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Platelet-Rich Plasma Injections Are Inferior to Corticosteroid Injections for Short-Term Pain Relief: A Prospective, Double-Blinded, Randomized Controlled Trial

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ABSTRACT

Background: We aimed to evaluate and compare the clinical benefits of platelet-rich plasma (PRP) injections compared to corticosteroid (CS) injections in patients who have mild to moderate symptomatic knee osteoarthritis in a double-blinded randomized control trial. We aimed to compare improvements in the following outcomes at six weeks and three months: 1) pain scores, including Visual Analog Scale (VAS) and Numeric Pain Rating Scale (NPRS); and 2) functional scores, including Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS).

Methods: In this double-blinded randomized control trial, 52 patients who had symptomatic, radiographically confirmed knee osteoarthritis were enrolled. A power analysis determined that a sample size of 52 was required. Patients were randomized to receive treatment with an intra-articular injection of CS (n = 26) or PRP (n = 26). We evaluated clinical outcomes, including VAS, NPRS, WOMAC, and KOOS scores at baseline, six weeks, and three months after injection. We also determined if our clinical outcomes met the minimal clinically important difference (MCID) based on the following scores reported in the literature: 19.9 for VAS and 2 for NPRS.

Results: There was no difference in baseline VAS, NPRS, KOOS, or WOMAC scores between the CS and PRP cohorts. At six weeks, CS patients had significantly greater reductions from baseline in VAS (−24.26 versus −7.38, $P = 0.033$) and NPRS (−2.24 versus −0.92, $P = 0.042$). The MCID for both VAS and NPRS was met in the CS cohort at 6 weeks, but not in the PRP cohort. At three months, CS and PRP patients experienced similar improvements in VAS (−18.27 versus 13.27, $P = 0.610$) and NPRS (−1.81 versus −0.65, $P = 0.798$), respectively. Neither cohort met the MCID at three months. Both groups experienced similar improvements in KOOS and WOMAC.

Conclusions: When comparing PRP to CS injections in patients who have mild to moderate knee osteoarthritis, CS demonstrated greater pain reduction at six weeks. Based on these findings, expectations regarding the clinical utility of PRP should be tempered.

Over the past several years, intra-articular platelet-rich plasma (PRP) injections have gained attention as a possible treatment option for knee osteoarthritis (OA). However, this treatment is not approved by the Food and Drug Administration (FDA) for knee OA and currently only has a "limited" recommendation by the American Academy of Orthopaedic Surgeons [1]. Additionally, the cost of a single intra-articular PRP injection can range from $350 to $2,815, with a median cost of $800 [2]. Thus, PRP injections are very costly for patients, particularly when compared to standard treatment

Trial Registration: This trial was registered at ClinicalTrials.gov. The identifier key was assigned as NCT06703970.

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options such as corticosteroid (CS) injections, which endorse a moderate recommendation by the American Academy of Orthopaedic Surgeons [1]. Proponents of PRP have claimed several benefits, including regenerative effects on cartilage, anti-inflammatory effects, pain relief, and improved function [3,4]. However, literature demonstrating the superiority of PRP remains scarce, particularly when compared to standard therapies.

Previous randomized controlled trials (RCTs) have assessed the efficacy of PRP compared to medical therapies, normal saline injections, and hyaluronic acid (HA) injections. Results of these studies have been variable, with studies demonstrating differing results concerning the efficacy associated with PRP when compared to other therapies [5–8]. However, very few studies have directly compared PRP to CS, which is effective at reducing pain for up to three months and is cost-effective. These studies have only demonstrated a difference in symptom relief after six months [9,10]. The lack of short-term superiority of PRP should be communicated to patients, particularly those seeking more immediate pain control.

As the population ages and the incidence of knee OA increases, orthopaedic surgeons must strive for improvement in the efficacy and value of treatment options offered to patients. In the present study, we conducted a double-blind RCT to investigate the efficacy of a single intra-articular PRP injection for the treatment of knee OA when compared to an intra-articular CS. We aimed to compare the following between treatment arms at baseline, six weeks, and three months: 1) patient-reported pain scores (Visual Analog Scale (VAS) and Numeric Pain Rating Scale (NPRS)) and 2) patient-reported functional scores (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS) for Joint Replacement.

