Platelet-Rich Plasma Injections for Advanced Knee Osteoarthritis

A Prospective, Randomized, Double-Blinded Clinical Trial

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Background: Intra-articular injections of platelet-rich plasma (PRP) to treat symptoms of knee osteoarthritis (OA) have been successfully used in young patients and in the early stages of disease. No previous studies have analyzed outcomes of PRP injections during the late stages.

Hypothesis: PRP reduces pain and leads to a more effective and lasting functional recovery than corticosteroid with local anesthetic.

Study Design: Randomized controlled trial; Level of evidence, 2.

Methods: A total of 75 patients with symptomatic knee OA (Kellgren-Lawrence grade 3 to 4) were enrolled in this study between August 2013 and July 2014. Patients were randomized to treatment either with a single leukocyte-reduced PRP or corticosteroid intra-articular injection. The primary variable was visual analog scale assessment at 1 month. Secondary outcomes were the Knee injury and Osteoarthritis Outcome Score (KOOS) and Short Form–36 (SF-36) at 1, 3, and 6 months after treatment. Patient satisfaction at final follow-up was assessed. Both groups were homogeneous and comparable in baseline characteristics.

Results: All variables improved in both groups. Statistical differences between groups were not found for the majority of the outcome variables, although the magnitude of improvements tended to be greater in the PRP group. Quality-of-life differences between values at 3 and 6 months versus baseline increased significantly more in the study group ($P = .05$ and $.03$, respectively), and so did general health perception differences at 6 months ($P = .018$).

Conclusion: A single PRP intra-articular injection is effective for relieving pain and improving activities of daily living and quality of life in late-stage knee OA. For patients with late-stage knee OA who are 67 years or older, 1 intra-articular injection of PRP has similar results to 1 shot of corticosteroid.

Keywords: platelet-rich plasma; osteoarthritis; knee; intra-articular injections

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Osteoarthritis (OA) is the most common joint disease in the world and a major cause of pain and disability in older adults.[24] Analysis from primary care databases of different countries found higher incidence of knee OA than hip or hand OA and a large increase in newly diagnosed cases of knee OA in the past decade, especially in younger adults.[1,26,34] The main symptom of patients with knee OA is pain, often accompanied by stiffness and limited mobility of the knee.

Initial OA treatment combines nonpharmacological methods with oral medications. In more advanced or very symptomatic stages, intra-articular injection (IAI) is used: corticosteroid with local anesthetic (CSA), hyaluronic acid (HA), or biological products such as platelet-rich plasma (PRP). However, current studies have changed the prescribing pattern, using IAI as a first-line treatment because it has proven effectiveness for pain with fewer side effects than some oral medications.[2,3,9,10,14,16,28] The use of PRP in the treatment of degenerative knee OA has been extended

in recent years given its high margin of safety and easy production and administration.[30] Published studies regarding PRP IAI for knee OA have varying levels of scientific evidence.[4,5,7,18,22,31] Usually they note the effectiveness of PRP for pain treatment and knee joint function, its superiority compared with HA or placebo, and its better results in the early stages of knee OA. In addition, compared with HA, its effects last longer (6-12 months). Published clinical trials also confirm the superiority of PRP in comparison with other IAIs.[6,25,27,29,30,32] Nearly all published data have found good results in young patients and in early-stage knee OA, but no previous studies have analyzed the clinical outcomes of PRP injections during the late stages of disease.

The hypothesis of this study was that PRP reduces pain and leads to a more effective and lasting functional recovery compared with CSA. Our objective was to compare the efficacy of a single PRP IAI for relieving pain and improving knee function during late-stage OA with a CSA IAI. We have compared PRP with CSA rather than placebo so as not to leave any patient untreated (in previous published trials, placebo has been shown to be unsuccessful[30]). For this reason, we considered CSA to be the gold standard for pain treatment through IAI in late-stage knee OA.

METHODS

Trial Design

This was a prospective randomized, double-blind, parallel group, active-controlled study with 2 groups receiving different treatments. This clinical trial was conducted in accordance with the principles of the Declaration of Helsinki, authorized by the Spanish Agency for Medicines and Health Products, and registered with the European Clinical Trials Database.

Volunteer participants were assigned to 1 of 2 intervention groups and assessed on a number of variables before and at 3 points after treatment (1, 3, and 6 months). We decided to perform the first assessment at 4 weeks after the infiltration, assuming clinical improvement after corticosteroid injection has an effect between 1 and 4 weeks. The reason not to extend the study beyond 6 months was to prevent patients from having to wait a year to receive a new treatment, if necessary. Note that most publications observed symptomatic deterioration from the sixth month in patients treated with PRP and from the first month in patients treated with CSA.[3,5,7,13,16,18-23,31]

Sample

Sample size calculation was performed using the hypothesis of superiority. In the assessment of pain by visual analog scale (VAS) (range, 0-100 points) 1 month after the procedure, we assumed an average score of 33.7 in the control group and a standard deviation of 23.6 in both groups. To detect a reduction of 17 points in the treatment group versus the control group with a power of 80% and 2-sided significance level of .05, it would be necessary to include a total of 64 patients (32 patients per group). A difference of 17 points between the 2

TABLE 1
Study Inclusion and Exclusion Criteria

Inclusion criteria
  Age 40-80 years
  Knee osteoarthritis[a]
  Eligibility for total knee arthroplasty
  Walking ability with or without external support
  Visual analog scale baseline value >60
  Informed consent obtained
Exclusion criteria
  Inability to obtain informed consent
  Received intra-articular injections of steroids, anesthetics, or hyaluronic acid in the past year
  Underwent arthroscopic surgery in the past 3 months
  Received open surgery on occasion
  Compromised bone metabolism (except for osteoporosis)
  Fibromyalgia
  Chronic fatigue syndrome
  Liver disease
  Clotting deficiency (blood dyscrasias)
  Thrombocytopenia (<150,000 platelets per mm^3, hemoglobin <11 g/dL)
  Treated with anticoagulants
  Active infection
  Cancer
  Neuromuscular disease
  Severe cardiovascular disease
  Immunosuppressed patients
  Pregnancy
  Severe damage of homolateral hip or ankle
  Rheumatoid arthritis
  Inflammatory diseases of the connective tissue
  Involved in proceedings for legal incapacitation or financial compensation
  Documented history of allergy to steroids, bupivacaine, or blood products
  Valgus deformity >15° or varus deformity >20°
  Severe ligamentous instability of the knee joint
  Limitation of knee range of movement: flexion <90°, extension deficit >20°
  Positive serology

