrasound	Modest pain caused by the injection in a few; no long-term adverse effects
Sanchez *et al.*[43] (2008)	Knee OA (Ahlback grades 1-4)	Observational retrospective cohort study (60 patients)	PRGF: 63.53 ± 8.91 years; hyaluronan: 60.90 ± 8.63 years	PRGF (BTI, Vitoria, Spain): 30 patients; 3 injections at weekly intervals	Hyaluronan injections: 30 patients; 3 injections at weekly intervals	WBC content below detection level of the haematological analyzer	Calcium chloride	5 weeks after treatment	WOMAC score	Mild pain and inflammation for short duration in both groups in a few patients

PRP = platelet-rich plasma; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis—Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; NA = not available in abstract or full text; SF-36 = Short Form-36; OA = osteoarthritis; HA = hyaluronic acid; KOOS = Knee Injury and Osteoarthritis Outcome Scores; IKDC = International Knee Documentation Committee; EQ-VAS = EuroQoL Visual Analog Scale; WBC = white blood cells; PRGF = platelet-derived preparation rich in growth factors; MRI = magnetic resonance imaging; LMW = low molecular weight; NRS = Numerical Rating Scale; US = ultrasound.

[a]Referred to in the article as "Anitua's Method."

[b]Same cohort as Kon *et al.* (2010)[40] investigated at follow-up of 2 years.

Table 2. Randomized Controlled Trials.

Authors	Diagnosis	Number of Patients	Age Group	PRP Preparation (Number of Injections and Intervals)	Control Group (Number of Injections and Interval)	Leucocytes	Activator	Follow-Up	Outcome Measures	Adverse Effects
Raeissadat *et al.*[15] (2015)	Knee OA, grade 1-4 of Kellgren-Lawrence scale	Controlled randomized clinical trial (160 patients)	40-70 years	Rooyagen Kit for PRP—concentrations of 4 to 6 times (n = 87), 2 intr-articular injections at 4-week intervals	HA group; Hyalgan (n = 73), 3 doses of intraarticular injection at 1-week interval	PRP containing leukocytes	NA	12 months after the treatment	WOMAC and SF-36 questionnaires	No adverse reactions
Raeissadat *et al.*[16] (2014)	Knee osteoarthritis; grades 1-4 of Kellgren-Lawrence scale	Randomized clinical trial with control group; not blinded; 31 patients in the PRP group and 31 patients in the control group	44-67 years	Rooyagen Kit for PRP—concentrations of 4 to 6 times (n = 87), 2 intraarticular injections at 4-week intervals; plus exercise	Exercise and acetaminophen 500 mg (without codeine); no injections	PRP containing leukocytes	No activator	6 months after the treatment	WOMAC and SF-36 questionnaires	No adverse reactions
Battaglia *et al.*[21] (2013)	Hip OA	Controlled randomized clinical trial (100 patients)	25-76 years	Independent technique; consecutive (once every 2 weeks) intraarticular ultrasound-guided injections of 5 mL autologous PRP—5 ml	Consecutive (once every 2 weeks) intraarticular ultrasound-guided injections of vial (30 mg/2 mL) of high-molecular-weight (1500 kD) HA (Hyalubrix; Fidia Farmaceutici Spa, Padova, Italy)	PRP containing leukocytes	Calcium chloride	1, 3, 6, and 12 months	The Harris Hip Score (HHS) and Visual Analog Scale (VAS)	No adverse reactions
Vaquerizo *et al.*[22] (2013)	OA of the knee (Kellgren-Lawrence grades 2-4)	96 patients	>50 years	PRGF-Endornet (3 injections of 8 mL at 1-week interval)	Durolane HA 48 patients (1 injection)	Avoided leucocyte pick up	Calcium chloride	24 weeks and 48 weeks	WOMAC and Lesquene scores. OMERACT-OARSI responders	Mild postinjection pain after PRGF (8 patients); mild postinjection pain after Duralane (6 patients); pseudo-septic reaction after Duralane (2 patients)
Patel *et al.*[23] (2013)	Early OA	148 knees	NA in abstract	Independent technique: single injection—52 knees; 2 injections (3 weeks apart)—50 knees	Saline injections (46 knees)	WBC filtered PRP	NA	6 weeks, 3 months, and 6 months posttreatment	WOMAC and VAS scores	Nausea and dizziness in 22.2% and 44% patients in single and double injection groups

(continued)

Table 2. (continued)

Authors	Diagnosis	Number of Patients	Age Group	PRP Preparation (Number of Injections and Intervals)	Control Group (Number of Injections and Interval)	Leucocytes	Activator	Follow-Up	Outcome Measures	Adverse Effects
Cerza *et al.*[33] (2012)	Gonarthrosis of the knee	120 patients	NA	PRP (Arthrex ACP): 60 patients, 4 PRP injections at weekly intervals	Hyaluronic acid: 60 patients 4 injections at weekly intervals	NA	NA	1, 2, and 6 months	WOMAC score	No adverse reactions
Filardo *et al.*[34] (2012)	OA knee (Kellgren-Lawrence grades 1-3)	109 knees	NA (exclusion beyond 80 years); mean age 55 and 58 years in each group	Independent technique: 54 PRP injections weekly for 3 weeks	55 Hyaluronan injections weekly for 3 weeks	NA	10% Calcium chloride	2, 6, and 12 months	IKDC, EQ-VAS, Tegner, and KOOS scores	No major adverse effects
Sanchez *et al.*[35] (2012)	Symptomatic OA of knee Ahlback grades 1-3	176 patients	41-74 years	PRGF-Endoret; 3 injections at weekly intervals	3 HA injections; each at a weekly interval	Leucocyte poor plasma	400 µL calcium chloride	6 months	WOMAC and VAS pain subscale	1 patient who received HA felt numbness in the infiltration area, and another patient had itching on the outside area of both thighs; 1 treated with PRGF-Endoret had pain after the third infiltration
Kon *et al.*[38] (2011)	Cartilage degenerative knees and mild to severe OA knees (Kellgren-Lawrence grades 0-4)	150 patients	30-81 years	Independent technique: 50 patients; 3 autologous PRP injections	50 patients; high molecular weight HA; 50 patients low molecular weight HA	NA	10% Calcium chloride	2 and 6 months	IKDC and EQ-VAS scores	No adverse reactions

PRP = platelet-rich plasma; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis—Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; NA = not available in abstract or full text; SF-36 = Short Form-36; OA = osteoarthritis; HA = hyaluronic acid; KOOS = Knee Injury and Osteoarthritis Outcome Scores; IKDC = International Knee Documentation Committee; EQ-VAS = EuroQoL Visual Analog Scale; WBC = white blood cells; PRGF = platelet-derived preparation rich in growth factors.

Table 3. PRP Preparation, Concentration, Number of Injections, Interval, and Classifications.

