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Analytical Review: Systematic

Use of Platelet-Rich Plasma in Intra-Articular Knee Injections for Osteoarthritis: A Systematic Review

Lawrence P. Lai, MD, MS, Todd P. Stitik, MD, Patrick M. Foye, MD, John S. Georgy, MD, MBA, Varun Patibanda, MD, Boqing Chen, MD, PhD

Abstract

Objective: To systematically analyze the literature on the use of platelet-rich plasma (PRP) for intra-articular injections of the knee and its efficacy in the treatment of knee osteoarthritis (OA).
Design: Systematic literature reviews were conducted in PubMed, Embase, and CINAHL (ie, Cumulative Index to Nursing and Allied Health Literature) on October 30, 2013, using the keywords "platelet-rich plasma" and "knee" and "osteoarthritis." Inclusion criteria included (1) studies with human subjects, (2) prospective clinical studies (including either clinical trials or observational studies), and (3) full-text articles published in English. Exclusion criteria were: (1) animal studies; (2) retrospective studies; (3) patients with previous surgical intervention with total knee arthroplasty or reconstruction of the anterior cruciate ligaments; and (4) articles not published in English
Results: A total of 319 abstracts and titles were reviewed (60 from PubMed, 250 from Embase, and 9 from CINAHL). A total of 8 relevant journal articles were identified, all of which were published between 2010 and 2013. One-half of the studies were prospective observational studies that included only PRP treatment; the rest were prospective comparative studies including both PRP and controls—2 were randomized controlled trials. Of the 4 comparative studies, 3 compared PRP with hyaluronic acid, which was considered as a commonly used effective treatment for knee OA; the other one used saline injection (ie, placebo) as the control. Although most of the analyses suffered from small sample size and was thus inconclusive, the findings consistently indicated that PRP might have better outcomes in patients with a lesser degree of degeneration and in younger patients.
Conclusion: PRP intra-articular injections of the knee may be an effective alternative treatment for knee OA. However, current studies are at best inconclusive regarding the efficacy of the PRP treatment. A large, multicenter randomized trial study is needed to further assess the efficacy of PRP treatment for patients with knee OA.

Introduction

Osteoarthritis (OA) is a prevalent disease, affecting approximately 27 million adults in the United States [1]. The prevalence increases with age, with a prevalence of 13.9% among adults 25 years and older and 33.6% among those 65 and older [2]. The most common areas affected by OA are in the knees, which accounted for 41.2% of 847 OA cases in one study [3]. The Framingham cohort study showed that the prevalence of knee OA has been increasing for the past 20 years from 1974 to 1994 [4], primarily as the result of increased physical activity and aging of the population.

Knee OA is characterized by articular cartilage degeneration. Because the cartilage is avascular and the cells have a low mitotic activity, it has limited healing potential once injured and eventually leads to irreversible damage. Knee OA is associated with pain and loss of mobility and can significantly impair quality of life. It is one of the top causes of disability in the United States [5].

The goals for the treatment of knee OA are relieving pain, improving function and quality of life, and reducing disability. A variety of modalities have been used in the treatment of knee OA, including both conservative methods and surgical methods. Surgical options include arthroscopy, osteotomy, and arthroplasty. Although surgical treatments can be effective, they are associated with some serious complications such as infection, deep-vein thrombosis, and prosthesis loosening and thus often are reserved after failure of nonsurgical or minimally invasive methods. Conservative methods include oral medications (such as anti-inflammatory agents), topical agents, therapeutic exercise, braces, in-shoe orthotics, acupuncture, and injections including intra-articular

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corticosteroid and hyaluronic acid (HA) viscosupplementation injections. These treatments at times, however, have limited effectiveness, and some have potential safety concerns. Their benefits often are limited to the short term without impact on the natural history of the disease, and some may even have negative impact on knee structures [6]. Therefore, innovative methods are needed to more effectively treat knee OA, especially if the disease process itself can be altered.

Recent development in biologic research has highlighted the importance of growth factors in maintenance of normal tissue structure and tissue lesion repair [6,7]. Platelet-rich plasma (PRP) comprises the concentrated platelets from centrifuged-spun whole blood [8]. This product contains a concentration of multiple growth factors that can be used for tissue regeneration. PRP was first used in the dental field in the healing process of implants and jaw reconstruction. It has now been explored widely in numerous medical specialties, including neurosurgery, ophthalmology, dermatology, otolaryngology, orthopedic surgery, and sports medicine. Because PRP is relatively simple, potentially low-cost, and minimally invasive, it has generated substantial interest in the treatment of knee OA in recent years. Its clinical efficacy, however, remains unclear. The aim of this study was to systematically synthesize the literature on the use of PRP for intra-articular injections of the knee and its efficacy in the treatment of knee OA.

