

Clinical outcomes of intraarticular PRP and corticosteroid combination in advanced osteoarthritis

PRP and corticosteroid combination

Mehmet Cenk Turgut¹, Erhan Okay², Kutsi Tuncer^{1,3}, Ömer Selim Yıldırım³¹Department of Orthopaedics and Traumatology, Erzurum Atatürk University, Erzurum²Department of Orthopaedics and Traumatology, Istanbul Medeniyet University Goztepe Education and Training Hospital, Istanbul³Anesthesiology Clinical Research Office, Erzurum Ataturk University, Erzurum, Turkey

Abstract

Aim: The objective of this study is to compare the clinical response of corticosteroid (CS) and platelet-rich plasma (PRP) treatment in 2 groups of patients affected by advanced osteoarthritis

Material and Methods: A total of 68 patients affected by clinically and radiographically documented with grade 4 gonarthrosis according to the Kellgren-Lawrence classification were included in this study. The patients were identified into 2 study groups. Thirty-two patients (Group 1) received 3 intra-articular injections of PRP (5mL) and steroid (1 cc – 5 mgr triamcinolone). Thirty-six patients (Group 2) received 3 intra-articular injections of PRP with one-week interval (5 mL). An unblinded physician performed injection once a week for 3 weeks into the affected knee in both groups. All patients were evaluated with the VAS score and the Knee injury and Osteoarthritis Outcome Score (KOOS) subscales before the infiltration, at 2nd and 6th month after the first injection.

Results: Two groups are similar with regard to demographic variables (age, gender, BMI, stage of arthritis). The combination of intra-articular PRP with steroids resulted in a significantly superior clinical outcome, with sustained lower VAS ($p < 0.01$) and improved KOOS subscales ($p < 0.01$) except for KOOS sporting activity and quality of life within 6 months compared to intra-articular PRP only injection.

Discussion: Treatment with intra-articular PRP and steroids showed a significantly better clinical outcome than did treatment with PRP, with sustained better KOOS scores.

Keywords

Advanced osteoarthritis; Intraarticular injection; PRP; Steroid

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Corresponding Author: Erhan Okay, Department of Orthopaedics and Traumatology, Istanbul Medeniyet University Goztepe Education and Training Hospital, Eğitim Mah. Dr. Erkin Cad. 34722 Kadikoy, Istanbul, Turkey

E-mail: erhanokay@yahoo.com GSM: +90 532 386 5174

Corresponding Author ORCID ID: <https://orcid.org/0000-0003-2443-2505>

Introduction

Advanced osteoarthritis is affecting the elderly population, which reacts via catabolic and inflammatory joint environment. Operative treatment is advised in the setting of decreased ability to walk and the presence of night pain. First-line nonoperative treatments are still needed to delay surgery, decrease the progression of arthritis, deformity, functional limitation, and joint stiffness.

During the past few decades, attention has shifted towards the development and effects of biologic applications. Intra-articular applications are considered in patients, who do not benefit from oral medications. Two options among these biologic instruments are PRP and steroid treatments. These are extensively evaluated in clinical application also as emerging molecules used for in-vitro studies of osteoarthritis pathogenesis [1]. Increased emphasis has been placed on their therapeutic efficacy along with their safety concerns.

Platelet-rich plasma is under the application in maxillofacial and plastic surgery for more than a decade. FDA approved its use for orthopaedic conditions since 2012. It has anti-inflammatory potential via reducing nuclear factor kappa B (NF- κ B), a major pathway in osteoarthritis [2]. It has also chondroprotective role by increasing hyaluronic acid production and a decrease in matrix metalloproteinases synthesis, scaffolding effect via fibrinogen and anabolic effect via a great variety of growth factors secreted by alfa granules [1, 3]. Variation in preparation methods, injection volume, leukocyte and fibrine amount, activation method, number of injections reported in studies leave the question about its ideal formulation unanswered [4]. A standard classification based on preparation is needed to compare its effect in various studies. Although PRP has not been favored as a first-line treatment for moderate to severe knee OA, one recent study demonstrated its efficacy for clinical outcomes with similar results of one injection of PRP compared to one dose corticosteroid [5]. PRP is considered when the patient has failed previous treatment, is unable to tolerate oral NSAIDs and severe symptoms enough to consider surgery, but unwilling to surgery. AAOS guidelines were not able to recommend for or against its use, but one meta-analysis stated its beneficial effect up to 12 months based on 14