Authors	PRP Preparation	PRP Volume	PRP Concentration	Number of Injections	Interval Between Injections	Leucocytes	Activator	PAW Classification	Dohan Ehrenfest Classification	Mishra Classification
Raeissadat *et al.*[15] (2015)	Rooyagen Kit	4-6 mL	4x-6x	2	4 weeks	PRP containing leukocytes	No	P3B	LP-PRP[a]	IA/B
Rayegani *et al.*[16] (2014)	Rooyagen Kit	4-6 mL	4x-6x	2	4 weeks	PRP containing leukocytes	No	P3B	LP-PRP[a]	IA/B
Guler *et al.*[17] (2014)	Autologous PRP	2 mL	4.3x	3	1 week	Leucocyte rich PRP; X4.7	NA	P3A	LR-PRP	I/2A
Mangone *et al.*[18] (2014)	Regen Kit Athena for PRP	2-2.5mL	3x-5x	3	3 weeks	Leucocyte rich PRP	Calcium gluconate	P2xA	LR-PRP	2A
Gobbi *et al.*[19] (2014)	Regen ACR-C	4 mL	2x	3	1 month	Leukocytes poor PRP	NA	P2 Bβ	LP-PRP[a]	3A
Filardo *et al.*[20] (2014)	ACP Preparation Kit (Arthrex Inc., Naples, FL)	2-4 mL	2x-3x	3	1 week	Leukocytes poor PRP	NA	P2B	LP-PRP[a]	3B
Battaglia *et al.*[21] (2014)	Autologous PRP	5 mL	6x	3	2 weeks	8300/μL	Calcium chloride	P3xB	LP-PRP	4A
Vaquerizo *et al.*[22] (2013)	PRGF-Endornet	8 mL	2x-3x	3	1 week	Minimal-none	Calcium chloride	P2xBβ	P-PRP	4B
Patel *et al.*[23] (2013)	PRP	NA	Mean platelet count: 310.14 × 10^3/μL	1 or 2	3 weeks	Minimal-none	NA	P4B	P-PRP	4B
Hart *et al.*[24] (2013)	Autologous PRP	NA	2x-2.5x	9	1 week (1st 6 injections) 3 months between 6 and 7 and 1 month between next 3	NA	NA	NA	NA	NA
Torrero *et al.*[25] (2013)	GPS mini set (BIOMET)	NA	2x-8x	1	Not applicable	Minimal-none	Calcium chloride	P2Aα	P-PRP	4A/B
Jang *et al.*[26] (2013)	Magellan Autologous Platelet Separator	3 mL	2.8x-7x	1	Not applicable	NA	Nil	P3Aα	P-PRP[a]	3A/B
Halpern *et al.*[27] (2013)	PRP cascade system	6 mL	1.3x-1.7x	1	Not applicable	Minimal-none	Calcium chloride	P2Bβ	P-PRP	4B
Say *et al.*[28] (2013)	Anitua method	2.5 mL	4x	1	Not applicable	Minimal	Calcium chloride	P2Bβ	P-PRP	4B
Gobbi *et al.*[29] (2012)	Regen Lab-ACR C	4 mL	2x-2.5x	2	4 weeks	Decreased below baseline	Nil	P2Bβ	LP-PRP	3B

(continued)

Table 3. (continued)

Authors	PRP Preparation	PRP Volume	PRP Concentration	Number of Injections	Interval Between Injections	Leucocytes	Activator	PAW Classification	Dohan Ehrenfest Classification	Mishra Classification
Filardo *et al.*[30] (2012)	PRP and (PRGF)	5 mL	4.5x (1.5x)	3	3 weeks	1.4x (none)	Calcium chloride	P3A (P2B)	L-PRP (P-PRP)	2B (4B)
Napilitano *et al.*[31] (2012)	Regen Lab	5 mL	2x-2.5x	3	1 week	Decreased below baseline	Calcium gluconate	P3B	LP-PRP	4B
Spakova *et al.*[32] (2012)	Independent technique	3 mL	4.5x	3	1 week	3.6x	NA	P3A	LR-PRP[a]	1B
Cerza *et al.*[33] (2012)	PRP (Arthrex ACP)		5x	4	1 week	Minimal-none	Nil	P3Bβ	P-PRP[a]	3A
Filardo *et al.*[34] (2012)	Independent technique	5 mL	5x	3	1 week	1.2x	10% Calcium chloride	P4xA	P-PRP	2A
Sanchez *et al.*[35] (2012)	PRGF-Endoret	8 mL	2x-3x	3	1 week	Minimal-none	400 µL Calcium chloride	P2Bβ	P-PRP	4B
Sanchez *et al.*[36] (2012)	PRGF, Vitoria, Spain	6-8 mL	2x-3x	3	1 week	Minimal-none	10% Calcium chloride	P2Bβ	P-PRP	4B
Battaglia *et al.*[37] (2011)	Independent technique	5 mL	NA	3	2 weeks	NA	NA	NA	NA	NA
Kon *et al.*[38] (2011)	Autologous PRP injections	5 mL	6x	3	2 weeks	With WBC	10% Calcium chloride	P4xNA	L-PRP	2A
Wang-Saegusa *et al.*[39] (2011)	PRGF	5 mL	2x-3x	3	2 weeks	Minimal-none	10% Calcium chloride	P2Bβ	P-PRP	4B
Kon *et al.*[40] (2010); Filardo *et al.*[41] (2011)	Autologous PRP	5 ml	6x	3	3 weeks	With WBC	10% Calcium chloride	P4xNA	L-PRP	2A
Sampson *et al.*[42] (2009)	GPS system (BIOMET)	6 mL	2x-8x	3	4 weeks	Minimal-none	10% Calcium chloride	P4Aα	P-PRP	4B
Sanchez *et al.*[43] (2008)	PRGF	6-8 mL	2x-3x	3	1 week	Minimal-none	10% Calcium chloride	P2Bβ	P-PRP	4B

PRP = platelet-rich plasma; LP-PRP = leukocytes poor PRP; LR-PRP = leukocytes rich PRP; WBC = white blood cell; PRGF = platelet-derived preparation rich in growth factors.
[a]No activation used.

As for adverse effects, no severe adverse effects of intraarticular PRP injections were reported in any of the studies. Most studies reported no adverse effects at all. Mild and self-limiting adverse effects were reported in a small number of patients in 7 studies (see **Tables 4** and **5**).

