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Comparison between the effect of intra-articular injections of platelet-rich plasma and corticosteroids in advanced knee osteoarthritis

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Abstract

Objective

The objective of this study was to compare intra-articular injections (IAIs) of platelet-rich plasma (PRP) and corticosteroid injections in reducing pain and studying which has a more effective and lasting functional improvement.

Patients and methods

A total of 60 patients with chronic knee osteoarthritis (Kellgren–Lawrence grades 3 and 4) were enrolled in this study. Patients were randomized to treatment either with a single leukocyte-rich PRP or corticosteroid IAIs. Patients were assessed by visual analog scale, and Knee injury and Osteoarthritis Outcome Score at 1, 3, and 6 months after treatment.

Results

Our results showed improvement in all variables in both groups. Statistical differences between groups were found for the majority of the outcome variables, and the degree of improvement was more in the PRP group.

Conclusion

IAI of PRP is effective for relieving pain and improving activities of daily living and quality of life in old patients with late-stage knee osteoarthritis. IAI of one shot of corticosteroid has similar results but for a short term and with more side effects.

Keywords: Intra-articular injections, knee, osteoarthritis, platelet-rich plasma

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease that causes pain and disability in older adults. Knee OA is found to have a higher incidence than hip or hand OA. Pain is the main symptom of patients with knee OA, accompanied by stiffness and limited mobility of the knee [1].

In more advanced stages of OA, intra-articular injection (IAI) of corticosteroid with local anesthetic (continuous spinal anesthesia), hyaluronic acid, or biological products such as platelet-rich plasma (PRP) are used in very symptomatic cases [2]. Ayhan *et al.* [3] found that IAI is a first-line treatment; it is effective for pain relief with few side effects compared with some oral medications.

Injection of PRP is thought to be safe and does not interfere with the biomechanical function of the knee. It is a component of whole blood that is centrifuged to a concentrated state, treated with an activating agent, and injected into the affected area [4].

The basic biologic mechanism of action of PRP after injection is simple: it induces a local inflammation. The proinflammatory mediators together with the growth factors released from the granules of the platelets trigger the localized inflammation and

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the wound healing cascade, resulting in the cellular migration and proliferation, glycosaminoglycan and collagen deposition, collagen maturation, and remodeling of the healing [5].

Recently, the use of PRP in the treatment of degenerative knee OA has more safety and easy production and administration [6]. Richmond *et al.* [7] noted that it is effective for pain treatment and improvement of knee joint function; moreover, it has better results in the early stages of knee OA and is superior in comparison with other IAIs, and its effects last longer (6–12 months). However, no previous studies have studied the clinical outcomes of PRP injections during the late stages of the disease.

Other clinical trials also suggested the superiority of PRP in comparison with other IAIs and 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 [8].

The aim of our study was to compare the effect of a single PRP IAI versus a single CSA IAI on relieving pain and improving knee function in patients at late stages of knee OA.

PATIENTS AND METHODS

Patients

The study protocol was approved by the Ethics Committee of GOTH. The study included 60 patients with knee OA Kellgren–Lawrence (K–L) classification grades 3 and 4, had the walking ability with or without external support, already on the waiting list for knee replacement, with ages ranging between 40 and 80 years. They were selected from the rheumatology outpatient clinic of Al-Mataria Teaching Hospital. A group of 30 patients was treated with an IAI of PRP, and another group of 30 patients was treated with an IAI of corticosteroids.

History and clinical examination were performed for every patient; complete blood count was assessed to exclude anemia and thrombocytopenia. OA was diagnosed by the American College of Rheumatology Criteria and staged as K–L radiological classification [9].

All radiographs were taken under weight-bearing conditions. Assessment of pain after treatment is measured using visual analog scale (VAS), whereas the assessment of outcomes is carried out using the Knee injury and Osteoarthritis Outcome Score (KOOS) at 0, 1, 3, and 6 months after treatment [10].