Methods

Trial Design

Institutional review board approval was received at the primary institution for this prospective, multicenter, double-blinded, randomized control clinical trial comparing PRP versus CS injections for the treatment of symptoms of knee OA. The purpose of the study was to determine which therapy provides a greater reduction in patient-reported outcome measures of pain and function.

Eligibility Criteria

To be eligible to participate in this study, an individual was required to meet all of the following criteria: 1) provision of a signed and dated informed consent form; 2) stated willingness to comply with all study procedures and availability for the duration of the study; 3) men or women, aged 35 to 80 years; 4) a radiographic diagnosis of Kellgren–Lawrence (KL) grades II or III knee OA [11]; 5) indicated for a knee injection to treat knee OA symptoms. Individuals who met any of the following criteria were excluded from participation in this study: 1) any injections into the target knee within three months; 2) current overlying skin infection; 3) current or previous diagnosis of “chronic pain”; 4) previous or current opioid abuse; 5) allergy to any potential ingredients or medications utilized in any of the two groups; 6) treatment with another investigational drug or other intervention for pain; 7) diagnosis of diabetes mellitus; 8) if a woman, pregnant or planning to be pregnant within the following three months or study duration; and 9) any condition(s) or diagnosis, both physical or psychological, or physical examination finding in the opinion of the investigator that would preclude participation. A detailed flowchart of patient recruitment and randomization can be seen in Figure 1.

Randomization and Blinding

Patients were randomized into one of two knee injection groups. A permuted block randomization schedule was generated, creating an online randomization tool (Sealed Envelope Ltd. 2020, London, United Kingdom). Research staff assigned subjects to each group when enrolled and before the day of the procedure. No randomization code was reused once assigned.

Both injections are routinely used as part of care for knee OA. Both groups had blood drawn (approximately 30 to 60 mL) to maintain the blindness of the study participants. For the participants who were injected with PRP, the blood was processed according to the manufacturer insert (Magellan, ISTO Biologics, Massachusetts, United States) in a centrifuge machine. Without physician interference, the research staff prepared the CS and PRP for injection. Injections were placed in an opaque syringe to ensure physician blindness during the administration of the injection.

Each patient was assigned a unique number that only the research staff could decrypt to identify the treatment received by the patient. Physical documents and electronic data storage related to the study were secured with badge access and password encryption available only to research staff.

Study Intervention

Patients received a randomized, double-blinded administration of one of the following interventions: 1) an approximately 3-mL injection of autologous PRP (Magellan Autologous Concentration System, ISTO Biologics, Massachusetts, United States); or 2) a 5-mL injection of CS (1-mL triamcinolone acetonide and 4-mL lidocaine).

Outcomes

Outcome measures were obtained through blinded paper surveys. These surveys were administered by research staff at each visit without the physician present.

Primary Endpoints

1. Pain score
    1. The VAS was measured at baseline, six weeks, and three months.

Secondary Endpoints

2. Pain Score
    1. The NPRS was measured at baseline, six weeks, and three months.
3. Functional scores
    1. The KOOS is a knee-specific instrument developed to assess the patient’s opinion about their knee and associated problems. It holds 42 items in five separately scored subscales: pain, other symptoms, function in daily living, function in sport and recreation (Sport/Rec), and knee-related quality of life (QOL) [12]. This score was collected at baseline, six weeks, and three months.
    2. WOMAC is widely used in the evaluation of hip and knee OA. It is a self-administered questionnaire consisting of 24 items divided into three subscales (pain, stiffness, and physical function). This score was collected at baseline, six weeks, and three months.