Discussion

When analyzing the results of our search, what stood out most was the lack of uniformity in treatment protocol with respect to PRP preparation, administration, and dosing. While some articles have mentioned the specific company product that was used for the preparation and reported the platelets concentrations, others have not, presenting an obstacle in the attempts to understand and interpret the results. The large spectrum of variations in treatment protocols included more than 12 different preparation techniques (commercially available and independent noncommercially available methods), different administration protocols varying in number of total injections (from 1 injections up to 9), and intervals between injections (1 week to 1 month). A total of 3 injections was the common protocol used in 18 studies. A 1-week interval was the common protocol used in 10 studies. Additional major differences were noticed in the volumes of PRP injections, which varied from 2 mL to 8 mL; platelet concentrations, which varied from 1.3 times to 8 times the blood concentration; WBC concentration, which varied from none to 4.7 times the blood concentration; and the use of an activator, which varied from none, calcium gluconate, and calcium chloride (the most commonly used, 14 studies). In addition, it is important to mention that some studies did not report all of the above-mentioned parameters (PRP kit used, platelets and WBC concentration, PRP volume, activator used, etc.) as illustrated in **Tables 1** and **3**. One study included in our results differed significantly in the administration protocol.[24] The authors administered 9 injections of PRP over a 12-month period (6 injections in 6 weeks, a 3-month interruption, followed by 3 additional injections at 1-month intervals). This raises questions regarding the number and frequency of injections, considering there have been reports of improved knee function following protocols that involved less injections and even after only a single injection.[25] The injections were initiated 6 weeks after a diagnostic arthroscopy, in which the grade of chondromalacia was determined. The study included a control group, in which mesocaine was injected at the same time points. The PRP preparation method, although described, was independent and data were lacking regarding the leukocytes profile in the preparation and activation. As portrayed in **Table 1**, there was lack of consistency with regard to the PRP preparation techniques in the studies in our review. Eleven different types of PRP preparation techniques were used, with the PRGF technique (PRGF-Endoret, BTI, Vitoria, Spain) being the most common (6 studies). Filardo and Kon used a reproducible independent technique in 3 interventions, leading to 4 studies. The rest of the studies separately used 9 different preparation methods, 4 of which were independent and 5 were commercially available systems. There was also variability in terms of the resulting volumes in each injection in different studies, ranging from 3 mL up to 8 mL per injection. Two studies did not report the injected volume. Platelet concentration or level in relation to the basal platelet count were reported in only 12 studies, while information was lacking in 9 studies. The significant differences mentioned above emphasize the great difficulty of analyzing the results of the studies included in this review, as all the parameters mentioned have a direct biological effect on the activity of the administrated PRP preparation. When trying to understand the biological activity of PRP, it should be taken into consideration that PRP contains many prochondrogenic growth factors, including TGF-β1, IGF-1, bFGF, and bone morphogenetic protein-2; however, most preparations also contain high levels of antichondrogenic growth factors, such as VEGF, IGF binding proteins, PDGFs, and EGF. Investigations have shown that although chondrogenic growth factors such as TGF-β1 directly stimulate COL1 production in skin, synovium, and tendons, PRP preparations containing the same amount of TGF-β1 actually inhibit collagen production.[43] An insight to this paradoxical action suggests that the platelet concentration of PRP preparations is crucial to its potency and its effect on different conditions and injuries. Preparations containing only moderately elevated platelet concentrations have been suggested to induce optimal biological benefit, whereas lower platelet concentrations produce suboptimal effects and higher concentrations produce inhibitory effects. The "therapeutic dose" of PRP is considered at a range of at least 2 to 6 times higher than the normal platelet count. These observations reflect the complex molecular pool contained in PRP. It is therefore believed that maintaining what can be a delicate balance between pro-chondrogenic and anti-chondrogenic effects is crucial and the volumes of the PRP preparations and platelet concentrations play an important role, emphasizing the importance of optimal characterization of the studied PRP preparations. An additional factor contributing to the biologic characteristics of the PRP preparation is the activation method. Platelet activation triggers degranulation and release of the growth factors. The activation method (endogenous or exogenous with CaCl or CaG) determines the timing and cumulative release of the growth factors. However, this release may continue throughout the platelets' 7- to 10-day life span,[1] thus offering the benefit of maintaining the normal physiologic ratios of these molecules.

Proper terminology for classifying and describing the many different variations of platelet concentrates are essential, especially when comparing results of several studies and analyzing the benefits of these treatments. The need for clarification, terminology, categorization, or classification was

Table 4. PRP Preparation Systems.

System	Volume of Whole Blood (mL)	Centrifugation Force	Spin Time (Minutes)	Volume of PRP (mL)	Platelet Concentration (Fold Change)	Activation	Leukocyte Concentration
Rooyagen Kit	35-40	1,600 rpm 2,800 rpm Double spin	15 7	4-6	X4-6	No activation	Yes
AG Curasan	10	1,200*g*	10	6-7	2x	$CaCl_2$	Yes
Arthrex ACP System (Naples, FL)	9	1,500 rpm single spin	5	2-4	2x-3x	None if used within 30 minutes	No
Regenlab	8	1,500*g* single spin	5	4	1.7x	Autologous thrombin or calcium gluconate	Yes
Biomet GPS Recover Platelet separation Kit (Warsaw, IN)	Mini GPS3 27 mL or 54 mL	3,200 rpm single spin	15	3-6	2.07x	Thrombin $CaCl_2$	Yes (fold change 5.4); platelet concentrate buffered by adding 0.05 mL of 8.4% sodium bicarbonate to each mL of platelet concentrate
Cascade Fibrinet Platelet Rich fibrin Matrix (PRFM)	9-18	1,100*g* and 1,450*g* single spin for PRP, double spin for PRFM	6 minutes for PRP + 15 minutes for PRFM	4-9	1.6x	$CaCl_2$	No
Plateltex	16	160-180*g* and 100-1,200*g*	10 and 10	6 and 10	1x-2x	Batroxobin for gel	Yes
Cytomedix Angel	40-180	3,200 rpm	15-28	2-5	4.3x	None	Yes
Harvest (Plymouth, MA); Smart PReP2APC (Warsaw, IN)	50 or 100	3,650 rpm double spin	14	3-9 or 10-20	7x	Thrombin $CaCl_2$	Yes (fold change 2.3)
Magellan-Medtronic (Minneapolis, MN)	30-60	3,800 rpm double spin	4-6	6	2.8x to 7x	$CaCl_2$	Yes (fold change 3.2)
Emcyte (Fort Myers, FL)/Genesis CS/Exactech (Gainesville, FL) Accelerate	30 or 60		12	3 or 10	7x to 10x		Yes
BTI PRGF (Vitoria-Gasteiz, Spain)	9-72	460*g* single spin	8	4-32	2x-3x	$CaCl_2$	No

PRP = platelet-rich plasma; PRGF = platelet-derived preparation rich in growth factors.

Table 5. Studies Included in This Systematic Review: Description and Results.