Patients stopped NSAIDs 1 week before the study. Patients were excluded if they had any of the following criteria:

- (1) Had received IAIs of steroids, or hyaluronic acid in the past year
- (2) Underwent arthroscopic surgery in the past 3 months
- (3) Hematological disorders like anemia (hemoglobin <7.0 g/dl), thrombocytopenia (platelets <15 000/ μ l) or bleeding dyscrasias
- (4) Compromised bone metabolism (except for osteoporosis)
- (5) Any autoimmune diseases

- (6) Documented history of allergy to steroids, or blood products
- (7) Valgus deformity more than 15° or varus deformity more than 20°
- (8) Had severe ligamentous instability of the knee joint
- (9) Limitation of knee range of movement: flexion less than 0°, extension deficit more than 20°.

Preparation of platelet-rich plasma

It began with a venous puncture and subsequent collection of a specific volume of autologous blood from the patient (20 ml of venous blood sample) into a tube containing an anticoagulant (sterile sodium citrated tubes) for preparing 4–6 ml of PRP with platelet concentration of three to six times the average normal values. The PRP contained a median value of 0.87×10^6 platelets/ml (range: $0.47\text{--}1.42 \times 10^6$ platelets/ml) and a median value of 0.6×10^6 white blood cell (WBC)/ml (range: $0.1\text{--}1.5 \times 10^6$ WBC/ml) (PRP: PAW classification system) [11]. The absolute platelet number is generally greater than 750 000/ μ l of platelets. The tubes were centrifuged at 3500 rpm for 10 min, separating the plasma (top layer) from packed red blood cells (bottom layer). The red blood cell layer is discarded, and the second centrifuge at 4000 rpm for 7 min yields a more concentrated platelet layer after extraction of platelet-poor plasma. Platelets rich in growth factors were obtained. Our study technique is close to Choi's technique (1a 2). Finally, 4–6 ml of PRP was dispensed in a syringe for injection.[12]

Injection technique

Patients were made to sit in a supine position. The skin of the knee was disinfected by betadine. For the PRP group, after injecting 2 ml of local anesthesia (medicine), PRP was injected by the same syringe using the anteromedial or anterolateral approach of knee injection. As soon as the needle was out, we placed a bandage over the injected area. After 15–20 min of rest and observation, patients were asked to actively flex and extend their knees, so that the PRP could spread evenly across the joint space before changing into a gel. The patient was then discharged. The same steps were followed for the steroid group of patients.

Postinjection instructions

After they received the injection, patients were given the following injections:

- (1) Not allowed to bear weight for 3 days
- (2) Avoid running and other high impact activities for 10 days
- (3) As PRP effectively induces an inflammatory response, some patients experienced minimal to moderate discomfort following the injection, which lasts for up to 1 week. They were instructed to ice the injected area if needed for pain control three times a day, each time for 10 min, and modify activity as tolerated
- (4) Use acetaminophen as the optimal analgesic, and avoid the use of NSAID's aspirin or any steroids throughout our 3 months' follow-up period, as they exhibit antiplatelet and anticoagulant effects, which may diminish the effectiveness of PRP

(5) They could resume their usual activities of daily living (ADL) 1 week after injection. For the PRP group, exercise was started a week after injection with lower intensity in the first days, and then it increased progressively to be continued on a normal level.

Statistical analysis

All tabulated data are expressed as mean ± SD. Comparisons between patients and control groups were carried out by using the Student *t*-test. For all statistical tests, the significance was determined using the correlation coefficient (*r*) test, in which significance is defined as the level of probability of *P* value of less than 0.05. Computations will be carried out using an SPSS statistical program, version 12, and graphs will be assessed using Microsoft Excel XP version 2010, SPSS statistical program, version 12, Microsoft, town, state (if USA), and country. One-way analysis of variance was used to compare categorical variables.