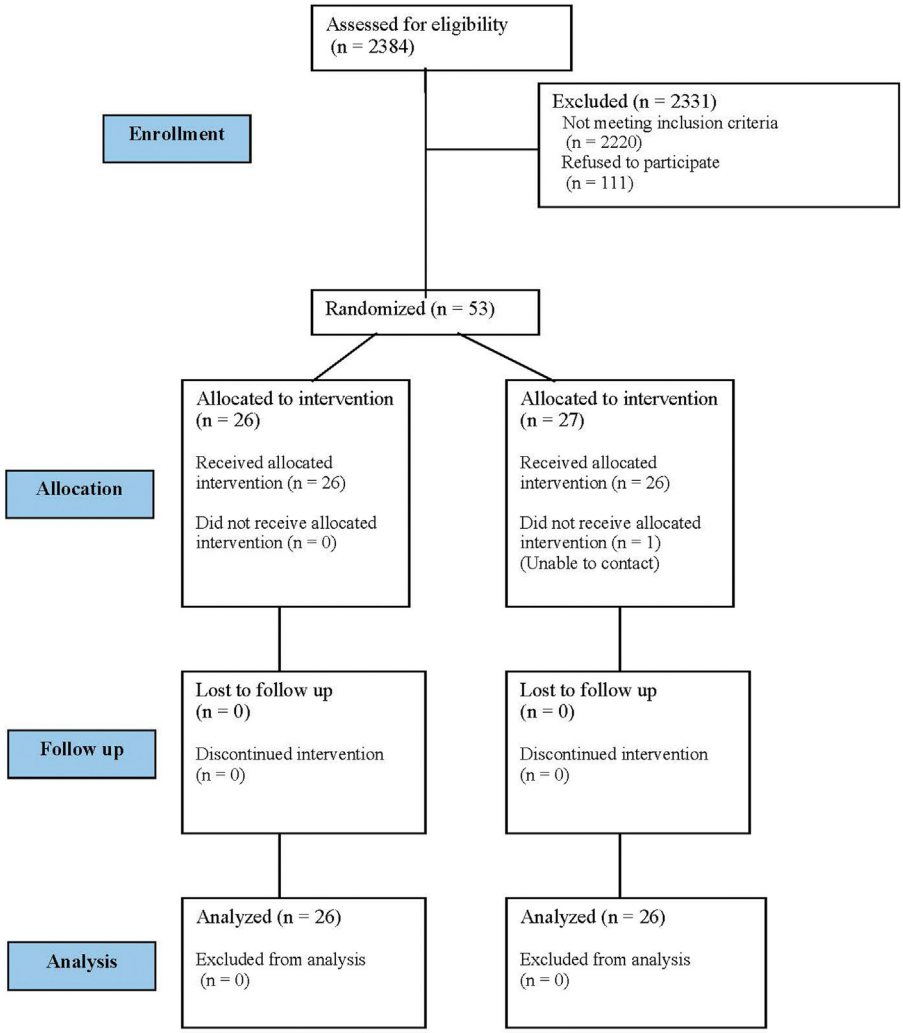

Figure 1. CONSORT Flow Diagram of Patient Recruitment.

Sample Size

A doctorate statistician was contracted to perform a power analysis in an effort to ensure adequate sample sizes to detect differences between treatment arms. In accordance with assumptions of previous clinical trials that were powered on the VAS for comparing pain assessment modalities after total knee arthroplasty, a 17-mm reduction on the VAS was deemed significant [13]. Assuming $\alpha = 0.05$, 80% power, a mean difference of 2.415 points, a standard deviation of 1.131 points, a 1:1 allocation ratio, and a 10% dropout rate, a minimum sample size of 52 patients was required (26 in the PRP group and 26 in the CS group). All patients presenting to the clinic from February 2, 2022, to March 16, 2024, who had a diagnosis of symptomatic KL grades II or III knee OA were screened. After the research staff excluded patients who did not meet the inclusion criteria and patients who either declined to participate or requested a specific treatment, a total of 52 patients were ultimately enrolled and randomized into the PRP (n = 26) and CS (n = 26) groups.