Authors	Diagnosis	Design	Purpose	PRP Preparation	PRP Concentration	Outcome Measures	Results
Raeissadat *et al.*[15] (2015)	Knee OA, Kellgren-Lawrence grades 1-4	Randomized controlled clinical trial (160 patients); 87 patients received 2 PRP injections; 73 received 3 HA injections.	To study the long-term clinical effect of intraarticular injections of PRP and HA and quality of life in patients with knee OA	Rooyagen Kit	4x-6x	WOMAC and SF-36 questionnaires	At 12-month follow-up, WOMAC pain score and bodily pain significantly improved in both groups; however, the PRP group showed better results compared to the HA group ($P < 0.001$). Other WOMAC and SF-36 parameters improved only in the PRP group. More improvement (not statistically significant) was achieved in patients with grade 2 OA in both groups.
Raeissadat *et al.*[16] (2014)	Knee OA, Kellgren-Lawrence grades 1-4	Randomized controlled clinical trial; 31 patients per group. Same therapeutic exercise program was prescribed for both groups. The PRP group received 2 courses of leukocyte rich PRP with a 4-week interval.	To investigate the effects of PRP on pain, stiffness, function and quality of life in patients with knee OA	Rooyagen Kit	4x-6x	WOMAC and SF-36 questionnaires	At 6-month follow-up mean changes in total WOMAC, physical component summery and the mental component summery of SF-36 in the PRP group showed better improvements than the control group ($P < 0.05$).
Guler *et al.*[17] (2014)	Knee OA, Kellgren-Lawrence grades 1-2	Retrospective study. 132[a] patients; 63 (86 knees) in the HA group and 69 (89 knees) in the PRP group. Patients received 3 injections at 1-week interval.	To compare short-term clinical outcomes between intraarticular PRP and HA in early-stage OA patients	Independent technique	4.3x	Knee Society's Knee Scoring System (KSS) and the Visual Analog Scale (VAS) scoring system	The PRP group had significantly higher KSS scores at the 2- and 6-month follow-up. Pretreatment, 2 months, and 6 months VAS scores were significantly lower in the PRP group than in the HA group: Pretreatment VAS mean difference of 0.46; 2 and 6 months VAS mean difference of 1.64 and 1.67. respectively
Mangone *et al.*[18] (2014)	Knee OA. Kellgren-Lawrence grades 2-3	Prospective case series; 72 patients	To evaluate and quantify the effects of PRP on QOL and pain in patients with OA (3 injections of PRP)	Regen Kit Athena for PRP	3x-5x	WOMAC, VAS at rest and VAS in movement	Significant improvement both in functional and pain scores ($P < 0.005$). The improvement lasted for almost 1 year. Stiffness decreased significantly ($P < 0.005$) during the first month, but afterwards there was no sizable improvement.
Gobbi *et al.*[19] (2014)	Early knee OA. Kellgren-Lawrence Grades 1-2	Randomized prospective, study. 119 knees were followed for 2 years with 50 knees randomly selected to receive a second cycle of PRP injections 1 year from first cycle	To assess the outcome of intraarticular PRP injections in patients with early stages of knee OA and the effect of cyclical dosing after 1 year	Regen ACR-C. A cycle consisted of 3 injections, given at a monthly intervals	2x	KOOS, VAS, Tegner and Marx scores	At 12 months, both groups showed similar and significant improvement. At 18 months, except for KOOS (Symptoms) and Tegner scores, all other parameters showed a significant difference between the 2 groups in favor of the second cycle group ($P < 0.001$). At 2 years, the scores declined in both groups but remained above the pretreatment values with no significant difference between groups
Filardo *et al.*[20]	Knee OA. Kellgren-Lawrence grades 1-4	Therapeutic case series of 51 knees	To describe the clinical results obtained after intraarticular injection of a leukocyte-poor PRP preparation for the treatment of knee OA	Autologous Conditioned Plasma (ACP) Preparation Kit (Arthrex Inc.)	2x-3x	IKDC-Subjective, EQ-VAS, Tegner, and KOOS scores	The overall clinical outcome was positive and the treatment proved to be safe. In the "early/moderate OA" group, the IKDC-Subjective score increased from 36.4 at baseline evaluation to 57.3 at the mean 14.5-month follow-up ($P < 0.0005$) and a similar trend was shown by the EQ-VAS, Tegner, and KOOS scores. Although an improvement was also recorded in the "severe OA" group, the clinical outcome of patients in this group was poorer, less benefit was reported. In the "early/moderate OA" group, BMI and longer symptom duration before treatment were found to be correlated with clinical outcomes.

(continued)

Table 5. (continued)

Authors	Diagnosis	Design	Purpose	PRP Preparation	PRP Concentration	Outcome Measures	Results
Battaglia *et al.*[21]	Hip OA; Kellgren-Lawrence grades 2-4	Randomized controlled clinical trial (100 patients)	To compare the clinical efficacy of PRP versus HA at 12 months of follow-up in patients with hip OA	Autologous PRP—Independent technique	6x	Harris Hip Score (HHS) and VAS	An overall improvement was detected in both groups between 1- and 3-month follow-up. Despite a slightly progressive worsening between 6- and 12-month follow-up, the final clinical scores remained higher compared to baseline values ($P < 0.0005$), with no significant differences between PRP and HA groups.
Vaquerizo *et al.*[22] (2013)	Knee OA	Randomized controlled trial; 48 patients received 3 injections of PRP (PRGF). 46 patients received 1 HA injection.	To compare the efficacy and safety of 3 injections of PRP versus a single intraarticular injection of HA for reducing symptoms in patients with knee OA	PRGF (BTI, Vitoria, Spain)	2x-3x	WOMAC and Lesquene scores	Treatment with PRGF was significantly more efficient than HA in reducing knee pain and stiffness and improving function in knee OA patients. Response rate to PRGF was significantly higher than the rate of response to HA in all scores including pain, stiffness, and function on WOMAC, Lequesne index, and OMERACT-OARSI responders at 24 and 48 weeks.
Patel *et al.*[23] (2013)	Early knee OA	Randomized, controlled trial; single (52 knees) versus double PRP (50 knees) injections versus saline injection (46 knees)	To compare outcomes following single and double PRP injections compared to a control group receiving placebo (saline)	Independent technique	Mean platelet count: 310.14 × $10^3/\mu L$	WOMAC and VAS scores	Significant improvements in WOMAC scores at all follow ups when PRP was administered, with no difference between single and double injections. Deterioration in WOMAC from baseline values when saline was used.
Hart *et al.*[24] (2013)	Grades 2-3 knee chondromalacia	Prospective study; 50 patients, 9 injections administered over 1 year	To assess if PRP can increase tibiofemoral cartilage regeneration and improve knee function	Autologous PRP—Independent technique (2-2.5 fold platelet concentration)	2x-2.5x	Lysholm, Tegner, IKDC, Cincinnati scores and MRI at 12 months	Significant improvement in all scores at 12 months, $P < 0.05$. No significant cartilage regeneration. MRI did not confirm any significant cartilage condition improvement.
Torrero *et al.*[25] (2013)	Knee OA. Outerbridge grades 1-3	Prospective study; 30 patients (18-65 years) 1 intraarticular injection; 6-month follow-up	To assess single PRP injection as a treatment for early moderate chondropathy	GPS mini set, (BIOMET)	2x-8x	KOOS, VAS scores	Significant improvement in KOOS and VAS scores at 1, 3, and 6 months ($P < 0.05$) follow-up.
Jang *et al.*[26] (2013)	Knee OA (grade not mentioned)	Prospective study; 65 patients; 12-month follow-up	To determine effect duration of a single PRP injection for knee OA	Independent technique	2.8x-7x	IKDC and VAS scores	VAS score decreased from 7.4 at baseline to 4.2 at 6 months, but increased slightly to 5 at 1 year. Pain relapse was noticed at 8.8 months after the injection. Advanced degeneration stage according to the Kellgren-Lawrence grade reduced the clinical effects of PRP ($P < 0.05$) and also accelerated the time for relapsing pain ($P < 0.05$).
Halpern *et al.*[27] (2013)	Knee OA. Kellgren-Lawrence grades 1-2	Prospective cohort study; 22 patients (30-70 years); 1-year follow-up	To investigate whether a single PRP injection for early knee OA is associated with good clinical outcomes and a change in MRI structural appearances	MTF Cascade system	1.3x-1.7x	WOMAC and VAS scores, and MRI at 1 year	VAS scores significantly decreased, whereas functional and clinical scores (WOMAC and Functional VAS) significantly improved at 6 months and 1 year from baseline. Qualitative MRIs demonstrated no change in at least 73% of cases at 1 year.

