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Multiple injections of PRP/steroid combination result in better clinical outcomes in advanced osteoarthritis: A prospective randomized study

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Abstract: The impact of PRP/steroid combination in advanced osteoarthritis is unclear. Multiple intraarticular injections are thought to sustain better clinical scores. The objective of this prospective study is to evaluate the effect after repeated injections of corticosteroid (CS) and platelet-rich plasma (PRP) treatment compared to single dose PRP/steroid injection in patients affected by advanced osteoarthritis. A total of 98 patients affected by clinically and radiographically documented with grade 3-4 gonarthrosis according to Kellgren- Lawrence classification were included. The patients were randomized into 2 study groups. Forty-nine patients (Group 1) received three intra-articular injections of PRP (5mL) and steroid (1 cc-5 mgr triamcinolone). Forty-nine patients (Group 2) received one intra-articular injection of PRP/steroid (5 mL). In multiple injection group, an unblinded physician performed the injection once a week for three 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 2 and 6 months after the first injection. The combination of intra-articular PRP with steroids resulted in a significantly superior clinical outcome. This study demonstrated that multiple intraarticular injections of PRP/steroid combination are more effective in advanced osteoarthritis when compared to single injection.

Keywords: Platelet Rich Plasma; Corticosteroid; Intraarticular Injection; Advanced Arthritis.

1. Introduction

Osteoarthritis (OA) is a degenerative disorder that leads to loss of function and increased pain. It also causes work loss and increased dependency. This condition affects 38% to 47% of the population aged older than 60 years (1). Many factors are thought to play in its pathogenesis. These can be summarized as age, gender, obesity, genetic predisposition, and activity level. The treatment options can be classified into nonoperative

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and operative treatment. Operative treatment includes high tibial osteotomy, unicondylar prosthesis, and total knee arthroplasty (2). In nonoperative treatment, non-steroidal anti-inflammatory drugs (NSAIDs), analgesic drugs, and physical rehabilitation is started. Second-line treatment are intraarticular therapies (3).

Intraarticular injections maintain their role for nearly half a century in the treatment of osteoarthritis. Its first use begins with corticosteroid injections (4). Thanks to advances in injection therapies, hyaluronic acids, platelet-rich plasma (PRP), and stem cell-based therapies have been recently performed. Although approved by Food and Drug Administration, AAOS does not recommend its use of these therapies. However, recent articles suggested the positive factors of intraarticular injections (5). One recent meta-analysis indicated the superiority of PRP over steroid and hyaluronic acids (6). These therapies have different characteristics regarding dose and preparation method, the number of injections, the content of active agent (i.e., platelet and white blood cell content). Available studies report different clinical efficieny and preparation formulas. Therefore, it is difficult to compare these results (7, 8).

It is plausible to consider that the improvement in pain relief is less as the grade of arthritis increases. In our practice, we observed that some patients are reluctant to undergo surgery due to increased risk of arthroplasty and other alternative surgeries. Corticosteroids have been demonstrated to detrimental to cartilage tissue but this would be not important in end-stage arthritis with extensive cartilage loss (9, 10). Corticosteroids decrease pain in short-term and is costeffective. PRP injection provides clinical improvement up to one year, but its clinical effect in advanced osteoarthritis is lacking (11).

The pain relief obtained after multiple injections of hyaluronic acid or PRP injections have been shown (12, 13). However, it needs further investigation (14). It can be assumed that the simultaneous use of longlasting PRP and steroids providing shortterm intense pain relief, this combination can be palliative in advanced arthritis. Also, it is unknown whether multiple PRP steroid combinations result in improved clinical outcomes in patients with advanced osteoarthritis. This study aims to compare multiple versus single PRP-steroid combination concerning clinical outcomes in advanced knee osteoarthritis.

2. Material and Methods

Research and Publication Ethics were followed at all stages of the study. The study is in compliance with the Helsinki Declaration. Ethics committee approval was received from the ethics committee of Ataturk University Medical Studies Department Head on 04.10.2018 at the 6th meeting with regards to the document written on 04.10.2018 with number 25. Informed consent was obtained from every participant. A priori power analysis indicated that a study population of 98 patients was planned with an alfa level 0.05 and beta level 0.2. The patients were randomized by opening a sealed envelope. The envelopes were prepared by a health professional blinded to the study. 98 patients with advanced arthrosis (grade 3-4 osteoarthritis) were randomized to receive either three dose PRP/steroid injection or a single PRP/steroid injections. Patients were informed about the study. Randomization was performed by opening a sealed envelope.