Methods

Systematic Literature Review

Systematic literature reviews were conducted in PubMed, Embase, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) on October, 30 2013, using the keywords "platelet-rich plasma" and "knee" and "osteoarthritis." Two levels of screening were applied. At level 1, titles and abstracts were reviewed to exclude irrelevant studies; at level 2, full-text articles were reviewed to determine the relevance of the studies. In addition, the bibliographies of the articles were reviewed to identify additional relevant studies that had not been included in the level 1 and 2 searches.

Inclusion criteria included (1) studies with human subjects; (2) prospective clinical studies (including either clinical trials or observational studies); and (3) full-text articles published in English. Exclusion criteria were as follows: (1) animal studies; (2) retrospective studies; (3) patients with previous surgical intervention with total knee arthroplasty or reconstruction of the anterior cruciate ligaments; and (4) articles not published in English.

Literature Synthesis

Identified studies were reviewed systematically. The following information was extracted from each study: year and geographic locations, study design, treatment arms, major inclusion/exclusion criteria, PRP treatment, patient baseline characteristics, study duration, outcomes measures (function, pain, quality of life and others), and key findings.

Results

Description of Included Studies

A total of 319 abstracts and titles were reviewed (60 from PubMed, 250 from Embase, and 9 from CINAHL). A total of 8 relevant journal articles were identified, all of which were published between 2010 and 2013 (Table 1). Two studies (Kon et al [9] and Filardo et al [10]) were kin studies that presented results at different follow-up times. Half of the studies were prospective, observational studies that included only PRP treatment; the rest were prospective comparative studies that included both PRP and controls—2 were randomized controlled trials (RCTs). Of the 4 comparative studies, 3 compared PRP with HA, which was considered as a commonly used effective treatment for knee OA; the other one used saline injection (ie, placebo) as the control. Sample size for the PRP arm varied substantially, ranging from 14 knees to 115 knees; however, the majority (5 studies) had a sample size of 50-60 in the PRP groups. Three studies had 6 months' follow-up, 4 had 12 months, and 1 study had a 2-year follow up. Of the 8 studies, 5 were conducted in Europe (4 in Italy and 1 in Slovakia), 1 in the United States, 1 in India, and 1 conducted jointly in the United States and Italy.

All studies included only adults and required patients to have symptomatic knee degeneration (Table 2). The mean/median age of the studies was relatively comparable (between 47 and 58 years), although the age range varied across studies. Mean body mass index also was comparable across studies, ranging from 25 to 27. Substantial differences, however, were observed across these studies. Particularly, the degree of degeneration (mostly measured as Kellgren-Lawrence grade) and proportion of patients receiving previous surgical treatment varied considerably in the study populations.

The administration of PRP also varied in terms of frequency and treatment intervals. The intervention ranged from single administration to 3 times during the treatment course. If multiple administrations were implemented, the interval ranged from 1 week to 1 month.

With respect to outcomes assessed in these studies, all studies included function and pain measures (Table 3). Six studies also included quality of life outcomes. The most commonly used measurements included International Knee Documentation Committee subjective scale, Western Ontario and McMaster Universities Arthritis Index, Knee Injury & Osteoarthritis Outcome Score, pain visual analog scale (VAS) and EuroQol visual analog scale (EQ VAS). In addition, some studies also included International Knee Documentation Committee objective assessment and ultrasound assessments.