(continued)

Table 5. (continued)

Authors	Diagnosis	Design	Purpose	PRP Preparation	PRP Concentration	Outcome Measures	Results
Say *et al.*[28] (2013)	Symptomatic mild to moderate knee OA (Kellgren-Lawrence grades 1-3)	Prospective study; 90 patients; 3 and 6 months follow-up	To compare the effects of a single PRP versus 3 HA injections in knees with degenerative arthritis	PRGF (BTI, Vitoria, Spain)[b]	4x	KOOS and VAS scores	Improved KOOS and VAS scores in the PRP group at 3 and 6 months follow-up.
Gobbi *et al.*[29] (2012)	Knee OA. Kellgren-Lawrence grades 1-3	Prospective case series; 50 patients with 2 intraarticular autologous PRP injections; 25 patients had undergone prior surgical intervention	To determine the effectiveness of intraarticular PRP injections in active patients with knee OA and to evaluate clinical outcomes in patients with and without previous surgical treatment for cartilage lesions.	Regen Lab-ACR C	2x-2.5x	VAS, IKDC Subjective, KOOS, and Tegner scores	Significant improvement in all scores at 6 and 12 months ($P < 0.01$); all returned to previous activities. No significant difference in improvement between subgroups ($P < 0.01$).
Filardo *et al.*[30] (2012)	Symptomatic knee degenerative lesions and OA	Prospective clinical study; 144 patients: 72 treated with 3 PRP injections prepared with a single-spinning procedure; 72 with 3 PRP injections prepared with a double-spinning approach.	To compare the safety and efficacy of 2 different approaches of PRP production methods as intraarticular injection treatment for knee cartilage degenerative lesions and osteoarthritis (OA)	Independent technique: Single-spin—580 rpm 8 minutes, 5 mL PRGF. Double-spin—PRP product: 1,800 rpm 15 minutes and 3,500 rpm 10 minutes, 5 mL PRP	4.5x (1.5x)	IKDC, EQ-VAS, and Tegner scores	Significant clinical improvement with respect to the baseline level in both groups. Better results in younger patients with less cartilage degeneration.
Napilitano *et al.*[31] (2012)	Knee OA >1 year	Prospective study; 27 patients (18-81 years) 3 infiltrations of PRP at weekly intervals	To evaluate 3 PRP injections as a treatment for knee OA (first group, Kellgren Lawrence grades 1-3) and degenerative cartilage lesions (second group, Outerbridge grades 1-2)	Regen Lab	2x-2.5x	NRS and WOMAC scores	Significant improvement in NRS and WOMAC scores at 1 week in both groups; substantial decrease in pain right after the first infiltration (1 week). Improvement in WOMAC scores at 1 week and 6 months in both groups (NRS not measured at 6 months).
Spakova *et al.*[32] (2012)	Knee OA; Kellgren Lawrence grades 1-3	Prospective, cohort study with a control group; 120 patients: 3 injections of PRP versus 3 injections of HA	To find a simple, cost-effective, and time-efficient method for the preparation of PRP and to explore the safety and efficacy PRP application to treat knee OA	Independent technique	4.5x	WOMAC and the 11-point pain intensity Numeric Rating Scale	Statistically significantly better results in the WOMAC and Numeric Rating Scale scores were recorded in a group of patients who received PRP injections after a 3- and 6-month follow-up.

(continued)

Table 5. (continued)

Authors	Diagnosis	Design	Purpose	PRP Preparation	PRP Concentration	Outcome Measures	Results
Cerza *et al.*[33] (2012)	Knee gonarthrosis	Randomized controlled trial; 60 patients; 4 PRP injections at weekly intervals versus 60 patients with 4 HA injections at weekly intervals	To compare the clinical response of PRP hyaluronic and HA treatment in 2 groups of patients affected by gonarthrosis	Arthrex ACP	5x	WOMAC score	PRP had a significant effect which continuously improved up to 24 weeks ($P < 0.001$). In the HA group, the worst results were obtained for grade III gonarthrosis, whereas the clinical results obtained in the PRP group did not show any statistically significant difference in terms of the grade of gonarthrosis ($P < 0.001$).
Filardo *et al.*[34] (2012)	Knee OA; Kellgren-Lawrence grades 1-3	Prospective randomized controlled double-blinded trial; 54 PRP injections weekly for 3 weeks versus 55 HA injections weekly for 3 weeks	To compare the clinical efficacy of a series of PRP injections versus a series of HA injections for treatment of knee OA	Independent technique: 150 mL whole blood, 1,480 rpm 6 minutes and 3,400 rpm 15 minutes, 5 mL PRP	5x	IKDC, EQ-VAS, Tegner, and KOOS scores	Both groups showed clinical improvement but the comparison between the 2 groups showed statistically insignificant difference in all scores. Favorable results for the PRP group in patients with low-grade articular degeneration (Kellgren-Lawrence score up to 2).
Sanchez *et al.*[35] (2012)	Knee OA	Randomized, double-blind, HA-controlled, multicenter trial; 176 patients (41-74 years)	To evaluate the efficacy and safety of intraarticular injections of PRGF-Endoret in the treatment of knee OA	PRGF-Endoret (BTI, Vitoria, Spain)	2x-3x	WOMAC and VAS Pain subscale	Rate of response to PRGF-Endoret (50% decrease in knee pain from baseline to week 24) was 14.1 percentage points higher compared to the HA-treated group. No statistically significant difference between groups in secondary outcomes.
Sanchez *et al.*[36] (2012)	Hip OA	Prospective case series; 40 patients; 3 PRP injections, administered weekly	To assess the safety and symptomatic changes of PRP injections in patients with hip OA	PRGF (BTI, Vitoria, Spain)	2x-3x	WOMAC, VAS, and Harris hip score subscale	Statistically significant reductions in VAS, WOMAC, and Harris hip scores for pain and function at 7 weeks and 6 months. 23 (57.5%) patients reported a clinically relevant reduction of pain. 16 (40%) of these were classified as excellent responders who showed early pain reduction at 6 weeks, which was sustained at 6 months and a parallel reduction of disability.
Battaglia *et al.*[37] (2011)	Hip OA; Kellgren Lawrence grades 1-3	Prospective case series; 20 patients; 3 US-guided injections	To assess efficacy of PRP for hip OA	Independent technique	NA	Harris Hip Score and WOMAC scores	Both HHS and WOMAC scores improved at the 12-month follow-up. An initial clinical improvement was observed at the 1-month and 3-month follow-up, which then decreased, but remained significantly higher at 12 months with respect to the baseline values.
Kon *et al.*[38] (2011)	Cartilage degenerative knees and mild to severe knee OA	Prospective comparative study; 50 patients—3 PRP injections; 50 patients—high molecular weight HA injections; 50 patients—low molecular weight HA injections	To compare the efficacy of PRP and HA intraarticular injections for the treatment of knee cartilage degenerative lesions and OA	Independent technique: 150 mL whole blood, 1,480 rpm 6 minutes and 3,400 rpm 15 minutes, 20 mL PRP	6x	IKDC and EQ-VAS scores	At 2m both PRP and LMW HA groups improved, with better results compared to the HMW HA group ($P < 0.005$). At 6 months better results were observed in the PRP group ($P < 0.005$). PRP showed better results in younger patients and early OA stages.
Wang-Saegusa *et al.*[39] (2011)	Knee OA; Outerbridge grades 1-4	Nonrandomized prospective study; 261 patients; 3 intraarticular PRGF injections at 2-week intervals	To assess quality of life and functional capacity following a series of PRP injections for knee OA	PRGF (BTI, Vitoria, Spain)	2x-3x	VAS, SF-36, WOMAC score, and Lequesne Index	Statistically significant differences ($P < 0.0001$) between pretreatment and follow-up values were found for pain, stiffness, and functional capacity in the WOMAC Index; pain and total score, distance and daily life activities in the Lequesne Index, the VAS pain score, and the SF-36 physical health domain.