RESULTS

A group of 30 patients with 52 knees with advanced OA and K–L grades 3 and 4 received an IAI of PRP, and the other 30-patient group with 40 knees with advanced OA and K–L grades 3 and 4 received an IAI of corticosteroids. There was no significant difference between the two groups as regards age, disease duration and all clinical and radiological parameters (Table 1).

VAS score decreased for both groups, with no significant differences between groups at different timepoints (Table 2).

The differences in VAS score at 1 and 3 months compared with baseline showed no statistically significant differences between groups (*P* = 0.08 and 0.06); however, the difference was significant between groups at 6 months (*P* = 0.05). Considering that the difference tended to be greater in the PRP group (Fig. 1).

Our study showed a significant difference in VAS score at 6 months between both groups of patients with K–L grade 3, and at 3 and 6 months with a K–L grade 4 (*P* ≤ 0.05). However, there are no significant differences between groups at other different timepoints in patients with K–L grades 3 and 4, as seen in Table 3.

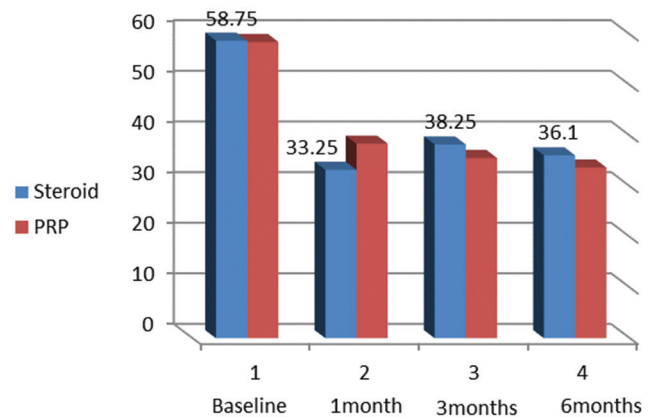


Figure 1: Trends in mean pain visual analog scale (VAS) scores of both groups at baseline and subsequent follow up. PRP, and steroid injections.

Table 1: Baseline characteristics of study patients

Parameters	PRP group (n=52)	Steroid group (n=40)	<i>t</i>	<i>P</i>
Age (years)				
Range	44-80	45-82	0.721	0.984
Mean	62.9±11.6	61.1±11.6		
Sex: female/male [n (%)]	29/23 [51.8 (41.1)]	31/9 [77.5 (22.5)]	2.08	0.04
Disease duration				
Range	8-32	11-30	0.98	0.32
Mean	16.7±7.09	17.6±7.8		
External support to walk (no/yes) [n (%)]	8/44 [14.3 (78.6)]	7/33 [17.5 (82.5)]	-0.57	0.21
Side (right/left) [n (%)]	28/24 [53.2 (46.15)]	22/18 [55 (45)]	0.4	0.63
K-L classification [n (%)]				
Grade 3	30/22 [53.6 (46.4)]	24/16 [60 (40)]	0.47	0.63
Grade 4	22/30 [46.4 (53.6)]	16/24 [40 (60)]	0.39	0.69
BMI (kg/m ²)	21-41 (29.36±5.1)	22.8-43.6 (29.3±4.9)	-0.09	0.61
The range of motion (deg.)				
Flexion	67-135 (97.9±15.1)	80-138 (97.3±13.1)	0.2	0.29
Extension	0-12 (5±2.9)	0-5 (6.5±3.5)	-2.28	0.53
VAS	40-90 (58.5±12.5)	45-92 (58.7±12.7)	-0.9	0.67
KOOS subscale				
Pain	10-75 (42.8±18.1)	8-75 45.8±16.4	-0.81	0.41
Symptoms	20.2-78.4 (42.4±17.1)	17.3-73.8 (41.07-16.5)	0.37	0.68
Activities of daily living	10.4-70.6 (36.11±15.3)	9.3-66.5 (35.8±15.8)	0.08	0.94
Sport/recreation	0-45 (22.3±11.8)	0-44.3 (21.3±12.01)	0.4	0.75
Quality of life	0-55 (22.0±12.5)	0-47.6 (24.1±14.4)	-0.62	0.24

K-L, Kellgren-Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; PRP, platelet-rich plasma; VAS, visual analog scale.