This double-blind prospective randomized study was conducted between October 2018 and March 2021. Radiographs of the affected knees were evaluated by a blinded physician with ten-year experience in orthopedic practice. 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 3-4), intraarticular injection of unilateral knee, age >65 years, having BMI >30 (morbid obesity), resistant pain unresponsive to NSAIDs more than 1 year, normal coagulation profile and whole blood count, no history of surgery on bilateral knees, history of septic arthritis, local superficial lesion and infection on the knee, presence of complete outcome and demographic data. Exclusion criteria included NSAID use within last 30 days prior to injection, previous intraarticular 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.

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. One patient for each group had local superficial lesion. Therefore, they are excluded from the study. First group received three PRP/steroid injections. Group 2 received single PRP/steroid injection.

Demographic data such as gender, age, BMI, and follow-up were collected. 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). 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 Group 1. Group 2 received only one injection. In both groups, 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. Possible side effects like mild swelling and pain were recorded within 48 hours after drug administration. Physical activity was prohibited in this time period.

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. The double spinning method was applied as described by Mazzocca (15). 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. 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 ten 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 140.3±45.4x103/μL and 550.8±287.9x103/μL, respectively. The mean white blood counts in the peripheral whole blood and PRP were 5.1±1.4x103/μL and 9.76±2.8x103/μL, respectively.

2.1. Statistical Analysis

Analyses were conducted using SPSS Statistics 21.0 (IBM Corp, Armonk, NY). Data normality was checked using the Shapiro-Wilkins test. Categorical and continuous variables were given as frequencies, mean and standard deviation, respectively. The Chi-square test was used to compare categoric variables (gender, paracetamol use). An independent t-test was used to compare two treatment groups based on continuous data (BMI, age) and comparison of two treatment arms based on outcome scores. Temporal changes in the groups' outcome scores (KOOS, VAS) were evaluated using a general linear model for repeated measures test. Statistical significance was set as $p<0.05$. T-test was used to compare quantitative variables between groups.

3. Results

Age and gender were similar in both groups. (p>0,05). VAS scores were different in both groups at each time point. Decrease in VAS scores was significantly more in multiple injection group. (Table 2) KOOS-Pain, KOOS-Symptom, KOOS-Sport Activities, and KOOS-Activities of Daily Living subscales demonstrated a significant increase in multiple injection group at each time point. KOOS QoL scores were similar at each time point in both groups. (p>0,05) (Table 3-7).

Table 1: Demographic Characteristics in two groups.

	Group		p
	multiple injection (PRP/steroid)	single injection (PRP/steroid)	
Age	68.12±7.34	67.78 ±7.62	.819
Body mass index	32.04±1.59	31.43±1.29	.039*
Gender (male/female)	15/22 (%30.6/44.9)	34/27 (%69.4/55.1)	.211

* indicates p<0.05.

Table 2: Comparison of VAS scores in two groups.

	Group		p
	multiple injection (PRP/steroid)	single injection (PRP/steroid)	
VAS Baseline	7,47±1,12	8,59±1,1	.000*
VAS 2-months	3,24±1,13	4,63±1,51	.000*
VAS 6- months	5,08±1,54	6,73±1,47	.000*

* indicates p<0.05.

Table 3: Comparison of KOOS-pain scores in two groups.

	Group		p
	multiple injection (PRP/steroid)	single injection (PRP/steroid)	
KOOS Pain Baseline	7.47±1.12	24.18±5.89	.328
KOOS Pain 2 months	41±10.02	28.61±8.95	.000*
KOOS6 Pain 6 months	43.69±8.79	33.14±7.21	.000*

* indicates p<0.05.

Table 4: Comparison of KOOS- symptom scores in two groups.

	Group		p
	multiple injection (PRP/steroid)	single injection (PRP/steroid)	
KOOS Symptom Baseline	47.63±6.42	40.76±6.77	.000*
KOOS Symptom 2 months	52.53±6.59	45.86±6.17	.000*
KOOS Symptom 6 months	61.63±7.9	52.31±8.13	.000*

* indicates p<0.05.

Table 5: Comparison of KOOS-Activities of Daily Living subscores in two groups.

	Grup		p
	multiple injection (PRP/steroid)	single injection (PRP/steroid)	
KOOS ADL Baseline	23.69±4.66	23.57±5.3	.904
KOOS ADL 2 months	38.49±8.52	29.78±7.91	.000*
KOOS ADL 6 months	47.45±7.3	38.65±7.31	.000*

* indicates p<0.05.

Table 6: Comparison of KOOS- Sport Activities subscores in two groups.