Steroid has been preferred as an intra-articular treatment for osteoarthritis since the 1950s. It is effective in relieving arthritis pain with few adverse effects. Steroids bind to nuclear steroid receptors, decrease the synthesis of inflammatory cytokines by inhibition of phospholipase A2 [6]. AAOS clinical guidelines reported its application for osteoarthritis as inconclusive; however, the duration of its effect has been reported up to 6 months [5, 7, 8]. Scientific debate with regards to the type of corticosteroid, dosage, number of injections, use of local anesthetic continues to determine its optimal effect.

The effect of PRP has been questioned in terms of its formulation and duration. Meanwhile, new forms of steroids are investigated to prolong its effect. Application of PRP and steroids alone and in combination with other substitutes are well documented [5, 8, 9], but no assessment has been made as yet of a combination of PRP and steroids on clinical outcomes of advanced osteoarthritis. Based on these findings, the aim of the present study is to evaluate the clinical effect of

combined applications of PRP and steroids. It was hypothesized that the simultaneous application of PRP and steroids would demonstrate improved clinical outcomes in advanced osteoarthritis compared to PRP application alone.

Material and Methods

The study is in compliance with the Helsinki Declaration and ethical approval was granted by the University Ethics Committee, and informed consent was obtained from every participant. Between January 2012 and September 2018, outcome tools were applied for osteoarthritis to screen clinical improvement of intra-articular biologic treatment and surgical procedures (arthroplasty, arthroscopic meniscectomy, high tibial osteotomy) in the clinic, which conducted this study. Osteoarthritis database was used for this study. Radiographs of the affected knees were retrospectively evaluated by a blinded physician with ten-year experience in orthopedic practice. Patients diagnosed as primary knee osteoarthritis according to the American College of Rheumatology criteria were retrospectively determined. Anterior-posterior radiographs were graded by the examining surgeon using the Kellgren-Lawrence classification. Patients with level 3-4 arthritis (advanced osteoarthritis) were included. Inclusion criteria were advanced osteoarthritis of the knee (Kellgren-Lawrence Grade 1-2), intraarticular injection of unilateral knee, age > 65 years, having BMI > 30, resistant pain unresponsive to NSAIDs more than 1 year, normal coagulation profile and whole blood count, no history of surgery on bilateral knees, presence of complete outcome and demographic data. Exclusion criteria included NSAID use within last 30 days prior to injection, previous intra-articular injection within 6 months, rheumatoid or autoimmune disease, immunodeficiency, existing hip osteoarthritis, systemic metabolic disease, use of corticosteroid, presence of smoking habitus and any agents affecting platelet activation. Finally, a total of 60 patients with primary osteoarthritis diagnosed by the American College of Rheumatology [10] were retrieved from hospital records with complete demographic data and outcome measures. Patients received an injection into unilateral knee. Home exercises were routinely prescribed to all patients. Informed consents were given by the patients about intraarticular steroid and PRP treatment with its advantages and disadvantages. The intraarticular injection was canceled when the patient has a history of septic arthritis and local superficial lesion and infection on the knee. While patients, who accepted and received intraarticular PRP- steroid treatment comprised the first group (Group 1), patients, who accepted only intraarticular PRP comprised another group (Group 2). Demographic data such as gender, age, BMI, and follow-up were collected. Patients were contacted by telephone. Data about analgesic consumption, satisfaction rate after injections were recorded.

Clinical evaluation: Functional assessment of patients was made based on pretreatment as well as 2nd and 6th month posttreatment results of the Knee injury and Osteoarthritis Outcome Score (KOOS) scores with its subscales and the Visual Analog Scale (VAS).