[a]As diagnosed by the American College of Rheumatology.[28]

groups was fixed based on published results.[19,20] The sample size calculation was performed using 2008 PASS (NCSS Statistical Software). Statistical data analysis was carried out using SPSS (version 17.0.2; IBM Corp).

Categorical variables were described by percentages and frequencies, while continuous variables were described by means, standard deviations, medians, interquartile ranges, and minimum and maximum values. The analysis of primary and secondary variables was accomplished using the intention to treat principle. Parametric tests (Student t test for independent samples) were used for normal distributions and the Mann-Whitney U test for nonparametric distributions. Data symmetry was analyzed using the Shapiro-Wilk test. If the P value was not significant, then the Student t test was used. Otherwise, the Mann-Whitney U test was used. Categorical variables were compared using chi-square tests. The level of statistical significance was set at $P < .05$.
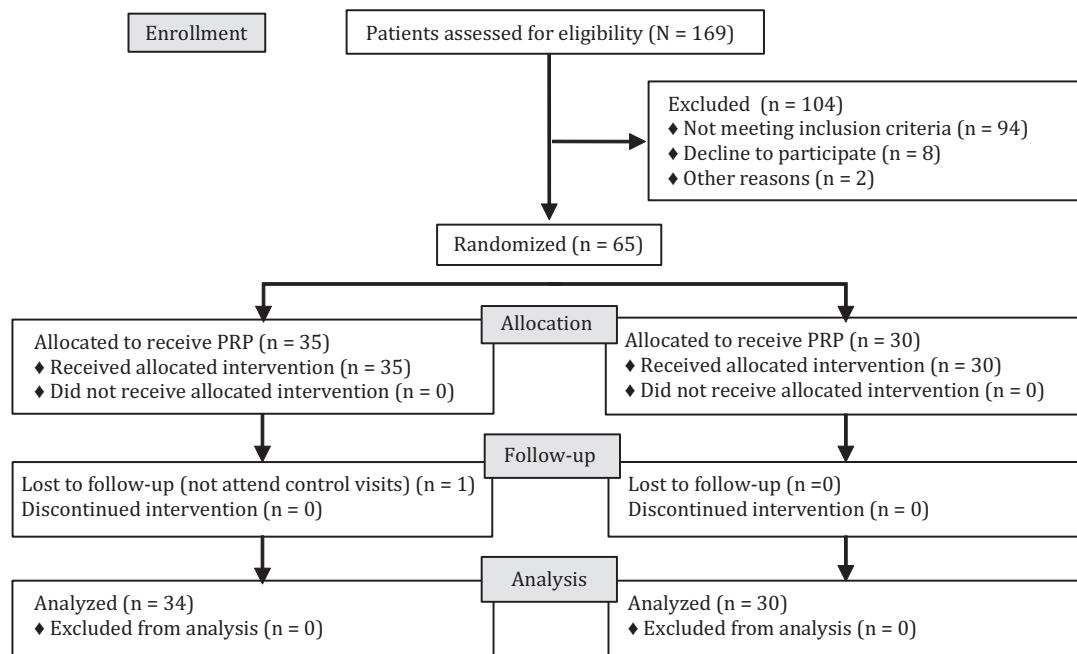
Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. PRP, platelet-rich plasma.

Data were collected and entered into a database by our Unit in Methodology for Biomedical Research (USMIB).

Participants

The study population consisted of patients already on the waiting list of the public health system for knee replacement. OA was diagnosed by the American College of Rheumatology criteria[33] and staged as Kellgren-Lawrence (K-L) radiological classification.[17] All radiographs were taken under weightbearing conditions. Patients who met eligibility criteria (Table 1) and signed consent to participate in the clinical trial were allocated (computer random sequence generated by USMIB) to 1 of 2 intervention groups: the study group (4 mL autologous PRP) or the control group (2 mL betamethasone: 6 mg betamethasone sodium phosphate and betamethasone acetate 6 mg [Merck] and 2 mL bupivacaine 0.25% [B.Braun]). Before treatment assignment, blood collection was performed for serological study. Patients with positive serology for HIV, hepatitis, or syphilis were discarded. All patients were blinded to the treatment they received.

All included patients provided a 60-mL sample of peripheral blood. Blood of patients assigned to the control group was discarded. Blood of patients assigned to the study group was analyzed and prepared according to the protocol of the hospital blood and tissue bank (BST).

PRP Preparation

The BST prepared leukocyte-reduced PRP using a double-spin methodology. The entire process was performed in a class C clean room and under the laminar flow of a BioII/A biological safety cabinet (LAbGard; Nuaire). Approximately 60 mL of venous blood was drawn from the antic-ubital vein and collected into tubes containing 3.2% of citrated dextrose as an anticoagulant (Becton Dickinson Biosciences). Tubes were then centrifuged at 280g for 15 minutes at room temperature on a table-top centrifuge, the entire plasmatic fraction was isolated in a separate sterile tube avoiding the buffy coat layer, and a 10% vol/vol of anticoagulant (ACD-A Solution; Grifols) was added. The isolated plasma was centrifuged at 680g for 20 additional minutes, and platelets were then completely resuspended in 6 mL of autologous plasma. Finally, 4 mL of PRP were dispensed in a syringe for further injection, and the remainder volume was dedicated to count platelets and white blood cells (WBC) in a hematology analyzer (AcT diff2; Beckman Coulter). We did not use exogenous factors for the activation process.