Data Analyses

Subject disposition, demographics, and baseline disease characteristics were summarized descriptively by treatment and overall for all randomized subjects. Statistical tests were performed to assess the comparability of the randomized treatment groups. The two sample *t*-tests were used for numerical variables, and *Chi*-square tests or Fisher's exact tests were used for categorical/binary variables. Assumptions of normality for continuous variables were assessed using normal probability plots. Baseline comparisons between the two treatment groups were made using Student's *t*-tests or Wilcoxon-Mann-Whitney tests based on the viability of the normality assumption for continuous variables. Primary outcome measures at different time points were analyzed using repeated measures analyses of variance models (with one between-subject treatment group and one within-subject time). Factors and their interaction were followed with pairwise comparisons between the groups at each time point. Statistical significance will be set at $P < 0.05$. Minimal clinically important difference (MCID) was included for VAS and NPRS based on scores reported in the literature: 19.9 for VAS, 2 for NPRS [14,15].

Adverse Events (AEs)

All adverse events (AEs) had their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The investigator was responsible for determining

Table 1
Known Potential Risks.

Procedure	Known Potential Risks
Blood draw	Pain, bleeding, bruising, infection, hematoma
PRP injection	Pain in the injected area, infection at the injection site, no improvement in pain, allergic reaction, blood clot, skin discoloration, bleeding, nerve injuries, tissue damage
Corticosteroid injection	Increased risk of infection, injection site reactions, headache, joint pain, mood changes, mental health disorders (e.g., depression, anxiety, confusion), trouble sleeping, seizures, fainting, dizziness, swelling of face/lips/throat, breathing difficulties, skin itching/redness/rash (allergic reactions)
Research study	Inadequate pain control due to interventions and allowed pain medications

PRP, platelet-rich plasma.

whether an AE was expected or unexpected. An AE was considered unexpected if the nature, severity, or frequency of the event was not consistent with the risk information described in Table 1.

Consent

Institutional review board–approved consent forms describing the study in detail were signed by the participant, and written documentation of informed consent was required before starting the intervention/administering the study intervention.

Food and Drug Administration (FDA) Communications

The research site contacted the FDA to determine if an investigational device exemption would be required to conduct this investigation. The site concern was regarding the use of an FDA-cleared PRP collection and preparation device (Magellan Autologous Concentration System, ISTO Biologics) to support an injection for the treatment of the symptoms related to knee OA. As advised by the FDA, the institutional review board reviewing this study determined that this study did not meet the requirements of a significant risk device study. Nonsignificant risk device studies are not required to have an investigational device exemption application approved by the FDA.

Study Intervention/Discontinuation/Withdrawal/Lost to Follow-Up

Participants were not permitted to take opioids or anti-inflammatory medications for the duration of the study. The only permitted medication for the treatment of pain was acetaminophen if needed for the study duration. Participants were advised to discuss options with the investigator if the pain was inadequately controlled to determine the next options. Participants were free to withdraw from participation in the study at any time on request. A participant was considered lost to follow-up if he or she failed to return for scheduled visits and was unable to be contacted by the study site staff.

End of Study Definition

A participant was considered to have completed the study if he or she had completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities, Table 2. The end of the study was defined as the completion of the last visit or procedure shown in the Schedule of Activities in the study.

Results

Demographic results showed no significant difference between the CS and PRP cohorts in age (48.5 versus 53.0 years, $P = 0.18$), body mass index (33.0 versus 33.3, $P = 0.31$), or any concomitant diseases listed in Table 3.

Table 2
Schedule of Activities.

Procedures	Visit 1 Baseline	Visit 2 Six Weeks	Visit 3 Three months
Informed consent	X		
Inclusion/exclusion	X		
Demographics/medical history	X		
Concomitant medications	X	X	X
Randomization	X		
Injection details	X		
Pain assessment (VAS and NPRS)	X	X	X
KOOS	X	X	X
WOMAC	X	X	X
Adverse events	X	X	X

VAS, visual analog scale; NPRS, numeric pain rating scale; KOOS, knee osteoarthritis outcome score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