Intraarticular injection: All injections were routinely performed by one physician using standard protocol. Using aseptic

procedures, the injection was performed in an anterolateral approach (along the patellar tendon) with the knee in 90 degrees flexion. If effusion is present, joint aspiration was made before injection. The injections were repeated three times with one-week intervals. In the first group, one injection of PRP (5 cc) was performed with an 18-gauge needle. In the second group, after the injection of PRP (5 cc), 1 mL triamcinolone acetonide was injected with the same needle. No local anesthetic agent was used in all patients due to its possible chondrotoxic effect, which could deteriorate clinical outcomes in the arthritic knee. Adverse events (mild swelling and pain) were recorded within 48 hours after drug administration. Physical activity was prohibited in this time period.

PRP preparation: At the beginning of intraarticular PRP treatment in our clinic, our biochemical laboratory gave technical support in PRP preparation. Peripheral blood (60 mL) was taken from all patients. Three tubes of 20 mL syringes were prepared by adding 2 mL of acid citrate dextrose (ACD-A) to each. These tubes were placed into a centrifuge system with symmetric configuration to avoid unequal distribution of turning forces in centrifugation applied to samples. Double spinning method was applied as described by Mazzocca [11]. This method has been found to be comparable to the other two methods applied in the same study. The first centrifugation was performed for five minutes at 1500 rpm. After the removal of upper layers of plasma, samples were centrifuged for twenty minutes at 6300 rpm. We did not activate PRP before injections. Leucocyte filtration was not performed. Three injections with one-week interval were applied to the patients. The preparation process was repeated for every application and intraarticular injection was performed within 4-6 hours after preparation because an open system was used. PRP solution was not stored. The platelet number, number of red blood cells, and white blood cell components were measured by an automated hematology analyzer (Beckman Coulter, Brea, CA). Complete blood count was performed for the first 10 patients with advanced osteoarthritis to determine whole blood/PRP platelet and white blood cell count. PRP's platelet and white blood cell levels were compared with levels of the peripheral blood. The mean platelet counts in the peripheral whole blood and PRP were $152.3 \pm 51.4 \times 10^3/\mu\text{L}$ and $506.94 \pm 242.9 \times 10^3/\mu\text{L}$, respectively. The mean white blood counts in the peripheral whole blood and PRP were $5.6 \pm 1.7 \times 10^3/\mu\text{L}$ and $11.76 \pm 3.8 \times 10^3/\mu\text{L}$, respectively.

Statistical Analysis: Analyses were conducted using SPSS Statistics 20.0 (IBM Corp., 2011). Data normality was checked using the Shapiro-Wilkins test. Categorical variables were given as percentages and frequencies. Continuous variables were given as mean and standard deviation. The Chi-square test was used to compare categorical variables (gender, paracetamol use, satisfaction rate). To compare two treatment groups based on continuous data (BMI, age, time to knee replacement), an independent t-test was used. Temporal changes in outcome scores of the groups (KOOS, VAS) were evaluated using a general linear model for repeated measures test. Pair-wise comparisons within time were made using paired sample t-test. To compare two treatment arms based on outcome scores at each time point, the independent t-test was used. Statistical significance was set as $p < 0.05$.

Results

The demographic data and baseline disease characteristics of the two groups are shown in Table 1. There were no significant differences in the demographic or clinical data (use of paracetamol) used in the study (n.s.). At the time of diagnosis, the duration from the onset of knee pain was recorded as more than one year in all study groups. Retrospective review does not reveal any discontinuation of treatment or crossover to another treatment for the entire study group. No adverse effects were recorded regarding steroids and PRP (skin depigmentation, postinjection flares, fat necrosis, cutaneous atrophy).

Notably, there were significant improvements at the 2nd month for each treatment group. At the 2nd month after injection, between-group comparison showed that Group 1 (PRP/steroid injection) had significantly better VAS results than Group 2 (only PRP injection) ($p < 0.01$). At the 6th month, deterioration in VAS scores was observed for both groups relative to 2 months after injection; however, there is still a significant difference between the two groups, and final VAS scores for all groups remained better compared to baseline ($p < 0.01$).