(continued)

Table 5. (continued)

Authors	Diagnosis	Design	Purpose	PRP Preparation	PRP Concentration	Outcome Measures	Results
Kon *et al.*[40] (2010)	Degenerative cartilage lesions and knee OA	Prospective clinical trial; 91 patients received 3 PRP injections	To investigate the continuous outcomes of PRP injections in knee OA	Independent technique: 150 mL whole blood, 1,800 rpm 15 minutes and 3,500 rpm 10 minutes, 20 mL PRP (15 mL used)	6x	IKDC Objective and Subjective scores and EQ-VAS score	A statistically significant improvement of all clinical scores was obtained from the basal evaluation to the end of the therapy and at 6 to 12 months follow-up. The results remained stable from the end of the therapy to 6 months follow-up, whereas deterioration of scores was noted and they became significantly worse at 12 months follow-up ($P = 0.02$), even if still significantly better in respect to the basal level ($P < 0.0005$).
Filardo *et al.*[41] (2011)[c]	Degenerative cartilage lesions and knee OA	Prospective clinical trial; 91 patients received 3 PRP injections (90 patients available at 2 years)	To investigate the continuous outcomes of PRP injections in knee OA at 2 years	Independent technique; mentioned above	6x	IKDC Objective and Subjective scores and EQ-VAS score	All parameters deteriorated at 2 years with significantly lower levels with respect to the 12-month evaluation (IKDC Objective dropped from 67% to 59% of normal and nearly normal knees; IKDC Subjective score dropped from 60 to 51), though remaining higher than the basal level; better results in young patients with less cartilage degeneration ($P < 0.0005$). The median duration of the clinical improvement was 9 months.
Sampson *et al.*[42] (2009)	Primary and secondary knee OA	Single-center, uncontrolled prospective preliminary study; 14 patients; 3 PRP injections at 4 weekly intervals	To evaluate the efficacy of PRP injections in treatment of knee OA	GPS system (BIOMET)	2x-8x	Brittberg-Peterson VAS, and KOOS scores, and cartilage ultrasound at 2, 5, 11, 18, and 52 weeks	Most patients expressed a favorable outcome at 12 months after treatment. Significant and almost linear improvements in KOOS, including pain and symptom relief. Brittberg-Peterson VAS showed many improvements including reduced pain after knee movement and at rest. Cartilage assessment was limited due to a small sample size. The majority of patients expressed a favorable outcome at 12 months after treatment.
Sanchez *et al.*[43] (2008)	Knee OA	Observational retrospective cohort study using HA injections as control; 2 groups of 30 patients with 3 weekly injections of PRP or HA	To assess effectiveness of intraarticular injections of PRP (PRGF) versus HA for knee OA	PRGF (BTI, Vitoria, Spain)	2x-3x	WOMAC score	WOMAC and pain scales improvement at 5 weeks was associated solely with treatment modality in favor of PRGF.

OA = osteoarthritis; PRP = platelet-rich plasma; HA = hyaluronic acid; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 = Short Form-36; QOL = quality of life; NA = not available in abstract or full text; KOOS = Knee Injury and Osteoarthritis Outcome Scores; IKDC = International Knee Documentation Committee; EQ-VAS = EuroQoL Visual Analog Scale; BMI = body mass index; PRGF = platelet-derived preparation rich in growth factors; OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis—Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; MRI = magnetic resonance imaging; NRS = Numerical Rating Scale; US = ultrasound; LMW = low molecular weight; HMW = high molecular weight.

[a]Some patients had both knees included.

[b]Referred to in the article as "Anitua's Method."

[c]Same cohort as Kon *et al.* (2010)[40] investigated at follow-up of 2 years.

highlighted in recent years and yielded several classification systems. The first described and most comprehensive classification system, also known as the Dohan Ehrenfest classification,[44] is based on the presence of cell content (mostly leukocytes) and the fibrin architecture. Four main families were defined: Pure Platelet-Rich Plasma (P-PRP)—or Leukocyte-Poor Platelet-Rich Plasma—products are preparations without leukocytes and with a low-density fibrin network after activation; Leukocyte- and Platelet-Rich Plasma (L-PRP) products are preparations with leukocytes and with a low-density fibrin network after activation; Pure Platelet-Rich Fibrin (P-PRF)—or Leukocyte-Poor Platelet-Rich Fibrin—are preparations without leukocytes and with a high-density fibrin network; and Leukocyte- and Platelet-Rich Fibrin (L-PRF) products are preparations with leukocytes and with a high-density fibrin network. This terminology and classification are now considered as a basis of consensus in many fields. Another 2 classification systems were proposed in recent years, but are considered limited and applicable for sports medicine applications only. These are the Mishra classification and the PAW classification. Mishra *et al*.[45] proposed a classification that takes into consideration the presence of leukocytes, activation of platelets, and platelets concentration. This classification established 4 types of PRP: type 1 PRP is an L-PRP solution, type 2 PRP is an L-PRP gel (with activation), type 3 PRP is P-PRP solution, type 4 PRP is a P-PRP gel (with activation). Each type can be described as an A or B subtype. A subtype is 5 times or more the blood concentration of platelets, and B subtype is less than 5 times the blood concentration of platelets. The PAW classification[46] is similar to the Mishra classification and is based on the absolute number of platelets, the manner in which platelet activation occurs, and the presence or absence of white cells. **Table 3** illustrates the different PRP preparations used in the studies included in this review according to currently used classifications.

Only 2 studies were PRP controlled, one comparing different PRP administration protocol: 1 versus 2 PRP injections[23] and the other comparing different preparation method: single spinning versus double spinning procedures.[30] Both studies showed no significant changes between groups. These studies emphasize the fact that current literature is lacking randomized controlled studies aimed to introduce the optimal PRP treatment (preparation characteristics, administration protocol, etc.) for knee or hip OA.

Randomized Controlled Trials

Nine RCTs were included in the results,[15,16,21-23,33-35,38] 3 of which were double blinded (**Table 2**). Hyaluronic acid was used for the control groups in 7 RCTs, saline was used in 1 study, and an exercise program was used in another.

Eight studies targeted knee OA whereas 1 study targeted hip OA.[21] The follow-up period in these studies ranged from 6 to 12 months.

Overall, all RCTs reported on improved symptoms at the last follow-up when compared to the baseline scores; however, 2 RCTs—one for knee OA[34] and one for hip OA[21]—did not report significantly superior results for the PRP group compared to the control group (HA). All other studies showed significantly better results for the PRP group.