Table 1
Study articles

Study	Geographic Location	Study Design	Duration of Study	Treatment Arms	PRP Treatment and Image Guidance	PRP Formulations
Kon et al, 2010 [9]	Bologna, Italy	Single-arm, prospective observational study	12 mo; measurements were conducted at 2, 6, and 12 mo	PRP (n = 91 patients and 115 knees)	Three injections were administered 3 wk apart; 1st unit: laboratory analysis 2nd unit: injected within 2 hours of initial draw 3rd-4th unit stored at (−30°C) were thawed in dry thermostat at 37°C for 30 minutes before application	Initial venipuncture sample: 150 mL collected in 21 mL of sodium citrate. Centrifugations: 2. (1st: 1800 rpm for 15 min to separate erythrocytes; 2nd: 3500 rpm for 10 min to concentrate platelets) Quantity of PRP used: 20 mL total, 5-mL units. Concentration: total number of platelets per milliliter in PRP mean more than 6 million platelets given in every injection. Other: $CaCl_2$ was added before the injection No data on WBCs were recorded
Sampson et al, 2010 [13]	Santa Monica, CA	Single-arm prospective observational study	52 wk; measurements were conducted at 2, 5, 11, 18, and 52 wk	PRP (n = 14)	Three injections were performed 4 wk apart	Initial venipuncture sample: 54 mL mixed with 6 mL of anticoagulant citrate dextrose formula A. Centrifugations: 1; 15 min at 1700g. Quantity of PRP used: 6 mL Concentration: Not specified Other: 0.6 mL of a 1000 U/mL bovine thrombin suspension in 10% CaCl2 was added to PRP before injection. No data on WBCs were recorded
Kon et al, 2011 [6]	Three treatment centers in Bologna, Italy, and Santa Monica, CA	Prospective comparative observational study	6 mo; measurements were conducted at 2 and 6 mo	PRP n = 50; hyaluronic acid high molecular weight, n = 50; hyaluronic acid low molecular weight, n = 50	Three injections were administered 2 wk apart; 1st unit: laboratory analysis 2nd unit: injected within 2 hours of initial draw 3rd-4th unit stored at −30°C were thawed in dry thermostat at 37°C for 30 min before application.	Initial venipuncture sample: 150 mL. Centrifugations: 2: (1st: 1480 rpm for 6 min to separate erythrocytes; 2nd: 3400 rpm for 15 min to concentrate platelets). Quantity of PRP used: 20 mL total, 5-mL units. Concentration: total number of platelets per milliliter in PRP mean more than 6 billion platelets given in every injection. Other: CaCl2 (Ca+2 = 0.22 mEq × dose) was added before the injection No data on WBCs were recorded.

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Table 1 (*continued*)

Study	Geographic Location	Study Design	Duration of Study	Treatment Arms	PRP Treatment and Image Guidance	PRP Formulations
Filardo et al, 2011 [10]	Bologna, Italy	Single—arm, prospective observational study	2 y	PRP (n = 90 patients, 114 knees)	Three injections were administered 3 wk apart; 1st unit: laboratory analysis 2nd unit: injected within 2 hours of initial draw 3rd-4th unit stored at −30°C were thawed in dry thermostat at 37°C for 30 min before application	Initial venipuncture sample: 150 mL Centrifugations: 2: (1st: 1800 rpm for 15 min to separate erythrocytes, 2nd: 3500 rpm for 10 min to concentrate platelets) Quantity of PRP used: 20 mL total, 5-mL units Concentration: total number of platelets per milliliter in PRP mean more than 6 billion platelets given in every injection Other: CaCl2 was added before the injection. No data on WBCs were recorded.
Gobbi et al, 2012 [14]	Milan, Italy	Single—arm, prospective observational study	12 mo; measurements were conducted at 6 and 12 mo	PRP (n = 50)	Two injections with 1-mo intervals in between	Initial venipuncture sample: 8 mL Centrifugations: 1: 3500 rpm for 9 min. Quantity of PRP used: 4 mL Concentration: 200% of whole blood values Other: Pretreatment blood analysis of patients showed an average platelet count of 261,000 platelets. After centrifugation of 8 mL, platelet recovery of >95% and leukocyte recovery of 58% (mononuclear cell recovery, 93%) in 4 mL of PRP. Two-fold increase of platelets. No solution was added to activate PRP before injections.

Spaková et al, 2012 [7]	Kosice, Slovakia	Prospective comparative observational study	6 mo; measurements were conducted at 3 and 6 mo	PRP, n = 60; hyaluronic acid, n = 60	Three injections were administered at weekly intervals.	Initial venipuncture sample: 27 mL collected in 3 10-mL containers of 1 mL of 0.106 M sodium citrate. Centrifugations: 3: 1st: 3200 rpm for 15 min to separate erythrocytes/ leukocytes/plasma, 2nd: 1500 rpm for 10 min to separate leukocytes, 3rd: 3200 rpm for 10 min was performed to obtain a 2-part plasma: upper part consisting of platelet-poor plasma and the lower part consisting of PRP. The platelet-poor plasma was first discarded to avoid its mixing up with PRP. The tubes were shaken vigorously for 30 s to suspend platelets. The buffy coat layer, consisting of platelets, was then aspirated gently into a syringe in a volume of 3 mL of plasma and used for intra-articular injection within 30 min. Quantity of PRP used: 3 mL Concentration: 450% of whole blood values Other: Aliquot was removed to determine the initial platelet count. WBCs were incorporated in the PRP. Platelet count in the whole blood had a mean value of 150 $\pm$ 30 $\times$ 106 platelets/mL, and platelet count in PRP had a mean value of 680 $\pm$ 132 $\times$ 106 platelets/mL. The mean platelet density increased by 450% (4.5-fold) in average compared with the whole blood. Complete blood count after centrifugation increased white blood cell count concentration 3.6-fold. (6.4 $\pm$ 2.3 $\times$ 103/μL to 23.2 $\pm$ 7.6 $\times$ 103/ μL) and decreased the red blood cell concentration by 40% (3.8 $\pm$ 0.6 $\times$ 106/μL to 1.4 $\pm$ 0.9 $\times$ 106/ μL). The centrifuge increased the concentration 3.6-fold