Regarding KOOS scores, there was a statistically significant improvement for all KOOS subscales in all the treatment groups compared to baseline ($p < 0.01$). Values for KOOS-Sport and KOOS-Quality of Life subscales were similar between two treatment groups at each time point ($p > 0.05$). However, Group 1 (PRP/steroid injection) demonstrated greater improvement

Table 1. Baseline characteristics for two treatment groups

	Group 1 (PRP/steroid injection)	Group 2 (PRP injection)	p-value
Age	66,9 ± 7,9	67,6 ± 7,4	0.694
Gender (female/male), n (%)	27/5 (84.4/15.6)	20/16 (55.6/44.4)	0.13
BMI (kg/m ²)	31,9 ± 1,83	31,3 ± 1,30	0.814
VAS	7.13 ± 1.0	7.61 ± 1.07	0.06
Use of paracetamol, n (%)	13/32 (40.6)	20/36 (55.6)	0.219
KOOS subscale			
Pain	25.72 ± 5.27	23.86 ± 5.67	0.168
Symptoms	47.63 ± 7.41	41.28 ± 6.49	<0.01
Activities of daily living	24.31 ± 5.13	22.81 ± 5.03	0.226
Sport	5.94 ± 1.72	6.83 ± 1.52	<0.05
Quality of life	24.78 ± 6.38	25.06 ± 4.56	0.155

Table 2. VAS and KOOS subscales of two treatment groups during follow-up

	2nd month			6th month		
	Group 1	Group 2	p	Group 1	Group 2	p
VAS score	3,34 ± 1,45	4,61 ± 1,29	$p < 0.01$	4,75 ± 1,78 ^a	6,58 ± 1,46 ^a	$p < 0.01$
KOOS-Pain	43,53 ± 8,75	31,75 ± 7,77	$p < 0.01$	44,94 ± 8,80 ^b	34,06 ± 7,52 ^a	$p < 0.01$
KOOS-Symptoms	52,41 ± 7,67	45,94 ± 6,10	$p < 0.01$	61,41 ± 8,75 ^a	53,36 ± 8,80 ^a	$p < 0.01$
KOOS-Activities of daily living	40,66 ± 9,02	29,89 ± 7,41	$p < 0.01$	48,31 ± 8,11 ^a	39,06 ± 7,70 ^a	$p < 0.01$
KOOS-Sport	13,06 ± 3,94	12,53 ± 2,69	n.s.	17,69 ± 3,96 ^a	16,64 ± 3,16 ^a	n.s.
KOOS- Quality of life	19,53 ± 6,23	18,78 ± 4,20	n.s.	24,78 ± 6,38 ^a	25,06 ± 4,56 ^a	n.s.

Values are represented as mean ± SD. Group 1: PRP/steroid injection; Group 2: steroid injection. VAS: Visual Analogue Scale, KOOS: Knee injury and Osteoarthritis Outcome Score.
^a indicates significant improvement within the group over time. ^b indicates nonsignificant improvement within the group over time. P-values indicate statistical significance between-group comparison, n.s.: not significant between-group comparison.

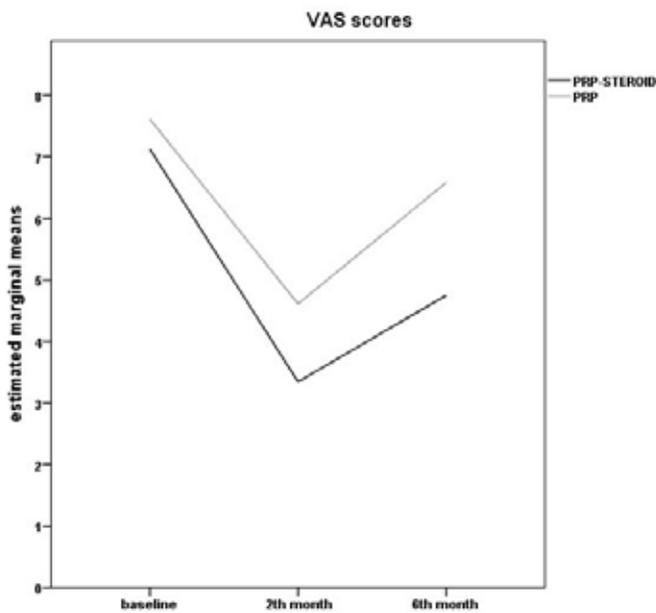


Figure 1. Line graph showing VAS pain scores over time with comparison between the two injection groups (0–10). There was a significant improvement in the visual analog scale (VAS) scores from before treatment to after treatment. By the 6th month, all patients showed deterioration compared to 2nd month; however the final mean is above baseline. Statistically significant difference was evident between PRP/steroid and only PRP injection at each time point.