Intervention Procedure

Under aseptic conditions, 4 mL of either control or study treatment were injected into the medial compartment with an intramuscular needle (0.8 × 40 mm) without local anesthetic, with knees hanging at 90° of flexion. Rest, depending on pain, and cryotherapy were indicated in the first 24 hours after injection. Patients were authorized to use painkillers and nonsteroidal anti-inflammatories along with routine clinical practice during the study period. This did not invalidate the study, as both groups were authorized.

Patients were monitored 1 week after injection to rule out side effects of the infiltration and returned at 1, 3, and 6 months after treatment.

TABLE 2
Baseline Characteristics of Study Subjects[a]

	Treatment Group		
	PRP	Control	P Value
Age, y[b]	65.56 ± 8.6	68 ± 7.17	.225
	(43 to 78)	(53 to 80)	
	66 [61, 72]	67 [63, 73.5]	
Sex (female/male), n (%)	23/12 (65.71/34.29)	24/6 (80/20)	.269
Smoker (no/yes), n (%)	29/6 (82.86/17.14)	26/4 (86.67/13.33)	.742
External support to walk (no/yes), n (%)	34/1 (97.14/2.86)	29/1 (96.67/3.33)	>.999
Knee Society patient category, (No. of knees) %[c]			.730
A	8 (22.86)	5 (16.67)	
B	25 (71.43)	24 (80)	
C	2 (5.71)	1 (3.33)	
Side (right/left), n (%)	16/19 (45.71/54.29)	14/16 (46.67/53.33)	>.999
K-L classification, n (%)			.026
Grade 1	0 (0)	0 (0)	
Grade 2	0 (0)	0 (0)	
Grade 3	10 (28.6)	17 (56.6)	
Grade 4	25 (71.4)	13(43.4)	
BMI, kg/m^2 [b]	31.20 ± 4.36	30.98 ± 4.16	.576
	(20.40 to 39.00)	(22.50 to 44.30)	
	30.40 [27.00, 33.80]	30.60 [28.30, 32.90]	
Use of pain medication, n (%)			.63
Analgesics	18 (48.65)	19 (51.35)	
NSAIDs	18 (52.94)	16 (47.06)	
Opiates	4 (57.14)	3 (42.86)	
Range of motion, deg[b]			
Flexion	111.29 ± 14.37	140.63 ± 162.62	.914
	(70 to 140)	[90 to 130]	
	110 [100, 120]	110 [100, 120]	
Extension	−1.71 ± 3.42	−1.50 ± 2.33	.738
	(−10 to 0)	(−5 to 0)	
	0 [0, 0]	0 [−5, 0]	
Ambulation autonomy, min[b]	28.43 ± 25.60	28.83 ± 24.41	.973
	(0 to 120)	(0 to 90)	
	20 [15, 30]	20 [10, 45]	
VAS[b]	75.14 ± 10.11	75.00 ± 9.38	.953
	(60.00 to 90.00)	(60.00 to 90.00)	
	70.00 [70.00, 80.00]	70.00 [70.00, 80.00]	
KOOS subscale[b]			
Pain	35.11 ± 17.94	38.80 ± 18.99	.435
	(0.00 to 72.22)	(0.00 to 72.22)	
	32.29 [22.22, 44.44]	41.67 [27.78, 51.39]	
Symptoms	45.41 ± 12.45	47.98 ± 15.35	.464
	(21.43 to 71.43)	(17.86 to 75.00)	
	42.86 [37.50, 53.57]	50.00 [35.71, 60.71]	
Activities of daily living	36.05 ± 18.58	37.22 ± 17.83	.802
	(7.35 to 76.67)	(0.00 to 75.00)	
	34.56 [22.06, 45.59]	39.50 [27.30, 42.65]	
Sport/recreation	10.16 ± 14.89	15.62 ± 14.10	.070
	(0.00 to 55.00)	(0.00 to 45.00)	
	5.00 [0.00, 17.50]	15.00 [0.00, 30.00]	
Quality of life	16.36 ± 15.00	20.91 ± 17.30	.305
	(0.00 to 62.50)	(0.00 to 68.75)	
	12.50 [0.00, 25.00]	18.75 [6.25, 31.25]	
SF-36 subscale[b]			
Physical function	32.91 ± 19.38	30.15 ± 20.65	.580
	(5.00 to 90.00)	(0.00 to 80.00)	
	32.50 [15.00, 45.00]	31.39 [10.00, 45.00]	

(continued)

TABLE 2 (continued)

| | Treatment Group | | |
	PRP	Control	*P* Value
Physical role	17.83 ± 10.22 (0.00 to 25.00) 25.00 [6.25, 25.00]	18.10 ± 9.50 (0.00 to 25.00) 25.00 [12.50, 25.00]	.969
Bodily pain	30.65 ± 17.76 (0.00 to 62.00) 22.00 [22.00, 42.00]	34.87 ± 27.65 (0.00 to 100.00) 26.50 [12.00, 42.00]	.853
General health perception	37.12 ± 15.12 (15.00 to 70.00) 35.00 [20.00, 50.00]	46.35 ± 18.58 (0.00 to 92.00) 45.00 [35.00, 57.00]	.032
Vitality	38.97 ± 23.86 (0.00 to 100.00) 31.25 [25.00, 50.00]	40.69 ± 23.37 (0.00 to 87.50) 37.50 [31.25, 56.25]	.413
Physical role functioning	66.67 ± 25.90 (12.50 to 100.00) 75.00 [50.00, 75.00]	61.25 ± 26.94 (0.00 to 100.00) 62.50 [50.00, 87.50]	.419
Emotional role functioning	11.87 ± 11.42 (0.00 to 25.00) 8.33 [0.00, 25.00]	12.22 ± 11.93 (0.00 to 25.00) 8.33 [0.00, 25.00]	.905
Mental health	54.43 ± 20.50 (18.75 to 95.00) 55.00 [37.50, 68.75]	52.85 ± 19.05 (15.00 to 87.50) 55.00 [37.50, 68.75]	.765
Physical health component	−1.88 ± 0.40 (−2.62 to −1.02) −1.94 [−2.14, −1.63]	−1.82 ± 0.66 (−2.77 to −0.42) −1.99 [−2.28, −1.58]	.760
Mental health component	−1.59 ± 0.69 (−2.89 to 0.03) −1.65 [−2.00, −1.14]	−1.60 ± 0.79 (−3.13 to −0.15) −1.56 [−1.94, −1.20]	.956