The primary clinical measure of this study (VAS) did not show a statistical difference at baseline between the CS and PRP cohorts (58.0 versus 54.2, respectively, $P = 0.546$). At the 6-week follow-up, CS patients had significantly greater reductions from baseline in VAS compared to the PRP cohort (−24.3 versus −7.4, $P = 0.033$). There was no significant difference in VAS improvement at 3 months between the CS and PRP cohorts, respectively (−18.3 versus −13.3, $P = 0.610$). The MCID for VAS was met in the CS cohort at six weeks (24.3) but was not met at three months (18.3). The MCID for VAS was not met at any time point in the PRP cohort. At baseline, NPRS did not show a statistically significant difference between the CS and PRP cohorts (6.0 versus 5.9, respectively, $P = 0.720$). Similar to VAS, CS patients had a significantly greater reduction in NPRS from baseline compared to the PRP cohort at the 6-week follow-up (−2.4 versus −0.9, $P = 0.042$). No significant difference in NPRS improvement was noted at three months between CS and PRP patients, respectively (−1.8 versus −0.7, $P = 0.78$). The MCID for NPRS was met in the CS cohort at 6 weeks (2.4), but was not met at three months. The MCID for NPRS was not met at any time point in the PRP cohort. A detailed breakdown of VAS and NPRS scores can be seen in Table 4.

At baseline, KOOS did not show a statistically significant difference between the CS and PRP cohorts (mean 41.8 versus 36.2, respectively, $P = 0.198$). Patients in the CS cohort reported similar improvements from baseline as the PRP cohort at six weeks (11.71 versus 9.97, $P = 0.739$) and three months (13.40 versus 14.66, $P = 0.677$), respectively. At baseline, WOMAC did not show a statistically significant difference between the CS and PRP cohorts, respectively (49.85 versus 56.85, $P = 0.171$). There was no significant difference in improvement between CS and PRP patients at the 6-week follow-up (−14.00 versus −12.96, $P = 0.878$) or 3-month follow-up (−16.58 versus −14.81, $P = 0.789$), respectively. A detailed breakdown of KOOS and WOMAC scores can be seen in Table 5.

Discussion

Osteoarthritis (OA) of the knee affects at least 19% of those aged 45 years and older in the United States [16]. Though several therapies are available, none have been shown to modify the course of the disease. Thus, the goals of treatment for osteoarthritic patients revolve around reducing pain and improving function indefinitely or until arthroplasty is indicated. The PRP injections are being increasingly offered to patients, though they are expensive and are not FDA-approved for this indication [2]. Possible benefits of PRP include cartilage regeneration and anti-

Table 3
Baseline Demographics.

Demographics and Comorbidities	PRP (n = 26)	CS (n = 26)	*P*-value
	n (%)	*n* (%)	
Age (SD) in years	52 (15.6)	48 (15.6)	0.18
BMI (SD)	33.26 (5.04)	32.97 (5.33)	0.31
Sex (%)			0.44
Women	21 (80.8)	19 (73.1)	
Men	5 (19.2)	7 (26.9)	
Concomitant Disease (%):			
Asthma	4 (15.4)	4 (15.4)	1.00
Cancer	1 (3.8)	1 (3.8)	1.00
Cardiac	5 (19.2)	3 (11.5)	0.40
Endocrine	2 (7.7)	2 (7.7)	1.00
Gastrointestinal	5 (19.2)	4 (15.4)	0.77
Hypertension	12 (46.2)	12 (46.2)	1.00
Immune Deficiency	1 (3.8)	1 (3.8)	1.00
Nerve Disorder	0 (0)	1 (3.8)	0.49
Pulmonary	1 (3.8)	0 (0)	1.00
Renal	1 (3.8)	0 (0)	1.00
Vascular	0 (0)	1 (3.8)	0.49
Tobacco Use	2 (7.7)	3 (11.5)	0.61

PRP, platelet-rich plasma; CS, corticosteroid; BMI, body mass index; SD, standard deviation.

inflammatory effects, though these have not been consistently demonstrated in the literature [3,4]. Corticosteroid (CS) injections are considered a more standard treatment for knee OA, but high-quality RCTs comparing the clinical benefits of PRP to CS are scarce. Thus, this study aimed to identify whether PRP or CS injections were more effective at reducing pain and improving function. The results revealed that those who received CS experienced significantly greater reductions in VAS and NPRS. Perhaps even more important, patients who received CS met the MCID at 6 weeks for both pain scores, while those who received PRP did not. At 3 months, there was no difference between groups. When comparing improvements in functional scores, there were no differences observed between treatment arms at six weeks or three months.