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Table 1 (*continued*)

Study	Geographic Location	Study Design	Duration of Study	Treatment Arms	PRP Treatment and Image Guidance	PRP Formulations
Filardo et al, 2012 [12]	Bologna, Italy	Randomized active-controlled trial	12 m; measurements were conducted at 2, 6, and 12 mo	PRP, n = 54 hyaluronic acid, n = 55	Three injections were administered with weekly intervals. 1st unit: laboratory analysis 2nd−4th unit: stored at (−30°C) No data shows thawing temperature or duration before application.	Initial venipuncture sample: 150 mL Centrifugations: 2: (1st: 1480 rpm for 6 min to separate erythrocytes, 2nd: 3400 rpm for 15 min to concentrate platelets). Quantity of PRP used: 20 mL total, 5-mL units. Concentration: Total number of platelets per milliliter in PRP represented a mean increase of 5 times compared with whole blood values. Platelet concentration the presence of leukocytes was 1.2 times with respect to normal blood values. Other: WBCs were incorporated in the PRP. The centrifuge increased the WBC concentration 1.2-fold.
Patel et al, 2013 [11]	Chandigarh, India	Double-blinded randomized controlled placebo-controlled trial	6 mo; measurements were conducted at 6 wk, 3 mo, and 6 mo	PRP single injection n = 52 knees; PRP 2 injections n = 50 knees; saline n = 46 knees.	One group: single injection Second group: 2 injections at 3 wk apart	Initial venipuncture sample: 100 mL collected in a 100-mL bag with CPA-A1 (citrate phosphate dextrose and adenine) Centrifugations: (1: 1500 rpm for 15 min to separate PRP and residual red blood cells with the buffy coat). Quantity of PRP used: 8 mL per knee. Concentration: Platelets injected was average 2.5 billion. Other: Leukocyte filter was used; therefore, no WBCs were incorporated in the PRP. Total leukocyte count was zero in PRP due to leukocyte filter that was applied, and product is type 4B as per the Mishra classification. Mean platelet count achieved was 310.14 × 103/ μL, and the mean quantity of platelets injected was 238.56×10^7. In the PRP group, 1 mL of calcium chloride (M/40) was injected in a ratio of 1:4 for every 4 mL of PRP.

PRP = platelet-rich plasma; WBC = white blood cells.

Table 2
Patient characteristics and major inclusion/exclusion criteria

Study	Major Inclusion/Exclusion Criteria	Patient Baseline Characteristics
Kon et al, 2010 [9]	1. History of chronic (≥4 mo) pain or swelling of the knee and imaging findings of degenerative changes in the joint. 2. Exclusion criteria were systemic disorders, such as diabetes, rheumatoid arthritis, major axial deviation (varus >5 degrees, valgus >5 degrees), hematologic diseases (coagulopathies), severe cardiovascular diseases, infections, immunodepression, patients in therapy with anticoagulants —antiaggregants, use of NSAIDs in the 5 d before blood donation, patients with hemoglobin values of <11 and platelets values of <150,000/cubic mm.	62.6% men Median age: 47 y (range 24-82) 73.6% had monolateral lesion BMI was 25 ± 3 29.7% had previous surgery Kellgren: 50.4% in 0, 28.7% in I-III, 20.9% in IV.
Sampson et al, 2010 [13]	1. History of primary or secondary knee osteoarthritis >3 mo: damage to articular cartilage seen during arthroscopy or on weight-bearing radiographs, a visual analog pain score of 60 on a 100-mm scale, discontinued use of nonsteroidal anti-inflammatory drugs for at least 1 mo after the treatment, and pain that was unresponsive to at least 2 conventional therapies (local steroid injections, viscosupplementation, NSAIDs, physical therapy, acupuncture, bracing, assistive devices, and lifestyle modification). 2. Major exclusion criteria included: pregnancy or breastfeeding, younger than 18 y, intolerant to acetaminophen or Vicodin, a history of drug abuse, cortisone injection within 6 wk, use of NSAIDs 1 wk before, a history of anemia, bleeding disorders, rheumatoid arthritis, knee surgery within 3 mo of treatment, infection of the knee joint within 6 mo, active infection, or any active malignancy.	Median age: 51.8 y (range 18-87) 85.7% men BMI: mean 25.0
Kon et al, 2011 [6]	1. Patients affected by a unilateral lesion with a history of chronic (4 mo) pain or swelling of the knee and imaging findings (radiography or MRI) of degenerative changes of the joint. 2. Exclusion criteria included systemic disorders such as diabetes, rheumatic diseases, hematologic diseases (coagulopathies), severe cardiovascular diseases, infections, immunosuppression, patients receiving therapy with anticoagulants-antiaggregants, use of NSAIDs in the 5 d before blood donation (for reasons of caution, because disagreement exists on the use of concomitant NSAIDs before the PRP treatment), and patients with hemoglobin (g/dL) values of less than 11 and platelet values of less than 150,000/cubic mm.	Age: mean 50.6-54.9 y 50%-60% men BMI: 24.6-26.2 Kellgren: 38%-44% in 0, 38%-44% in I-III, 16%-20% in IV. Previous surgery: 26%-36%
Filardo et al, 2011 [10]	Follow up study of the one by Kon et al, 2010 [9]	Same as Kon et al, 2010 [9]