[a]BMI, body mass index; K-L, Kellgren-Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Scale; NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma SF-36, Short Form–36; VAS, visual analog scale.

[b]Data are provided as mean ± SD (range) and median [25th percentile, 75th percentile], unless indicated otherwise.

[c]Knee Society clinical rating system: A = unilateral or bilateral (opposite knee successfully replaced); B = unilateral, other knee symptomatic; C = multiple arthritis or medical infirmity.

TABLE 3
Patient Satisfaction at 6 Months[a]

| | Treatment Group | |
Patient Satisfaction, %	PRP	Control
Very good	52.94	46.67
Good	20.59	10
Regular	8.82	16.67
Poor	17.65	26.67

[a]PRP, platelet-rich plasma.

To keep the process double-blinded, BST prepared both treatments in an opaque syringe. To decrease bias, the same person performed all injections.

Outcome Measures

Pain VAS scores at 1 month (change from baseline) was considered the primary outcome variable. Secondary variables were VAS, functional knee evaluated with the Knee injury and Osteoarthritis Outcome Score (KOOS), and quality of life evaluated with the Short Form–36 (SF-36) at 1, 3, and 6 months after treatment. Other goals were to evaluate the correlation between PRP clinical effect on pain and platelet concentration of the infiltrated product and the degree of patient satisfaction at final follow-up.

Demographic variables (age, sex, body mass index [BMI]) and degree of radiological involvement were also collected. Mobility of the knee joint (flexion and extension), use of analgesics or nonsteroidal anti-inflammatory drugs, and VAS, KOOS, and SF-36 outcomes were evaluated before and at 1, 3, and 6 months after treatment by a blinded observer.

The type and severity of all adverse events presented during the study and appreciation of their relationship to treatment were collected. Platelet and leukocyte concentrations in the PRP injection were determined.

RESULTS

Between August 2013 and July 2014, a total of 34 patients in the study group and 30 individuals in the control group

TABLE 4
VAS Score Compared With Baseline at Each Follow-up for Both Groups[a]

Baseline			1 mo		
PRP	Control	P	PRP	Control	P
75.14 ± 10.11 (60.00 to 90.00) 70.00 [70.00, 80.00]	75.00 ± 9.38 (60.00 to 90.00) 70.00 [70.00, 80.00]	.95	35.88 ± 24.63 (0.00 to 90.00) 35.00 [20.00, 50.00]	31.67 ± 22.14 (0.00 to 80.00) 20.00 [20.00, 50.00]	.50
3 mo			6 mo		
PRP	Control	P	PRP	Control	P
33.38 ± 22.59 (0.00 to 80.00) 35.00 [10.00, 50.00]	41.00 ± 26.95 (0.00 to 80.00) 35.00 [20.00, 70.00]	.22	38.24 ± 24.80) (0.00 to 90.00) 35.00 [20.00, 50.00]	46.33 ± 29.88) (0.00, 90.00) 50.00 [20.00, 80.00]	.29

[a]Data are provided as mean ± SD (range) and median [25th percentile, 75th percentile]. PRP, platelet-rich plasma; VAS, visual analog scale.

were enrolled and observed (Figure 1). The PRP contained a median value of 0.99×10^6 platelets/μL (range, 0.34-1.54 $\times 10^6$ platelets/μL) and a median value of 0.6×10^6 WBC/μL (range, 0.1-1.8×10^6 WBC/μL) (LP-PRP: PAW classification system type 3B[8]). The 2 groups did not differ in any of the qualitative variables collected at baseline except for OA grade and SF-36 general health perception subscale, which were worse for the PRP group (Table 2).

No patient had adverse effects at injection or follow-up. No differences were found in the use of painkillers and nonsteroidal anti-inflammatories or dose or frequency between groups at any time point. At 6 months, patient satisfaction tended to be higher in the study group; however, we were unable to find statistically significant differences ($P = .472$) (Table 3).

VAS score decreased for both groups, with no significant differences between groups at different time points (Table 4). The differences in VAS score at 1, 3, and 6 months compared with baseline showed no statistically significant differences between groups ($P = .568$, .623, and .568, respectively). Considering that there were no significant differences at baseline for VAS, the difference tended to be greater in the PRP group (Figure 2).

KOOS outcomes are presented in Table 5. The difference magnitude between baseline and subsequent follow-ups tended to be greater in the PRP group for each of the dimensions, but these differences were not significant (Figure 3). The differences in KOOS–Quality of Life scores between baseline and 3 and 6 months increased significantly more in the PRP than in the control group (mean, 17.77 vs 4.91 at 3 months and 16.88 vs 3.56 at 6 months; $P = .05$ and .03, respectively).

The SF-36 scores are presented in Table 6. The improvement in SF-36 general health perception score between baseline and 6 months was greater in the PRP than the control group (4.25 vs −4.92; $P = .018$).