Though this study was carefully designed to produce reliable results, potential limitations do exist. This study only included patients who had KL grades II and III OA. Thus, these findings may not be generalizable to those who have KL grades I or IV arthritis. However, we felt that these exclusion criteria were necessary as these patients could respond differently to intra-articular injections. Another limitation of this trial and others considering patient-reported pain and functional scores is the subjectivity associated with these measures. To negate this, we excluded patients who had comorbidities and characteristics that could contribute to pain perception. Additionally, we used existing high-quality literature to determine our sample size to be able to detect differences between groups. However, it is important to note that our sample size calculation was based on the detection of differences in our primary outcome, VAS. The secondary outcomes were not included in this calculation. Thus, the findings demonstrating no difference in functional outcomes between study groups should be tempered. Another possible limitation of this study is the lack of long-term follow-up data over three months. It is important to advise patients that CS may provide better pain relief in the short term but may wear off faster than PRP. However, CS injections are more affordable and may be administered every three months. These considerations must be weighed by the physician and the patient.

Table 4
VAS and NPRS Scores.

Pain Scores	PRP (n = 26)	CS (n = 26)	*P*-value
VAS			
Baseline	54.23	58.00	0.546
6 weeks	46.85	33.54	
6 weeks Δ	−7.38	−24.26	0.033
3 months	40.96	39.23	
3 months Δ	−13.27	−18.27	0.610
NPRS			
Baseline	5.85	6.04	0.720
6 weeks	4.92	3.62	
6 weeks Δ	−0.92	−2.42	0.042
3 months	4.27	4.23	
3 months Δ	−0.65	−1.81	0.798

VAS, visual analog scale; NPRS, numeric pain rating scale; PRP, platelet-rich plasma; CS, corticosteroid.

Table 5
KOOS and WOMAC Scores.

Patient-Reported Outcomes Measures	PRP (n = 26)	CS (n = 26)	*P*-value
KOOS			
Baseline	36.23	41.80	0.198
6 weeks	46.20	53.51	
6 weeks Δ	9.97	11.71	0.739
3 months	50.89	55.20	
3 month Δ	14.66	13.40	0.819
WOMAC			
Baseline	56.85	49.85	0.171
6 weeks	43.88	35.85	
6 weeks Δ	−12.96	−14.00	0.878
3 months	42.04	33.27	
3 months Δ	−14.81	−16.58	0.789

KOOS, knee osteoarthritis outcome score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PRP, platelet-rich plasma; CS, corticosteroid.

Pain relief is the most important factor in the nonsurgical treatment of knee OA. This study demonstrated that CS was more effective at relieving pain at six weeks than PRP when comparing changes in VAS ($P = 0.033$) and NPRS ($P = 0.042$). Pain reduction was similar between cohorts at three months for both VAS ($P = 0.610$) and NPRS ($P = 0.798$). Patients in the CS cohort met the MCID of 19.9 at six weeks, but not at three months. Patients in the PRP cohort did not meet the MCID at either time point. These results expand on the existing literature, which includes few reports directly comparing PRP to CS. In a double-blind RCT of 27 patients who had bilateral knee OA and who received an injection of PRP in one knee and CS in the other, Pretorius et al. demonstrated that there was no significant difference in improvement of WOMAC or NPRS scores at six weeks, three months, or six months between treatment arms (all $P > 0.05$) [17]. Jubert et al., in a double-blinded RCT of 75 patients, demonstrated that patients receiving PRP and CS both experienced significant pain relief. However, there was no significant difference between groups at one ($P = 0.5$), three ($P = 0.22$), or six months ($P = 0.29$) [6]. When comparing PRP to other injectable therapies, such as HA and normal saline, authors have similarly reported the non-superiority of PRP in pain reduction. In a double-blinded RCT of 111 patients, Cole et al. compared PRP injections to HA injections, demonstrating no difference between HA and PRP when assessing improvement in the WOMAC pain subscale at 24 weeks ($P > 0.05$) or 52 weeks ($P > 0.05$). On the other hand, the authors did report a significantly lower VAS score among PRP patients at 24 weeks ($P = 0.0096$) and 52 weeks ($P = 0.0039$) [5].