In a multicenter study,[35] the efficacy and safety of intraarticular injections of PRGF were evaluated in 176 patients with knee OA (aged 41-74 years). At 6-month follow-up, the PRGF group had significantly more patients who achieved greater than 50% decrease in the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain score, compared to the HA group; however, although absolute WOMAC and VAS (Visual Analog Scale) scores were better in the PRGF group, there was almost no statistical significance compared to the HA hyaluronan group. In a double-blinded RCT,[34] Filardo *et al*. found no statistically significant difference between the PRP and the HA treated groups. A trend favorable of the PRP group was only found in patients with low-grade articular degeneration (Kellgren-Lawrence score up to 2) at 6 and 12 months of follow-up. In another RCT, Cerza *et al*.[33] compared treatment with ACP in 60 patients with knee OA to 60 patients treated with HA. The PRP showed a significant effect using the WOMAC score, which continuously improved up to 24 weeks ($P < 0.001$). In the HA group, the worst results were obtained for grade III gonarthrosis, whereas the clinical results obtained in the PRP group did not show any statistically significant difference in terms of the grade of gonarthrosis ($P < 0.001$). In their RCT, Patel *et al*.[23] used saline injections for the control group. The study included 78 patients with bilateral knee OA, divided into 3 groups: single PRP injection ($n = 52$ knees); 2 PRP injections ($n = 50$ knees); single saline injection ($n = 46$ knees). Significant improvement in WOMAC score was recorded at all follow-ups (1.5, 3, and 6 months) when PRP was administered, compared to the saline group, with no difference between the single and double injections groups. An interesting finding in this study was that the improvement was maximal at first follow-up with deterioration in the second and third follow-ups, suggesting a temporary nature of the benefits of PRP injections. In their multicenter RCT, Vaquerizo *et al*.[22] compared 3 injections of PRGF to one single intraarticular injection of HA. Each group included 48 patients. They reported that PRGF was significantly more efficient than treatment with Durolane HA in reducing knee pain and stiffness and improving function in patients with knee OA. The rate of response to PRGF was significantly higher than the rate of response to HA for all scores including pain, stiffness, and function on the WOMAC, Lequesne index, and OMERACT-OARSI responders at 24 and 48 weeks. In the most recent RCT,[15] Raeissadat *et al*. compared 2 intraarticular injections of PRP (Rooyagen Kit) to 3 injections of Hyalgan HA for patients with knee OA. The PRP group

included 87 patients and the HA group 73 patients. At the 12-month follow-up, WOMAC pain score and bodily pain significantly improved in both groups; however, better results were determined in the PRP group compared to the HA group ($P < 0.001$). Other WOMAC and SF-36 (Short Form-36) parameters improved only in the PRP group. Another interesting RCT by Raeissadat *et al*.[16] compared intraarticular PRP injections and a prescribed exercise program with a prescribed exercise program alone. After 6 months, the mean changes of total WOMAC, physical component summery, and mental component summery of SF-36 in the PRP group showed better improvement than the control group ($P < 0.05$). Only 1 RCT by Battaglia *et al*.[21] investigated intraarticular injections of PRP and HA in hip OA. One hundred patients with symptomatic hip OA were randomly assigned to 1 of 2 groups: group A received PRP and group B received HA intraarticular injections. Patients were evaluated at baseline and after 1, 3, 6, and 12 months using the Harris Hip Score (HHS) and visual analog scale (VAS). An overall improvement was detected in both groups between 1- and 3-month follow-up. Despite a slightly progressive worsening between 6- and 12-month follow-up, the final clinical scores remained higher compared with baseline ($P < 0.0005$), with no significant differences between PRP and HA.

HA Controlled Studies

Nine out of 11 HA controlled studies (7 RCTs, 2 prospective comparative studies, and 2 retrospective cohorts) showed significantly better results in the PRP groups. In most of the studies, improvement in pain and functional scales was noted in both the HA and PRP groups, with significantly better results in the PRP groups. Most studies in this subgroup followed the participants up to 6 months (6 studies), while 4 studies had a follow-up of up to 12 months. One study followed the patients only for 5 weeks.[43] In a prospective double-blinded RCT[34] both groups showed clinical improvement, and the comparison between the 2 groups showed statistically insignificant difference in all scores. In a recently published randomized controlled clinical trial (160 patients),[15] 87 patients received 2 PRP injections and 73 received 3 HA injections. At the 12-month follow-up, WOMAC pain score and bodily pain significantly improved in both groups; however, better results were determined in the PRP group compared to the HA group ($P < 0.001$). Other WOMAC and SF-36 parameters improved only in the PRP group. More improvement (not statistically significant) was achieved in patients with grade 2 OA in both the groups.

Prospective Case Series

Positive results for PRP treatment in knee and hip OA was evident in all 14 prospective case series studies included. These studies showed improvement in pain and functional performance compared to pretreatment measurements for follow-ups of up to 24 months. The majority of studies followed the patients up to 12 months. However, a deterioration in the positive effect of PRP was also noted during follow-up time. Kon *et al*.[40] showed a 9-month median duration of clinical improvement for knee OA patients treated with PRP. Despite this deterioration, functional and pain scores remained higher than the basal level of pretreatment in all studies.

Follow-Up Period

The majority of studies reported a follow-up period of 12 months (13 studies) or 6 months (12 studies). The shortest follow-up was 5 weeks in one study.[43] In a prospective study including 91 patients, a follow-up of 24 months has been reported.[40,41] In this study group, patients received 3 intraarticular PRP injections at monthly intervals showed symptomatic improvement at 12 months but significant worsening of symptoms at 2 years with respect to the 12-month evaluation (IKDC [International Knee Documentation Committee] objective decreased from 67% to 59% of normal and nearly normal knees; IKDC subjective score decreased from 60 to 51), although they remained higher than the basal level. This is an interesting finding and reiterates the need for studies with longer follow-ups. A closer analysis of the data in this study revealed that older patients had a weaker response compared to younger patients ($P = 0.049$) and that only 30% of patients over 65 years of age with advanced OA showed significant improvement. In another study with a follow-up of 24 months, 50 knees were randomly selected from 119 knees and received a second cycle of PRP injection at the completion of 1 year from first cycle. At 12 months, both groups showed similar and significant improvement. At 18 months, except for KOOS (Knee Injury and Osteoarthritis Outcome Score–Symptoms) and Tegner score, all other parameters showed a significant difference between the 2 groups in favour of the patients who had received the second cycle ($P < 0.001$). At 2 years, the scores declined in both groups but remained above the pretreatment value with no significant difference between the groups. This study raises many questions with regard to the temporary effect of PRP treatment and the proper ways of prolonging its positive effect.

Level of OA

A trend toward better results for PRP injections in patients with early knee OA changes and young age was observed in several studies.[15,20,26,30,34,38] This might suggest that PRP treatment should be considered more seriously in this subgroup. It is important to mention that improved outcomes have been shown in up to grade 3 OA (according to the Kellgren-Lawrence classification).[25,26]

Lack of uniformity was evident in terms of indications, inclusion criteria, pathology definitions, and classifications used in the different studies. In the knee studies, not all authors reported the degree of OA or degeneration, using a general description such as "degenerative joint disease," or "primary and secondary OA," or even "osteoarthritis," whereas others varied in the classifications used to quantify the level of OA. Another variable posing difficulty in uniformly assessing the data was regarding the methods of reporting the level of OA treated. The Outerbridge classification[47] was used to describe the lesions in 2 studies,[4,25] and another study[35] used the Ahlback classification,[48] whereas the Kellgren-Lawrence classification[49] was used in most others (18 studies). Some studies have simply used the broad term "early to severe OA."[23,33,26] Although most authors used the Kellgren-Lawrence classification, there was variability in the grades included in the studies, with some focusing only on grades 0 to 2 and others including also grade 3 and even grade 4. Six studies included patients with grade 0 Kellgren-Lawrence,[20,27,30,38,40,41] meaning symptomatic knees with no radiographic signs of OA, which could potentially add additional confounding factors to the results. Not all studies describe the distribution of the study population according to the OA grades. Although these studies have targeted degenerative cartilage pathology, the range of the age group included has been as wide as from 18 years to 81 years,[25,31] which could possibly generate a bias in the results.