There was no correlation between the concentration of platelets infiltrated into the joint and the VAS change from baseline at 1, 3, and 6 months ($P = .41$, .70, and .43, respectively), nor was there a difference found in relation to WBC concentration ($P = .75$, .67, and .40, respectively).
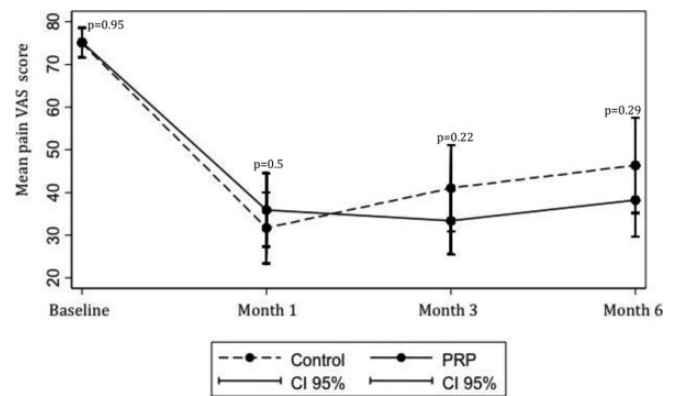

Figure 2. Trends in mean pain visual analog scale (VAS) scores of both groups at baseline and subsequent follow-up. PRP, platelet-rich plasma.

DISCUSSION

The results obtained in our study did not confirm our hypothesis with sufficient statistical value. Although we found that a single PRP IAI reduces pain, we could not prove its superiority in terms of effectiveness and lasting pain relief compared with CSA.

Most published works regarding the effectiveness of PRP IAI for the treatment of OA are series studies, with an average age less than 60 years and patients with early-stage OA. In the series by Kon et al[19,20] comparing PRP with HA at 6-month follow-up, the best results from the International Knee Documentation Committee questionnaire, VAS, and degree of patient satisfaction were achieved in the PRP group ($P < .005$), especially for younger patients, males, and those with early-stage OA. According to the systematic review by Meheux et al,[23] most of the studies included early-stage OA, with grades 3 and 4 being less common (9.4% of the knees were Ahlback grade 3, 37.9% K-L grade 3, and 12.6% K-L grade 4). In these studies, the worst results were obtained for K-L grades 3 to 4.

TABLE 5
KOOS Scores Compared With Baseline at Follow-up for Both Groups[a]

KOOS Subscale	Baseline			1 mo		
	PRP	Control	P	PRP	Control	P
Pain	35.11 ± 17.94	38.80 ± 18.99	.43	48.28 ± 21.61	54.21 ± 24.94	.31
	(0.00 to 72.22)	(0.00 to 72.22)		(13.89 to 94.44)	(2.78 to 100.00)	
	32.29 [22.22, 44.44]	41.67 [27.78, 51.39]		41.67 [30.56, 61.11]	55.56 [36.11, 71.88]	
Symptoms	45.41 ± 12.45	47.98 ± 15.35	.46	50.17 ± 11.19	52.17 ± 14.22	.21
	(21.43 to 71.43)	(17.86 to 75.00)		(25.00 to 71.43)	(7.14 to 71.43)	
	42.86 [37.50, 53.57]	50.00 [35.71, 60.71]		50.00 [42.86, 57.14]	57.14 [46.43, 60.71]	
Activities of daily living	36.05 ± 18.58	37.22 ± 17.83	.80	48.86 ± 21.39	51.90 ± 23.86	.59
	(7.35 to 76.67)	(0.00 to 75.00)		(13.24 to 95.59)	(4.41 to 100.00)	
	34.56 [22.06, 45.59]	39.50 [27.30, 42.65]		44.12 [35.29, 63.24]	47.06 [35.29, 73.44]	
Sport/recreation	10.16 ± 14.89	15.62 ± 14.10	.07	18.75 ± 21.84	29.61 ± 24.36	.04
	(0.00 to 55.00)	(0.00 to 45.00)		(0.00 to 75.00)	(0.00 to 100.00)	
	5.00 [0.00, 17.50]	15.00 [0.00, 30.00]		10.00 [0.00, 25.00]	25.00 [9.17, 42.50]	
Quality of life	16.36 ± 15.00	20.91 ± 17.30	.30	25.61 ± 17.59	29.65 ± 21.90	.45
	(0.00 to 62.50)	(0.00 to 68.75)		(0.00 to 68.75)	(0.00 to 75.00)	
	12.50 [0.00, 25.00]	18.75 [6.25, 31.25]		25.00 [12.50, 37.50]	31.25 [12.50, 43.75]	

KOOS Subscale	3 mo			6 mo		
	PRP	Control	P	PRP	Control	P
Pain	55.63 ± 23.71	55.14 ± 21.06	.93	53.09 ± 22.15	49.52 ± 23.70	.55
	(13.89 to 100.00)	(5.56 to 97.22)		(13.89 to 96.88)	(5.56 to 100.00)	
	55.56 [37.50, 72.22]	62.50 [47.22, 67.86]		50.00 [38.89, 69.44]	44.44 [34.38, 69.44]	
Symptoms	53.49 ± 14.06	55.30 ± 15.31	.62	50.92 ± 12.81	54.86 ± 12.08	.23
	(21.43 to 75.00)	(21.43, 85.71)		(21.43 to 71.43)	(21.43 to 75.00)	
	55.36 [42.86, 64.29]	57.14 [42.86, 67.86]		50.00 [42.86, 57.14]	57.14 [50.00, 60.71]	
Activities of daily living	55.21 ± 26.02	52.32 ± 20.05	.62	56.14 ± 21.70	46.75 ± 24.90	.12
	(5.88 to 98.53)	(10.29 to 94.12)		(13.24 to 97.06)	(4.41 to 96.67)	
	61.76 [36.76, 73.53]	54.41 [33.82, 67.65]		60.29 [39.71, 69.12]	45.59 [26.92, 66.18]	
Sport/recreation	24.72 ± 24.54	25.19 ± 23.10	.83	25.78 ± 24.23	22.92 ± 22.20	.68
	(0.00 to 87.50)	(0.00 to 90.00)		(0.00 to 90.00)	(0.00 to 70.00)	
	18.75 [5.00, 35.00]	25.00 [5.00, 35.00]		25.00 [5.00, 35.00]	12.50 [5.00, 40.00]	
Quality of life	33.52 ± 24.93	24.35 ± 16.31	.21	33.96 ± 23.37	23.92 ± 23.73	.08
	(0.00 to 93.75)	(0.00 to 56.25)		(0.00 to 93.75)	(0.00 to 87.50)	
	31.25 [12.50, 43.75]	25.00 [12.50, 31.25]		31.25 [18.75, 50.00]	16.67 [6.25, 37.50]	

[a]Data are provided as mean ± SD (range) and median [25th percentile, 75th percentile]. KOOS, Knee Injury and Osteoarthritis Outcome Score; PRP, platelet-rich plasma.