Though limited, some studies have demonstrated higher efficacy of PRP in reducing pain. In a double-blind RCT of 41 participants (48 knees), Forogh et al. compared the efficacy of one PRP injection to one CS injection. The authors reported that patients who received PRP experienced greater improvements in pain ($P = 0.007$), symptom control ($P < 0.001$), activities of daily living ($P =$

0.005), and QOL ($P = 0.02$) at six months [7]. However, a comparison at 6 months does not account for the fact that CSs only provide pain relief for up to three months [10]. A meta-analysis by Sax et al. revealed substantial heterogeneity ($I^2 \geq 76\%$) among RCTs assessing the efficacy of PRP in comparison to other therapies [8]. While PRP injections may provide a longer-lasting effect, the significant differences observed in short-term pain relief paired with the cost-effectiveness of CS injections must be considered when weighing the value of the two options.

This study demonstrated that patients who received PRP injections reported similar functional improvements to those who received CS injections when comparing improvement in KOOS for Joint Replacement scores at six weeks ($P = 0.739$) and three months ($P = 0.819$). Additionally, groups experienced similar improvements in total WOMAC scores at six weeks ($P = 0.878$) or three months ($P = 0.789$). This is in accordance with much of the existing literature. Jubert et al. reported no significant differences between patients who received PRP versus CS in any of the KOOS subscales at one, three, or six months. Additionally, the authors reported no difference between groups when assessing the SF-36 physical functioning subscale at one month ($P = 0.58$), three months ($P = 0.56$), or six months ($P = 0.21$) [6]. Pretorius et al. demonstrated no significant differences between WOMAC score improvement for patients who had bilateral knee OA who received PRP in one knee and CS in the other ($P = 0.84$). When compared to other therapies, such as HA injections, there appears to be no superiority associated with PRP injections when comparing functional improvement. Cole et al. demonstrated no difference in total WOMAC scores between patients who received PRP or HA at 24 weeks ($P > 0.05$) or 52 weeks ($P > 0.05$) [5].

Other studies have demonstrated higher improvement in function after PRP injection when compared to CS and other therapies, but only when looking at follow-ups that are greater than three months. In a double-blind RCT of 41 participants (48 knees), Forogh et al. compared the efficacy of one PRP injection to one CS injection. Compared to the group treated with CS's, the cohort that received PRP experienced greater improvements in activities of daily living ($P = 0.005$) and QOL ($P = 0.02$) at six months [7]. Huang et al. performed an RCT of 120 patients comparing PRP, CS, and HA injections. The authors demonstrated that up to three months, there were no significant differences between groups in total WOMAC score improvement ($P > 0.05$). However, they did demonstrate the superiority of PRP from six months to one year ($P < 0.05$) [18]. These findings may not be clinically relevant due to the short-acting nature of CS injections, as previously discussed [10].

Conclusions

Patients who received PRP injections reported inferior pain relief at six weeks compared to those who received CS. Changes in pain scores were similar between cohorts at three months. Improvements in functional scores were similar between cohorts at both six weeks and three months. These results, in conjunction with the high cost of PRP, should be taken into consideration by patients and physicians when deciding between CS and PRP injections for moderate OA of the knee.

CRediT authorship contribution statement

Sandeep S. Bains: Writing – review & editing, Methodology, Investigation. **Gabrielle N. Swartz:** Writing – review & editing, Writing – original draft. **Reza Katanbaf:** Writing – review & editing, Investigation, Formal analysis, Data curation. **James Nace:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Craig Bennett:** Supervision, Methodology, Investigation, Conceptualization. **Michael A. Mont:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Ronald E. Delanois:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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