Activator Use

Fourteen studies reported use of an activator right before PRP injection, with the majority[14] using calcium chloride 10%. Platelet activation triggers degranulation and release of the growth factors. The activation method determines the timing and cumulative release of the growth factors. However, this release may continue throughout the platelets' 7- to 10-day life span,[1] thus offering the benefit of maintaining the normal physiologic ratios of these molecules.

Imaging Evaluation

Two studies were using imaging modalities to evaluate cartilage changes following PRP administration. In an uncontrolled prospective study, in which 14 patients with knee OA were treated with PRP, the authors reported improvement using ultrasonographic measurement of femoral articular cartilage thickness in 6 out of 13 patients at 6-month follow-up.[42] In a prospective study by Halpern *et al*.[27] involving 22 patients, qualitative magnetic resonance imaging was performed at baseline and at 1 year of follow-up, demonstrated no change in at least 73% of cases at 1 year. Although these studies involved a small sample size and a short-term follow-up period, they point out the need for a more objective measure to evaluate the effects of PRP on cartilage, as none of the other studies used an arthroscopic or consistent radiological evaluation after treatment administration to assess cartilage regeneration and tissue histopathology for regenerative features.

Adverse Effects

Only 7 studies reported on mild and self-limiting adverse effects in a small number of patients.

Filardo *et al*.[20] reported mild pain and/or slight swelling, which resolved spontaneously within 24 to 48 hours, without reporting number of patients. Vaquerizo *et al*.[22] reported mild postinjection pain after PRGF injection in 8 patients (out of 48). Patel *et al*.[23] reported nonspecific 19 adverse effects during the course of PRP treatment (148 knees). These included local pain, stiffness, syncope, dizziness, headache, nausea, sweating, and tachycardia, all self-limited. Filardo *et al*.[30] reported temporary pain and swelling reaction for the PRP treatment (number of patients not mentioned). Spakova *et al*.[32] documented temporary mild worsening of pain in the knee joint after application of PRP in 6 cases (out of 60), which was spontaneously resolved after 2 days. Sporadic adverse effects of temporary mild rash, local numbness, and itching sensation were also reported.[35,36]

PRP for Hip OA

Only 3 studies[21,36,37] have been conducted to assess the efficacy of PRP for OA of the hip joint. While the first, published in 2011, showed clinical improvement in the short term, follow-up at 1 year was not as good. In a larger group of 40 patients, Sanchez *et al*.[36] reported 57.5% patients had clinically relevant relief of pain, assessed by the WOMAC subscale. Of these, 40% were classified as excellent responders who showed early pain reduction at 6 weeks, which was sustained at 6 months, with a parallel reduction of disability. A notable observation in this study was that 10 of the 11 patients in which treatment was not effective had a higher grade of hip OA (Tonnis grade 3). The authors concluded that PRP was effective for the management of pain from OA of the hip. However, the criteria for significance defined in the study was a 30% reduction in pain and disability, which, as shown by Richette *et al*.,[50] can also be achieved with a placebo. In a recent randomized controlled clinical trial (100 patients),[21] Battaglia *et al*. compared the clinical efficacy of PRP versus HA at 12 months of follow-up in patients with hip OA. They showed that an overall improvement was detected in both groups between 1- and 3-month follow-up. Despite a slightly progressive worsening between 6- and 12-month follow-up, the final clinical scores remained higher compared with baseline ($P < 0.0005$), with no significant differences between PRP and HA.

Leukocyte Concentration

Leukocyte concentration in PRP preparations is another major confounding factor when analyzing the results included in this study. There is no doubt that leukocytes have a biological effect that must be understood. The difficulty of reaching an acceptable conclusion or trend when considering the optimal leukocyte concentration is based on the large spectrum of leukocytes content in PRP preparations injected in the studies reviewed and the lack of an acceptable and clear definition of what can be considered leukocyte rich or poor concentration. As reported in the studies included in this review, 5 studies used PRP preparations with leukocytes content above blood concentration (1.2 to 4.7 times the blood concentration), 9 used leukocytes containing preparations, 13 used minimal or no leukocytes preparations, and 2 studies did not report on leukocyte content. No trend related to leukocyte content and better or worse results was identifiable. This issue is of major relevance in future studies to better understand the role of leukocytes content in PRP preparations. It is essential that the terms "leukocyte rich" and "leukocyte poor" be defined more precisely and perhaps a third group of leukocyte blood concentration should be introduced for that matter.

Despite the obvious methodological variability, all studies seem to show overall positive results and a clinical benefit for the use of PRP. These benefits are emphasized in RCTs when compared to HA as a control[15,22,33-35] and even saline.[23] The duration of these benefits is still very controversial, as long-term follow-up studies are lacking, and many of the existing studies report only up to 6 months of follow-up. Studies with 1 year of follow-up are inconsistent in terms of the outcomes at this time point, with some reporting an improvement trend and others already showing deterioration at this time point. One study[26] observed relapsed pain 8.8 months after PRP treatment. This is an important aspect when assessing the benefits of PRP treatment, suggesting it has a limited or short-term effect that might necessitate further treatment cycles to maintain and prolong these effects.

It should be emphasized that no correlation was found between better results and any specific type of PRP characteristics and/or administration protocol. Any discussion involving PRP therapies should carefully acknowledge the differences between the preparations and the administration procedures used. Regardless of the fact that pure PRP and leukocyte PRP formulations are not comparable in terms of leukocyte content, platelet count, or plasma volume, the resulting improvements in pain and function were not exclusive to any type of formulation. This finding leaves the mystery of the optimal PRP treatment (protocol and formulation) as an exciting challenge for future research.

As described earlier, intraarticular PRP injections are as safe as other intraarticular injection treatments and present no significant risk for serious adverse effect. In a minority of patients, adverse effects were minor and temporary, with no long-term implications.

Conclusion

Current clinical studies evidence support the concept that PRP treatment can be beneficial for degenerative joint pathology in the knee and hip. It has been proven to temporarily relieve pain and function of the involved joint with superior results compared with several alternative treatments. Current variability in methodologies used in different studies and the numerous PRP preparation methods, in addition to the highly inconsistent systems to classify PRP formulations, make it difficult to establish firm and uniform recommendations and guidelines regarding which type of PRP to use and for which indications. A broad overview of the results clearly implies a positive influence of PRP on knee OA with encouraging clinical results in almost all the studies included in this review. The simplicity and safety of PRP use makes it an interesting and promising option for both researchers and clinicians. Further research with RCTs that will address the issues of the optimal preparation protocol and formulation of intraarticular PRP injections for OA of the knee, hip, and other joints, as well as longer follow-ups and larger population sizes is of major need.

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