We expected that our results would be lower than previous ones (in terms of significance) since the average patient age was older and only patients with late-stage OA were included, with 58.5% of knees being classified as K-L grade 4. Nonetheless, in our study, the difference in VAS at 3 and 6 months was greater in the PRP group.

The primary objective of this study was to determine the clinical utility of PRP IAI in the treatment of late-stage knee OA for subjective pain relief 1 month after the infiltration compared with CSA infiltration, as determined by by VAS. At 1 month, results showed a decrease in VAS in both groups. Although there was no statistically significant difference between groups, there was a 4-point decrease in the control group compared with the study group. This could be explained by the prompt anti-inflammatory effect of corticosteroid. As expected, since corticosteroid effects are known to be short, the VAS for the control group worsened at 3 months while it improved in the study group. This

improvement decreased at 6 months, although remaining above that for the control group (8-point difference at 3 and 6 months). Although this difference was not statistically significant, the fact that the study group had worse OA involvement gives more value to the differences in absolute numbers. Both treatments improved the initial state as far as pain is concerned. These findings are consistent with the recently published study of Forogh et al,[13] which also compared a single injection of PRP with CSA. In a randomized double-blind clinical trial of 48 knees K-L grade 2 to 3, they found statistically significant differences between treatments as determined by KOOS scores.[13]

Although we could not find statistically significant differences between groups in most of outcomes, our results did not differ from published data[6,11-13,25,27,29]: PRP decreased joint pain and improved activity of daily living and quality of life in symptomatic knee OA.
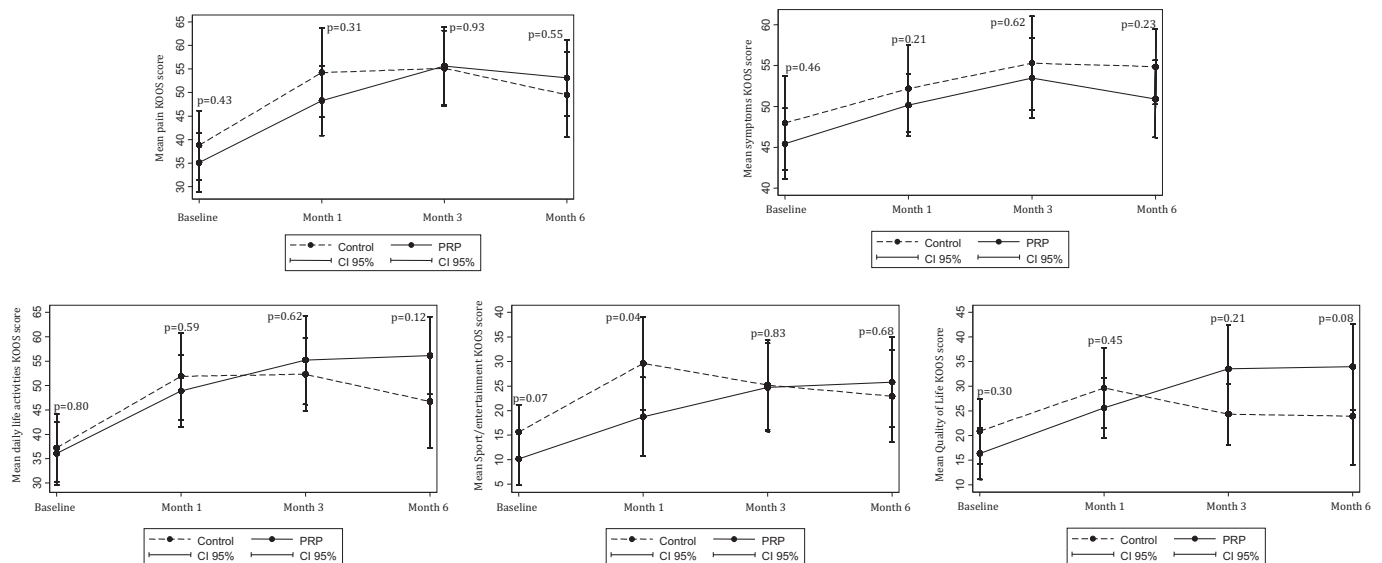
Figure 3. Trends in mean Knee injury and Osteoarthritis Outcome Score (KOOS) results of both groups at baseline and subsequent follow-ups. PRP, platelet-rich plasma.

Several factors could explain the lower improvement of our PRP results compared with previous randomized trials: greater degree of knee OA, greater proportion of women (72%), older mean age of participants (67 years), and higher mean BMI (31 kg/m^2)—all risk factors for symptomatic knee OA.[1] Kon et al[19] observed superior effectiveness of PRP in young men and patients with low BMI. Other studies[6,13,25,27,29,32] with a greater proportion of women found no differences between sexes. However, in our study, the mean age of the patients was greater than 65 years, and therefore, the results could be subdued. Furthermore, the mean BMI of our sample was 31 kg/m^2, meaning most patients were class I obese. The mean BMIs of patients in other published series[11,13,19,25,27,32] ranged from 25 to 30 kg/m^2, but with few overweight patients. In the trial by Forogh et al,[13] which, like ours, compared PRP with CSA, participants had a mean age 61 years and mean BMI of 29 kg/m^2, lower than that in our series.