Flexion deformity and extension lag decreased for both groups after injection, with significant differences between groups at 6 months with $P = 0.01$ and 0.02 , respectively; however, there was no significant difference between groups at 1 and 3 months, at time-point with $P = 0.40$ and 0.08 for flexion deformity and $P = 0.55$, and 0.25 , for extension lag, respectively, as seen in Tables 4 and 5.

KOOS outcomes are presented in Table 6. The difference between both groups after injection at 3 months was significant as regards pain and ADL ($P = 0.02$ and 0.02 , respectively), and at 6 months was significant as regards pain, ADL, and quality of life (QOL) ($P = 0.002$, 0.04 , and 0.04 , respectively); however, it was not significant as regards other parameters.

The differences in KOOS-QOL scores and ADL between baseline and 3 and 6 months increased significantly more in the PRP than in the steroid group. At 3 months, mean was 13.6 ± 11.5 vs. 11.5 ± 1.5 and 8.1 ± 7.4 vs. 1.1 ± 0.5 , respectively ($P = 0.03$ and 0.04), and, at 6 months mean was 25.4 ± 9 vs. 17.6 ± 3.0 and 9.6 ± 9.2 vs. 0.8 ± 0.5 ($P = 0.03$), for each group, respectively (Fig. 2).

DISCUSSION

Osteoarthritis is a chronic disease defined by progressive degeneration of the joint as well as loss of cartilage on joint surfaces. knee osteoarthritis (OA) present in approximately 11% of women and 7% of men older than 60 years [13].

The degeneration that occurs in the joint leads to changes in the catabolic and anabolic activity of chondrocytes. As a result,

other components of the joint get compromised which may lead to meniscus degeneration, bone deformity, sclerosis as well as subchondral tissue edema and intermittent synovial inflammation [14]. This condition impairs functional capacity and decreases quality of life (QOL) in patients by producing pain, stiffness and limitation in range of motion of the joint. Recently, treatments for cartilage tissue repair have been introduced, including mesenchymal stem cell therapy, autologous chondrocyte implantation, use of matrix metalloproteinase inhibitors, gene therapy and growth factors [15].

Various studies were performed on different platelet concentrations in plasma, classically, PRP is considered as a volume of plasma containing higher concentrations of platelets compared to blood base line level. In fact, this definition includes plasma and platelets. Platelets contain different growth factors and cells containing proteins and bioactive molecules. Today, the generic term PRP has progressed and include various products. These products are categorized based on the PAW classification system (platelet concentration, white blood cells and activation method) [11] [16]. Because PRP contains growth factors and plasma proteins, it can regulate anti-inflammatory signals and equilibrate angiogenesis. Based on this, its use in order to reduce the progression of OA has been suggested in some studies [17].

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 [18].

Table 2: Differences in visual analog scale score at baseline, 1, 3, and 6 months

Visual analog scale	Platelet-rich plasma group (n=52)	Steroid group (n=40)	t	P
Baseline				
Range	40-90	45-92	-0.9	0.67
Mean	58.5±12.5	58.7±12.7		
1 month				
Range	0-70	0-50	1.4	0.92
Mean	38.4±17.3	33.25±16.5		
3 months				
Range	0-65	0-70	-0.72	0.79
Mean	35.59±17.05	38.25±17.7		
6 months				
Range	0-60	0-70	-0.67	0.30
Mean	32.8±17.7	42.3±16.75		