in the remainder of KOOS subscales (KOOS-Pain; KOOS-Symptoms; KOOS-Activities of daily living) at each time point than Group 2 (only PRP injection) ($p < 0.01$). The combination of intra-articular PRP with steroid injection demonstrated overall improved clinical effect for both VAS and KOOS scores. With regard to satisfaction status of patients, % 65.6 (21/32) of the patients were satisfied. In Group 2, % 38.9 (14/36) of the patients were satisfied, demonstrating a significant difference between groups in favour of PRP/steroid injection. A comparison of two groups relative to outcome measures (VAS, KOOS) is summarized in Table 2 and Figures 1, 2.

Discussion

The most important finding of this study was that combined PRP and steroid injections resulted in improved clinical outcomes and reductions in pain up to 6 months in advanced osteoarthritis. Intra-articular applications are widely preferred to increase adaptation for physical therapy due to their pain relief and biological effects as several studies have demonstrated [12, 13].

Several studies investigated the comparison of combined intra-articular injections with one biologics alone. In a recent meta-analysis, Smith et al. [12] evaluated the clinical effect of combined intra-articular hyaluronic acid and steroid injection. They concluded that based on eight studies, combined therapy of hyaluronic acid and steroid injection was superior to intra-articular hyaluronic acid alone with prolonged pain relief up to