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Table 2 (*continued*)

Study	Major Inclusion/Exclusion Criteria	Patient Baseline Characteristics
Gobbi et al, 2012 [14]	1. Inclusion criteria: (1) Age between 30 and 60 y, BMI <30, normal results for complete blood count and coagulation control, minimum follow-up of 1 y; (2) Patients with symptomatic osteoarthritic knees and partial- or full-thickness cartilage lesions; (3) Patients with severe pain and under anti-inflammatory treatment without improvement >3 mo; (4) Patients with stable knees, normal tibiofemoral alignment, or patellofemoral tracking. 2. Exclusion criteria include: (1) Patients with blood diseases, systemic metabolic, immunodeficiency, hepatitis B or C, HIV-positive status, infection and septicemia, local infection; (2) Patients with advanced and tricompartmental osteoarthritis, rheumatoid or polyarticular arthritis, symptomatic hip osteoarthritis, or symptomatic contralateral knee osteoarthritis; (3) Significant joint swelling or clinical signs of acute inflammation (possible inflammation or infection); (4) Varus-valgus malalignment above 5°, patellofemoral maltracking or untreated instability, and total or subtotal meniscectomy (> 2/3 excised); (5) Pretreatment blood platelets value 25% below the reference value or alcoholism, smoking, drugs; (6) Treatment with corticosteroids <3 mo or medication <7 d that could interfere with platelet aggregation	Age: 47.7 y 62% men Kellgren: 22% in 1, 38% in 2, and 40% in 3 Previous surgery: 50%
Spaková et al, 2012 [7]	1. History of chronic pain of the knee lasting at least 12 mo and the radiologic signs of knee osteoarthritis Grade 1, 2, and 3 according to the Kellgren and Lawrence classification. All patients had previously been treated conservatively with analgesics and NSAIDs without success for at least 6 mo. 2. The exclusion criteria were thrombocytopenia (platelet count, G100 109/L), anemia (hemoglobin, G10 g/dL), systemic disease, hematologic disease, history of tumor or active tumor or hematologic malignant disease, severe cardiovascular disease, infection, immunosuppressive status, active anticoagulant therapy, and application of intra-articular depot glucocorticoids injection or hyaluronic acid within 3 mo before application of tested substance. The use of anti-inflammatory drugs was not permitted from 5 d before the beginning of treatment to 7 d after the last treatment dose of PRP.	52.5% men Age: mean 53 y BMI: mean 27.9 Kellgren: 3.3% in 1; 63.3% in 2; 33.3% in 3.
Filardo et al, 2012 [12]	1. History of chronic (at least 4 mo) pain or swelling of the knee and imaging findings (radiograph or MRI) of degenerative changes of the joint. 2. Exclusion criteria were systemic disorders such as diabetes, rheumatoid arthritis, major axial deviation (varus >5 degree, valgus >5 degrees), hematologic diseases (coagulopathy), severe cardiovascular diseases, infections, immunodepression, patients in therapy with anticoagulants or antiaggregants, the use of NSAIDs in the 5 d before blood donation, and patients with Hb values of <11 and platelet values of <150,000/cubic mm.	Age: mean 55 and 58 y Men: 68.5% and 56.4% BMI: 27 and 26 Symptoms: 64 and 63 mo Kellgren: mean 2.2 and 2.1 Previous surgery: 63.0% and 52.7%
Patel et al, 2013 [11]	1. Ahlbäck grade 1 or 2 knees without significant deformity. 2. Excluded patients included secondary osteoarthritis to inflammatory diseases, patient with generalized osteoarthritis, bone metabolic diseases, coexisting backache, advanced osteoarthritis, patients who had arthroscopic lavage in the previous year or who were receiving anticoagulants, low hemoglobin less than 10 gm% or comorbidities, infection, tumor, crystal arthropathies, significant joint effusion.	Age: 51.64 to 53.65 y Men: 20%-41% BMI: 25.81-26.28 Ahlbäck grade: 54%-72% in 1; 20%-40% in 2; 4%-13% in 3