Unlike others studies,[6,21,23,25,27,29,32] Filardo et al[11,12] did not find that PRP was superior to an active control. As mentioned by these authors, this could be explained by the use of a leukocyte-rich PRP.

In general, published data regarding PRP injections for knee OA have not analyzed its clinical efficacy in advanced-stage knee OA. Our study shows that, although only in absolute numbers, PRP treatment tends to improve pain and patient satisfaction at 6-month follow-up. Patient satisfaction was very good or good in 73.53% of the study group and 56.67% of the control group, and dissatisfaction was greater in the control (43.33% regular or poor) than in the study group (26.47% regular or poor).

Based on our results and noting that most published studies observed that PRP effectiveness lasts 6 to 12 months on average,[5,7,18,21-23,31] we might consider more than 1 PRP IAI to treat late-stage knee OA, and, as Patel et al[25] and Gobbi et al[15] have proposed, perform a cyclic treatment. Patel et al[25] found that a single dose of PRP was as effective as a double dose at an interval of 3 weeks and therefore propose a serial single injection at 6-month or 1-year intervals to relieve symptoms for longer periods. Gobbi et al[15] found that patients who received a second cycle after 1 year improved beyond 18 to 24 months. Since we could not find statistical differences between groups in most of the outcomes, we believe that for late-stage knee OA, a serial single injection of high-concentration PRP (PAW classification type 4) might reduce the pain enough and for longer periods, with an adequate quality of life, to delay knee replacement.

Our study has several limitations. Although a sample size calculation was performed to detect a reduction of 17 points in the treatment group versus the control group, given that pain is a difficult variable to quantify, the sample might need to be larger. Given that there is no difference in these 2 groups in such a small population, the study could be underpowered and a type II error cannot be ruled out. Note that we did not achieve our target enrollment of 32 patients in the control group. We might look for more objective parameters like joint inflammatory biochemical markers or biomechanical studies to determine the clinical improvement. Another limitation was the lack of imaging assessment to evaluate OA progression, but we consider that in late-stage knee OA, clinical improvement is more valuable than radiographic progression of the disease. The specificity of our work is the homogeneity of the sample: Only patients with K-L grade 3 or 4 OA with enough symptoms to receive joint replacement were included.

A large randomized clinical trial using a therapeutic regimen based on a serial single injection every 6 months, with objective indicators and imaging assessment to evaluate OA progression, is needed to further assess the efficacy of PRP treatment in patients with advanced knee OA.

TABLE 6
SF-36 Scores Compared With Baseline at Follow-up for Both Groups[a]

SF-36 Subscale	Baseline			1 mo		
	PRP	Control	P	PRP	Control	P
Physical functioning	32.91 ± 19.38 (5.00 to 90.00) 32.50 [15.00, 45.00]	30.15 ± 20.65 (0.00 to 80.00) 31.39 [10.00, 45.00]	.58	38.37 ± 21.53 (0.00 to 85.00) 35.00 [30.00, 50.00]	37.50 ± 25.48 (0.00 to 85.00) 35.00 [15.00, 55.00]	.88
Physical role functioning	17.83 ± 10.22 (0.00 to 25.00) 25.00 [6.25, 25.00]	18.10 ± 9.50 (0.00 to 25.00) 25.00 [12.50, 25.00]	.97	15.81 ± 10.46 (0.0 to 25.00) 21.88 [6.25, 25.00]	15.16 ± 9.61 (0.00 to 25.00) 18.75 [6.25, 25.00]	.78
Bodily pain	30.65 ± 17.76 (0.00 to 62.00) 22.00 [22.00, 42.00]	34.87 ± 27.65 (0.00 to 100.00) 26.50 [12.00, 42.00]	.85	37.00 ± 24.22 (0.00 to 100.00) 31.00 [22.00, 52.00]	40.90 ± 24.78 (0.00 to 100.00) 41.00 [22.00, 62.00]	.53
General health perception	37.12 ± 15.12 (15.00 to 70.00) 35.00 [20.00, 50.00]	46.35 ± 18.58 (0.00 to 92.00) 45.00 [35.00, 57.00]	.03	37.81 ± 14.10 (15.00 to 65.00) 35.00 [25.00, 50.00]	44.87 ± 17.32 (0.00 to 80.00) 45.00 [35.00, 57.00]	.09
Vitality	38.97 ± 23.86 (0.00 to 100.00] 31.25 [25.00, 50.00]	40.69 ± 23.37 (0.00 to 87.50) 37.50 [31.25, 56.25]	.41	41.24 ± 23.60 (0.00 to 87.50) 39.58 [25.00, 50.00]	44.76 ± 23.46 (0.00 to 87.50) 41.67 [31.25, 62.50]	.55
Social role functioning	66.67 ± 25.90 (12.50 to 100.00) 75.00 [50.00, 75.00]	61.25 ± 26.94 (0.00 to 100.00) 62.50 [50.00, 87.50]	.42	70.59 ± 31.06 (12.50 to 100.00) 87.50 [50.00, 100.00]	70.54 to 29.31 (0.00 to 100.00) 75.00 [56.25, 100.00]	.92
Emotional role functioning	11.87 ± 11.42 (0.00 to 25.00) 8.33 [0.00, 25.00]	12.22 ± 11.93 (0.00 to 25.00) 8.33 [0.00, 25.00]	.90	10.29 ± 12.15 (0.00 to 25.00) 0.00 [0.00, 25.00]	9.52 ± 12.15 (0.00 to 25.00) 0.00 [0.00, 25.00]	.80
Mental health	54.43 ± 20.50 (18.75 to 95.00) 55.00 [37.50, 68.75]	52.85 ± 19.05 (15.00 to 87.50) 55.00 [37.50, 68.75]	.76	53.28 ± 24.55 (5.00 to 91.67) 56.67 [30.63, 75.00]	57.50 ± 20.21 (8.33 to 93.75) 55.00 [50.00, 69.38]	.49
Physical health component	−1.88 ± 0.40 (−2.62 to −1.02) −1.94 [−2.14, −1.63]	−1.82 ± 0.66 (−2.77 to −0.42) −1.99 [−2.28, −1.58]	.76	−1.66 ± 0.51 (−2.89 to −0.91) −1.62 [−1.92, −1.23]	−1.65 ± 0.70 (−2.64 to −0.72) −1.74 [−2.29, −0.97]	.97
Mental health component	−1.59 ± 0.69 (−2.89 to 0.03) −1.65 [−2.00, −1.14]	−1.60 ± 0.79 (−3.13 to −0.15) −1.56 [−1.94, −1.20]	.95	−1.64 ± 0.87 (−3.28 to −0.12) −1.65 [−2.26, −1.04]	−1.56 ± 0.80 (−3.15 to −0.22) −1.51 [−1.92, −0.98]	.74