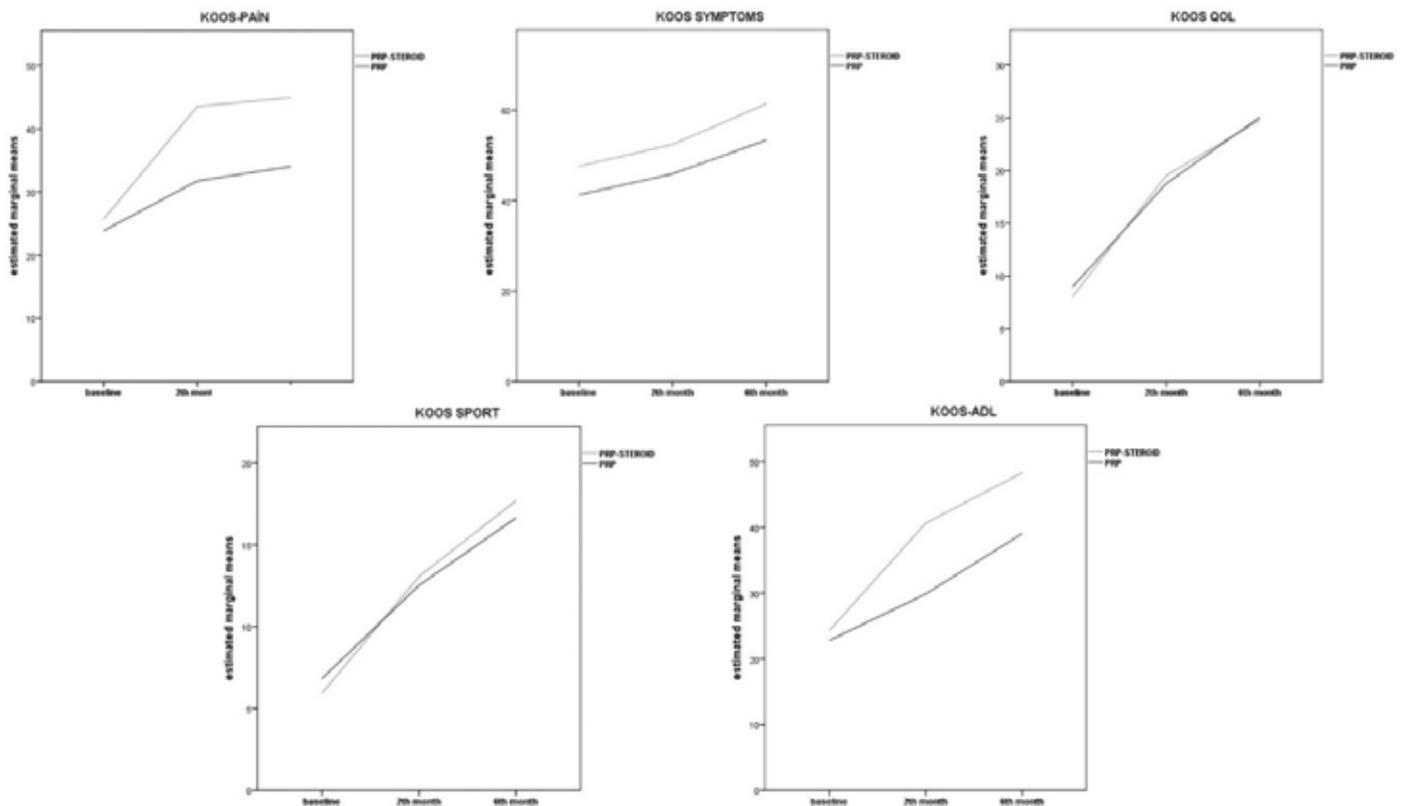


Figure 2. Line graph showing KOOS subscales over time with comparison of the two treatment groups for percentage change in KOOS subscales from baseline to 2 months (first follow-up) and 6 months (second follow-up). Group 1 (PRP/steroid injection) demonstrated significantly better improved scores for all subscales except for KOOS SPORT and KOOS-ADL compared to Group 2 (only PRP injection).

52 weeks. Rai et al. [13] performed a study using intraarticular combined PRP, hyaluronic acid and steroid injection. They applied 2 total doses with 3 months interval on 300 patients with various age groups (32-98 years). Improved clinical outcomes were observed at each age group (32-45; 46-60; 61-75, >76 years) and the clinical improvement in VAS, WOMAC, and TUG (Timed Up and Go test) scores becomes greater as age group increases (>76 years). Lana et al. [14] performed a prospective randomized study including 105 patients with grade 2 osteoarthritis, which were randomly assigned to one of the three different injection groups (PRP; PRP/ hyaluronic acid; hyaluronic acid). The results demonstrated superior clinical efficacy of PRP and hyaluronic acid to PRP or hyaluronic acid alone, with the least improvement for hyaluronic acid alone.

Despite the therapeutic value of combined intra-articular injections, there is a lack of data about intra-articular PRP and steroid injection. Only one study investigated the therapeutic effect of combined intra-articular PRP and steroid injection in mild to moderate osteoarthritis [15].

Except for this study, there are few recent studies comparing PRP and steroid injection for knee osteoarthritis [8, 9, 16]. These clinical studies comparing PRP and steroid alone provided data about the clinical effectiveness of both steroid and PRP treatment. Jubert et al. [5] in their prospective study, included 75 patients with grade 3-4 osteoarthritis and advanced age (>67 years) to compare PRP with one dose betamethasone. They obtained a decrease in VAS scores and improvement in KOOS scores with a tendency of PRP without significant difference. The reason for similar clinical results could be the lack of serial injection, contrary to the present study. To note, they did not have a group receiving serial PRP injections, which could extend the effect of PRP as stated by a systematic review [17]. Forogh et al. [16] randomly assigned 48 knees with mild to moderate osteoarthritis (50-75 years) into two groups according to receiving three intraarticular PRP injections or 40 mgr methylprednisolone acetate. After exclusion of allocated subjects over the study course, they obtained more clinical improvement in PRP groups (23 knees) compared to the corticosteroid group (16 knees). Corticosteroid provided pain relief only for 2 months. KOOS subscales were improved in both groups but corticosteroid group gained less clinical benefit compared to the PRP group for each time periods. Only KOOS sporting ability was similar between the two groups, consistent with the present study. The similarity in KOOS sporting ability could be explained by decreased mobilization ability and increased age of the entire study group. Güvendi et al. [9] reported on 50 patients having grade 3 knee osteoarthritis with a mean age of 61 years, which were randomly assigned to three groups (single injection PRP, three injection PRP, betamethasone treatment). At the 6th month after injection, WOMAC scores and VAS scores were significantly improved in PRP groups compared to corticosteroid group. Although they did not find any significant clinical difference between single and repeated PRP injections, they outlined the need for prospective studies comparing single and repeated PRP injections.