NSAIDs = nonsteroidal anti-inflammatory drugs; MRI = magnetic resonance imaging; BMI = body mass index.

Table 3
Function and pain measures

Study	Function Outcome	Pain Outcome	Quality of Life Outcome	Other Outcomes	Results
Kon et al, 2010 [9]	IKDC subjective	IKDC subjective	EQ VAS	IKDC objective	IKDC objective score increased from 46.1% of normal and nearly normal knees to 78.3%, 73.0%, and 66.9% at 2, 6, and 12 mo, respectively. IKDC subjective score increased from 40.5 to 62.5, 62.6, and 60.6 at 2, 6, and 12 mo, respectively. EQ VAS improved from 50.3 to 71.2, 70.6, and 69.5 at 2, 6, 12 mo, respectively.
Sampson et al, 2010 [13]	KOOS, including pain relief, symptom relief, activities of daily living, sports and quality of life	KOOS: pain relief, Brittberg Peterson VAS: resting, moving and bent knee	KOOS: quality of life	Ultrasound measurement of cartilage thickness	All 5 scores in KOOS improved from baseline to 52 wk. The pain relief and symptom relief scores showed a significant improvement in trend analysis. Brittberg-Peterson Pain VAS showed significant trends in reduction in resting, moving and bent knee pains. Ultrasound measurement showed some but nonsignificant thickening in lateral and central femoral cartilage
Kon et al, 2011 [6]	IKDC subjective	IKDC subjective	EQ VAS		At 2-mo follow-up, the PRP and hyaluronic acid low molecular weight groups showed a similar improvement (IKDC subjective score from 41.2 to 62.7 for and EQ VAS from 53.6 to 73.0 for PRP), with greater results compared with the hyaluronic acid high molecular weight group. At 6 mo follow-up, better results were observed in the PRP group (IKDC subjective score from 41.2 to 64.0 for and EQ VAS from 53.6 to 72.3 for PRP). PRP and low molecular weight hyaluronic acid treatments offered similar results in patients older than 50 y and in the treatment of advanced osteoarthritis. PRP showed a better performance compared with hyaluronic acid in younger patients affected by cartilage lesions or early osteoarthritis.
Li et al, 2011 [17]	WOMAC; Lequesne	WOMAC	IKDC		Better in PRP group at 6 mo
Filardo et al, 2011 [10]	IKDC subjective	IKDC subjective	EQ VAS	IKDC objective	All scores worsened at the 24-mo follow-up compared with the 12-mo follow up, although they were improved compared with baseline. IKDC objective decreased from 67% to 59% of the normal or nearly normal knees. IKDC subjective score decreased from 60 to 51. The median duration of clinical improvement was 9 mo. Results were better in younger patients and those with lower degrees of cartilage degeneration.

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Table 3 (*continued*)