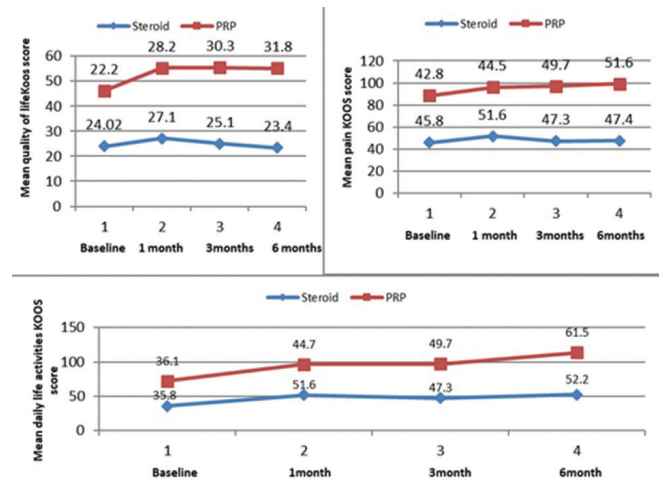


Figure 2: Trends in mean (KOOS) results of both groups at baseline and subsequent follow-ups PRP and steroid injections

Table 3: Differences in visual analog scale score at baseline, 1, 3, and 6 months as regards Kellgren-Lawrence grades 3 and 4 in both groups

K-L grade 3 and VAS	F	Significance	K-L grade 4 and VAS	F	Significance
Baseline	0.45	0.71	Baseline	0.972	0.41
1 month	1.67	0.77	1 month	2.17	0.09
3 months	0.23	0.87	3 months	2.69	0.05
6 months	2.71	0.05	6 months	3.26	0.025

K-L, Kellgren-Lawrence; VAS, visual analog scale.

Some studies were 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 [17].

Most of the studies included early-stage OA, However patients with grades 3 and 4 being less common. About (12.6%) with advanced knee OA were studied, only (3,37.9%) with K-L grade 3, and (9.4%) with K-L grade 4 of all the studied patients. In these studies, the worst results were obtained for K-L grades 3 and 4 [18].

Table 4: Differences in flexion deformity at 1, 3, and 6 months

Flexion deformity	Platelet-rich plasma group (n=52)	Steroid group (n=40)	t	P
1 month				
Mean±SD	111±12.2	105±11.5	0.407	NS
3 months				
Mean±SD	113.5±12.17	102.4±10.5	0.08	NS
6 months				
Mean±SD	116.4±13.34	101.9±9.35	0.01	S

Table 5: Differences in extension lag at 1, 3, and 6 months

Extension lag	Platelet-rich plasma group (n=52)	Steroid group (n=40)	t	P
1 month				
Mean±SD	-4.6±2.6	-5.4±3.1	0.55	NS
3 months				
Mean±SD	-4.4±2.3	-5.4±2.8	0.23	NS
6 months				
Mean±SD	-3.9±2.2	6.3±2.9	0.02	S

Table 6: Differences in Knee injury and Osteoarthritis Outcome Scores in both groups of patients after injection at baseline, 1, 3, and 6 months at the same timepoints

KOOS	Baseline	P	1 month	P	3 months	P	6 months	P
Pain (mean±SD)								
PRP	42.8±18.1	0.4	44.5±18	0.2	49.7±18.8	0.02	51.6±20.8	0.02
Steroid	45.8±16.4		51.6±15.8		47.3±14.3		47.4±13.9	
Symptoms (mean±SD)								
PRP	42.4±16.5	0.65	46.8±16.5	0.2	48.6±15.9	0.1	49.2±15.6	0.09
Steroid	41.0±16.5		48.2±19		46.1±18.4		46.1±18.4	
Activities of daily living (mean±SD)								
PRP	36.1±15.3	0.9	44.7±18.6	0.3	49.7±18.8	0.02	61.5±23.7	0.04
Steroid	35.8±15.8		51.6±15.8		47.3±14.3		52.2±18.8	
Sport/recreation (mean±SD)								
PRP	22.3±11.8	0.7	32.7±23.4	0.5	34±23	0.28	35.6±22.7	0.23
Steroid	21.3±12.01		36.2±20.1		30.9±17.8		30.5±16.8	
Quality of life (mean±SD)								
PRP	22.2±12.8	0.2	28.2±18.9	0.18	30.3±21.2	0.2	31.8±22.0	0.04
Steroid	24.2±14.4		27.1±15.2		25.1±14.9		23.4±13.	