Naderi Nabi et al. [8] compared the effect of triamcinolone and PRP on 77 patients with grade 2-3 osteoarthritis between the ages of 30-75 years. They observed improvement over time for

each group. Compared to corticosteroid, the PRP group showed less pain intensity and more improvement in PRP groups in terms of KOOS subscales.

Finally, Camurcu et al. [15] studied the use of combined intra-articular single dose methylprednisolone/PRP injection for grade 2-3 osteoarthritis. One hundred fifteen patients were randomized to three injection groups as follows: methylprednisolone/PRP, single-dose PRP, single-dose corticosteroid. PRP and steroid combination yields better pain relief and improved WOMAC scores at 1st and 3rd months; however this difference did not reach statistical significance at 6th and 12th months after injection compared to only PRP injection. Clinical superiority of combined injection over the single dose steroid injection lasts only up to 6 months. This can be explained by the short-term effect of methylprednisolone and single-dose PRP injections contrary to the current study. Based on these studies, higher reduction of pain and clinical improvement in the combined treatment refers also to early pain reduction observed in patients receiving intraarticular PRP injections alone. These results have been also verified by the present study.

Intra-articular local anesthetics were not used in this study, since controversy exists over the chondrotoxicity of intra-articular local anesthetics and this would interfere with the net clinical effect of PRP and steroid. Considering the short-term effect of corticosteroids, it could be reasonable to obtain similar results for each group injected with PRP. Improved clinical results in favour of PRP/steroid combination could be attributed to the fact that corticosteroids could prolong the effect of leucocyte-rich PRP with their anti-inflammatory effect.

When reviewing the literature, it was evident that there was inconsistency in terms of PRP preparation methods, which challenges the comparison of various studies with the present one. However, we obtained PRP with an approximately 3.3-fold platelet increase above baseline. The platelet counts found in our PRP preparation were comparable to studies using PRP and steroid injection reported by Forogh et al. (x4 more than baseline) [16], Jubert et al. (median platelet value of $990 \times 10^6 /\mu\text{L}$) [5], Güvendi et al. (x 3.5 more than baseline) [9]. The other two articles of Camurcu [15] and Naderi Nabi [8] did not provide data about PRP counts after preparation. Additionally, there are many forms of corticosteroids. Intra-articular triamcinolone was preferred due to suitability for diabetic patients and increased efficacy to other corticosteroids as shown by two previous studies [18, 19]. Additionally, although the preparation process prolongs, storage in cold conditions was not preferred for repeated injections, since this has been demonstrated to affect platelet's function [20]. Besides this, because of technical conditions, an open system could be used, which necessitates using prepared PRP in 4-6 hours.

The strength of this study is the homogeneity of the sample. Only patients with advanced osteoarthritis (grade 4 osteoarthritis) with enough symptoms to receive joint replacement were included. The main limitation of this study was that it was retrospectively designed. As a result, the control group receiving intra-articular saline injection was not available, as this would be unethical to leave these patients untreated, which have severe pain with late-stage osteoarthritis. Because no leukocyte filter was used, leukocyte-contaminated PRP is

inevitable. Presumably, possible catabolic effects of PRP due to increased leukocyte count may be mitigated by simultaneous intraarticular use of corticosteroids, which have been shown to inhibit leukocyte migration. This could also decrease costs to obtain high platelet counts with lower white blood cells.

Conclusion

The intraarticular application of PRP and steroid combination demonstrated pain relief for advanced osteoarthritis in short-medium term. Clinical effect of PRP and steroid combination could allow to increase adherence to physical rehabilitation and delay the need for total knee arthroplasty.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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