Study	Function Outcome	Pain Outcome	Quality of Life Outcome	Other Outcomes	Results
Gobbi et al, 2012 [14]	IKDC objective KOOS Tegner score Marx score	IKDC subjective pain VAS KOOS: pain relief	KOOS: quality of life		All scores showed significant improvements at 6 and 12 mo compared with baseline. Pain VAS: reduced from 4.1 at baseline to 2.2 and 1.2 at 6 and 12 mo, respectively. KOOS pain relief: improved from 73.6 at baseline to 81.9 and 88.7 at 6 and 12 mo, respectively; symptoms: improved from 72.0 at baseline to 78.2 and 86.4 at 6 and 12 mo, respectively; activities of daily living: improved from 77.8 at baseline to 86.3 and 94.8 at 6 and 12 mo, respectively; sport: improved from 42.3 at baseline to 50.6 and 63.8 at 6 and 12 mo, respectively; quality of life: improved from 41.3 at baseline to 52.5 and 68.0 at 6 and 12 mo, respectively. IKDC subjective improved from 48.2 at baseline to 65.2 and 75.4 at 6 and 12 mo, respectively; IKDC objective improved from 32% normal or nearly normal knees to 74% and 90% at 6 and 12 mo, respectively. Marx score improved from 4.0 at baseline to 6.9 and 9.4 at 6 and 12 mo, respectively. Tegner score improved from 2.9 at baseline to 3.9 and 4.8 at 6 and 12 mo, respectively.
Spaková et al, 2012 [7]	WOMAC	WOMAC 11-point pain intensity NRS			There were no significant differences in WOMAC and NRS scores between the 2 treatment groups at baseline. In each treatment group, there were significant improvements based on both measures at 3 and 6 mo compared with baseline (PRP: WOMAC 14.35 and 18.85 at 3 and 6 mo vs 38.76 at baseline; NRS 2.06 and 2.69 at 3 and 6 mo vs 5.27 at baseline). At 3 mo, patients treated with PRP had significantly better outcomes measured in both scores compared with those treated with hyaluronic acid. In both treatment groups, outcomes remained stable but nonsignificantly worse from the end of therapy to 6 mo.
Filardo et al, 2012 [12]	KOOS; IKDC subjective; Tegner	KOOS pain relief; IKDC subjective	EQ VAS KOOS quality of life	ROM and the transpatellar circumference	There were significant improvements in all scores in both treatment groups from baseline to 2, 6, and 12 mo. IKDC subjective: from 50.2 at baseline to 62.8, 64.3, and 64.9 at 2, 6, and 12 mo in the PRP group. Similar results were observed in EQ VAS and KOOS in all subcategories. Tegner score: from 2.9 at baseline to 3.8 at 12 mo. There were no significant differences in any measure between the 2 treatment groups; however, PRP had a trend toward better results in Kellgren II or less.
Patel et al, 2013 [11]	WOMAC	WOMAC Pain VAS			There were significant improvements in pain, stiffness, and physical function in the 2 PRP groups compared with placebo. There were no differences in outcomes between the 2 PRP groups. In both PRP groups, outcomes were slightly worse at 6 mo compared with 3 mo. Knees with Ahlbäck grade 1 fared better than those with grade 2.

IKDC = International Knee Documentation Committee; EQ-VAS = EuroQol visual analog scale; KOOS = Knee Injury and Osteoarthritis Outcome Scores; PRP = platelet-rich plasma; WOMAC = Western Ontario and McMaster Universities Asrthritis Index; NRS = Numeric Rating Scale; ROM = range of motion.

Outcomes Associated With PRP

Regardless of the outcome measures, all studies consistently have demonstrated the efficacy of PRP in improving function and quality of life and reducing pain among patients with knee OA (Table 3). The onset of treatment effects appeared fairly early in the treatment (within 2 months of treatment initiation) [6,9,11-13]; however, it seemed that the effects were only stable in the short term. In multiple studies, numerically worse outcomes were observed when a longer follow-up period was studied. For example, some studies showed that Western Ontario and McMaster Universities Arthritis Index, pain VAS, and EQ VAS were slightly worse at 6 months compared with the outcomes measured at 2 and 3 months [6,7,9,11]. Only 2 studies demonstrated that improved outcomes were maintained up to 12 months [13,14]. The only study with a follow-up time beyond 1 year [10] showed clearly worse outcomes at 2 years compared with those at 1 year, although the outcomes were still better compared at baseline. The median duration of clinical improvement was only 9 months [10].

The findings from the only placebo-controlled RCT demonstrated that PRP has superior efficacy in improving pain, stiffness, and physical function compared with placebo during a 6-month study [11]. The same study also suggested that frequency of PRP did not impact the treatment outcomes [11]. The studies in which the authors compared PRP versus HA revealed mixed findings. Although the 2 prospective observational studies [6,7] showed that PRP generally was associated with better function and reduced pain compared with HA, the RCT [12] suggested no differences in outcomes between the 2 groups in the overall trial population.

Several studies also assessed the outcomes of PRP in patient subgroups. Although most of the analyses suffered a small sample size and were thus inconclusive, the findings consistently indicated that PRP might have better outcomes in patients with lower degree of degeneration and in younger patients [6,10-12].