KOOS, Knee injury and Osteoarthritis Outcome Score; PRP, platelet-rich plasma.

In contrast to our study there was significant improvement in VAS score for OA patients with K&L grade 3 after 6 months and improvement was also significant for OA patients with K&L grade 4 at 3 and 6 months follow up, comparing both PRP and steroid group with $P \leq 0.05$, the differences in VAS were greater in the PRP group. This results were in agreement with other study that included (28.6%) old patients with late-stage OA knees being classified as K-L grade 3 ($n = 10$) & (71.4 %) with grade 4 OA knees ($n = 25$) injected with PRP. Also the study included (56.6%) K&L grade 3 ($n = 17$) & (43.4 %) K&L grade 4 ($n = 13$) injected with corticosteroids, they found that, there was significant difference in VAS score at 6 months with ($P \leq 0.05$) in patients with K&L grad 3 and 4, the difference tended to be greater in the PRP group compared to steroid group [18].

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 injection compared with CSA, as determined 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 5 point decrease in steroid group compared with PRP group, similar results were observed, by other authors where they found that, although there was no statistically significant difference between groups, there was a 4 point decrease in steroid group compared with PRP group [18]. This could be explained by the prompt anti-inflammatory effect of corticosteroid [19].

As expected, since corticosteroid effects are known to be short, the VAS for this group worsened at 3 months while VAS improved in PRP group. This improvement was above that for corticosteroid group by 10 points, similar to other study where the improvement observed in patients injected with PRP was 8 points above that for corticosteroid group [18]. Also, in our study there was more improvement in flexion deformity

and extension lag in prp group with significant differences compared with steroid group at 6 months.

These findings are in agreement with clinical trial compared a single injection of PRP or CSA. For 48 knees K-L grade 2 to 3, where they found statistically significant differences between treatments as determined by KOOS scores [7].

Pain, ADL and quality of life, were improved in our patients treated with PRP-IAI, as PRP IAI decreased joint pain and improved activity of daily living and quality of life in symptomatic knee OA. Several factors could explain improvement of our PRP results compared with previous trials where the improvement was only in quality of life at baseline compared with that at 3 and 6 months with $P = 0.05$ & 0.03 respectively, the improvement was greater in PRP group of patients.

This results were different from ours may be due to that in previous study there were greater women (72%), older mean age of participants (67 years), and higher mean BMI (31 kg/m²), however, in our study patients were with lesser mean age of participants (62 years), and lesser mean BMI (30kg/m²). Other studies observed superior effectiveness of PRP in young men and patients with low BMI [7].

Similar studies were done where they compared PRP with CSA, patients had a mean age 61 years and mean BMI of 29 kg/m², lower than that in our study [20,21]. However they did not find that PRP was superior to steroid, this could be explained by that in our study we use a leukocyte-rich PRP [22].

Most published studies observed that PRP effectiveness lasts 6 to 12 months on average, we might consider more than one shot PRP IAI to treat late-stage knee OA, while others have proposed, a cyclic treatment. Patel *et al*, 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*, 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 some outcomes parameters, we believe that for late-stage knee OA, a serial single injection of high-concentration PRP might reduce the pain enough and for longer periods, with an adequate quality of life, to delay knee replacement.

We recommend to 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.

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 assess the efficacy of PRP treatment in patients with advanced knee OA.

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Conflicts of interest

There are no conflicts of interest.

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