SF-36 Subscale	3 mo			6 mo		
	PRP	Control	P	PRP	Control	P
Physical functioning	42.37 ± 24.30 (0.00 to 90.00) 45.00 [20.00, 60.00]	39.03 ± 20.88 (5.00 to 90.00) 37.50 [25.00, 55.00]	.56	41.27 ± 22.47 (0.00 to 90.00) 40.00 [30.00, 50.00]	34.17 ± 21.01 (0.00 to 75.00) 30.00 [20.00, 55.00]	.21
Physical role functioning	16.10 ± 10.83 (0.00 to 25.00) 25.00 [6.25, 25.00]	15.95 ± 11.28 (0.00 to 25.00) 25.00 [0.00, 25.00]	.96	17.29 ± 8.94 (0.00 to 25.00) 18.75 [12.50, 25.00]	17.08 ± 9.56 (0.00 to 25.00) 21.88 [6.25, 25.00]	.97
Bodily pain	39.68 ± 25.65 (0.00 to 100.00) 36.00 [22.00, 62.00]	39.04 ± 23.08 (0.00 to 80.00) 41.00 [22.00, 52.00]	.92	38.10 ± 19.40 (0.00 to 74.00) 41.00 [22.00, 51.00]	34.10 ± 23.79 (0.00 to 74.00) 22.00 [22.00, 51.00]	.47
General health perception	39.04 ± 13.41 (15.00 to 65.00) 40.00 [30.00, 45.00]	45.71 ± 20.12 (5.00 to 87.00) 45.00 [27.50, 61.00]	.12	41.37 ± 14.66 (10.00 to 77.00) 45.00 [30.00, 52.00]	41.43 ± 21.27 (0.00 to 90.00) 40.00 [25.00, 53.50]	.99
Vitality	42.71 ± 21.89 (0.00 to 100.00) 37.50 [25.00, 56.25]	41.96 ± 23.82 (0.00 to 83.33) 42.71 [31.25, 57.29]	.90	41.04 ± 19.27 (8.33 to 81.25) 37.50 [25.00, 50.00]	36.67 ± 26.62 (0.00 to 91.67) 31.25 [18.75, 50.00]	.47
Social role functioning	66.91 ± 34.53 (0.00 to 100.00) 75.00 [25.00, 100.00]	68.97 ± 26.65 (12.50 to 100.00) 62.50 [50.00, 100.00]	.83	61.29 ± 33.60 (0.00 to 100.00) 75.00 [25.00, 87.50]	57.50 ± 33.41 (0.00 to 100.00) 56.25 [25.00, 87.50]	.66
Emotional role functioning	12.50 ± 12.01 (0.00 to 25.00) 12.50 [0.00, 25.00]	13.69 ± 12.26 (0.00 to 25.00) 20.83 [0.00, 25.00]	.70	13.98 ± 11.86 (0.00 to 25.00) 16.67 [0.00, 25.00]	13.89 ± 12.44 (0.00 to 25.00) 25.00 [0.00, 25.00]	.98

(continued)

TABLE 6 (continued)

SF-36 Subscale	3 mo			6 mo		
	PRP	Control	P	PRP	Control	P
Mental health	55.32 ± 23.49 (0.00 to 100.00) 55.00 [40.00, 66.67]	55.77 ± 22.29 (0.00 to 90.00) 56.25 [45.00, 68.75]	.94	52.23 ± 22.52 (0.00 to 91.67) 50.00 [40.00, 68.75]	45.63 ± 5.41 (0.00 to 90.00) 45.00 [35.00, 60.00]	.31
Physical health component	−1.66 ± 0.58 (−2.73 to −0.76] −1.56 [−2.11, −1.20]	−1.55 ± 0.62 (−2.57 to −0.10] −1.50 [−2.09, −1.16]	.51	−1.56 ± 0.53 (−2.40 to −0.37) −1.44 [−2.01, −1.24]	−1.65 ± 0.58 (−2.56 to −0.75) −1.67 [−2.19, −1.26]	.53
Mental health component	−1.62 ± 0.83 (−3.66 to 0.22) −1.56 [−2.02, −1.11]	−1.51 ± 0.92 (−3.56 to −0.30] −1.43 [−1.87, −0.84]	.64	−1.75 ± 0.79 (−3.28 to −0.19) −1.72 [−2.22, −1.25]	−1.98 ± 1.04 (−4.12, −0.10) −1.81 [−2.59, −1.29]	.37

*a*Data are provided as mean ± SD (range) and median [25th percentile, 75th percentile]. PRP, platelet-rich plasma; SF-36, Short Form–36.

CONCLUSION

A single PRP intra-articular injection is effective for relieving pain and improving activity of daily living and quality of life in patients with late-stage knee OA. For patients with late-stage knee OA who are 67 years or older, 1 intra-articular injection of PRP has similar results to 1 shot of corticosteroid.

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