PRP Formulations and White Blood Cells (WBCs)

The authors of this review acknowledged the concentrations of PRP used in the studies. One study derived 200% concentration of whole blood values [14]. Another study provided 6 billion platelets per injection [10]. This variation can be attributed to a few factors—the first being the quantity of venipuncture sample. Kon et al in 2010 [9] collected 150 mL of whole blood, whereas Sampson et al [13] collected 54 mL. The addition and type of anticoagulant also varied in each study. In 1 study authors used 1 mL of citrate-phosphate-dextrose-adenine (CPDA) for each milliliter of whole blood collected whereas another used 1 mL of 0.106 M sodium citrate [7,11]. The amount of centrifugations, the rpms, and the duration of each cycle differed within each study (Table 1). In 1 study authors centrifuged the whole blood thrice, whereas in another study the authors used just one cycle at 1500 rpm [9,11]. Even more, in certain studies investigators chose to include WBCs into the PRP at different concentrations whereas in another the authors elected to exclude them, using leukocyte filters instead [7,11,12]. In 2 studies the authors failed to mention a concentration of WBCs used in their respective methods [6,10].

Discussion

PRP has been gaining popularity in the treatment of knee OA because of its simplicity, low cost and minimally invasive nature. Although this innovative approach showed promising results in some preliminary clinical studies, no confirmative findings have been demonstrated in its efficacy. In the current review we systematically synthesized the clinical evidence on the impact of PRP on function, pain, and quality of life among patients with knee OA. Overall, the clinical research with this regard is very limited. The existing studies suggest that PRP could be an effective treatment in the short term to improve patients' function and quality of life and reduce pain. However, its long-term efficacy remains unclear. The only long-term study (2 years) suggests that the benefits of PRP are not sustainable [10], which may limit the utility of this new treatment in the clinical use. In addition, the incremental value of PRP compared with the existing treatments, particularly HA, remains a question, because the only RCT [12] did not reveal superiority of PRP. More evidence is indicated before PRP is widely adopted in the treatment of knee OA.

Also, it is important to acknowledge the variation in both platelet and leukocyte concentrations because they are the major forces behind the inflammatory responses after PRP administration. A systematic review of PRP literature revealed that only 1 of its 21 reports included an analysis of WBCs, platelet, and red blood cell (RBC) contents of their PRP formulations [15]. Braun et al [16] evaluated the viability of cultured human synoviocytes exposed to various formulations of PRP. Their results indicated that cell death was greater in cell cultures exposed to both leukocyte-rich PRP and RBC preparations.

Similarly, the authors of this review found that only a few studies included information on WBC concentrations, whereas others did not (Table 1). This confounding variable, along with the variations in venipuncture sample, centrifuge cycles and duration, and the amount and type of anticoagulant, all play a role in obscuring a clear connection between PRP and its benefits. Therefore, future research must focus on reducing these variations to establish a direct and clear correlation.

The current review also sheds light on future research directions. First, the existing studies are limited by small sample size and their observational nature. To demonstrate the efficacy of PRP in knee OA, larger-scale, multicenter RCTs are needed. Second, knee OA is a chronic disease, and long-term outcomes should be an important consideration in evaluating new treatments. Hence, clinical trials with longer follow-up are indicated. Third, the current findings suggest that PRP may have differential impacts across patient subgroups. To further assess the value of PRP, it is desirable to identify patients who can benefit most from this treatment, particularly compared to the existing conservative treatments with proven efficacy.

Conclusions

PRP intra-articular knee injections may be an effective alternative treatment for knee OA for patients who do not adequately symptomatically respond to more traditional treatments. However, current studies are, at best, inconclusive regarding the efficacy of PRP treatment. Significant variations in administration schedule likely make it difficult to draw definitive conclusions about PRP in general. Future studies also need to evaluate the impact of WBCs and RBCs. Recent in vitro work suggests that PRP formulations that are leukocyte-rich or contain RBCs may be cytotoxic in cultured synoviocytes. However, further human subject studies are needed to determine if these findings are present in vivo. Finally, a large multicenter randomized clinical trial employing a uniform method of administration schedule that stratifies subgroups with long-term follow up is needed to further assess the efficacy of PRP treatment for patients with knee OA.

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Disclosure

L.P.L. Department of Physical Medicine and Rehabilitation, Rutgers, New Jersey Medical School, 90 Bergen St., Newark, NJ 07103. Address correspondence to: L.P.L.; e-mail: laila@njms.rutgers.edu
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T.P.S. Department of Physical Medicine and Rehabilitation, Rutgers, New Jersey Medical School, Newark, NJ
Disclosure: nothing to disclose

P.M.F. Department of Physical Medicine and Rehabilitation, Rutgers, New Jersey Medical School, Newark, NJ
Disclosure: nothing to disclose

J.S.G. Department of Physical Medicine and Rehabilitation, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
Disclosure: nothing to disclose

V.P. American University of Antigua College of Medicine, New York, NY
Disclosure: nothing to disclose

B.C. Department of Physical Medicine and Rehabilitation, Rutgers, New Jersey Medical School, Newark, NJ
Disclosure: nothing to disclose

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