	Grup		p
	multiple injection (PRP/steroid)	single injection (PRP/steroid)	
KOOS SA Baseline	6.61±2.31	8.06±1.75	.001*
KOOS SA Baseline 2 months	13.29±3.89	12.67±2.71	.369
KOOS SA Baseline 6 months	17.92±4.15	16.22±3.06	.024*

* indicates p<0.05.

Table 7: Comparison of KOOS- Quality of Life in two groups.

	Grup		p
	PRP Stereoid 3lü enjeksiyon	PRP Steroid tek enjeksiyon	
KOOS QoL Baseline	8.2±2.71	9.43±2.18	.015*
KOOS QoL 2 months	19.61±5.44	18.9±4.43	.478
KOOS QoL 6 months	25.04±5.42	24.29±4.02	.435

* indicates p<0.05.

4. Discussion

The most important finding of this study was that multiple injection of PRP and steroid combination gives better KOOS scores and pain relief at 6 months in advanced osteoarthritis (p<0.05).

There are many studies which demonstrated the beneficial effects of PRP. A review concluded that multiple PRP injections decreases pain at 6 months in patienst with mild to moderate knee osteoarthritis (16). Patel et al showed that PRP injection gives better WOMAC scores at 6 months after injection. To note, he didn't find any difference between single and double PRP injections (17). Yaradilmis found better results with the use LR-PRP over hyaluronic acid at 12 months follow-up (18). In a network meta-analysis, Migliorini found that PRP injections are superior relative to steroids, hyaluronic acid and placebo at 3, 6, and 12 months after injection. There was no significant difference between corticosteroids, hyaluronic acid and placebo (6). Güvendi compared the effect of corticosteroid and PRP in grade 3 osteoarthritis. Both agents are effective, but the patients had more prolonged pain relief after PRP injections (19).

In a meta-analysis, Concoff suggested clinical improvement after 2-4 injections of hyaluronic acid compared to single injection (20). Smith pooled data regarding intra-articular corticosteroid and hyaluronic

acid combination. Based on 8 trials, he concluded that combination injections reduces pain to hyaluronic acid alone (21).

In mild to moderate osteoarthritis, Camurcu et al suggested that methlyprednisolone one week before to PRP injection resulted in significantly better clinical outcomes at 6 months but no significant difference at 12 months between combined injection, PRP and methlyprednisolone alone compared to PRP and MP injections alone in patients who had mild to moderate knee OA (22). In a prospective randomized study, Simental-Mendía found better VAS scores in triple PRP injection group compared to single injections at 12 months of follow-up (23). Kavadar et al randomized 102 patients with grade 3 arthritis according to number of PRP injections. Clinical improvement in VAS, WOMAC, Timed Up and Go Tests was noted in both groups, with greatest improvement in triple injection group (24). In a prospective study, Gormeli suggested the benefit of multiple PRP injections in mild to moderate arthritis over single PRP and hyaluronic acid in mild arthrits. But, he didn't observe any improvement in advanced arthritis (25). Munde et al found that three PRP injections with grade 3 osteoarthritis provided more pain relief compared to single and double injections (26). Rai et al investigated the use of combined injection including HA along with PRP and corticosteroid). In younger patients with mild-to-moderate osteoarthritis, improved function, pain relief, and quality of life are observed (27).

All these studies demonstrated the potential benefit of PRP and steroid injections. In the present study, improved VAS and KOOS scores after combined injection in advanced osteoarthritis are never evaluated before. Our results are in line with previous studies supporting the effect of multiple injections. Advanced arthritis is an endstage with extensive cartilage damage. The inflammatory cascade can be transiently blocked by simultaneous PRP and steroid injection. We didnt evaluate the need for arthroplasty and need for NSAID use in both groups. But, it seems that the decrease in VAS scores and improved KOOS scores are indicative of synergistic effect of PRP and steroid treatment.

5. Conclusions

In conclusion, our results demonstrated that multiple intraarticuler PRP and steroid injections result in clinical improvement compared to single injection. This injection regiment can be an alternative for patients unwilling to surgery or have high risk for anesthesia.

Limitations of the Study

Limitations include lack of comparison of different PRP preparation methods and evaluation of the need for arthroplasty at the end of the treatment.

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Conflict of Interests
No potential conflict of interest relevant to this article was reported.

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Author Contributions
Constructing the idea or hypothesis for research; CT, EO, MSA, OSY. Planning the design of the work; CT, EO, MSA, OSY. Execution of the experiments, patient follow-up; CT, EO, MSA, OSY. Analysis and interpretation of data; CT, EO, MSA, OSY. Providing financial support, tools and instruments; CT, EO, MSA, OSY. Biological materials, reagents and referred patients; CT, EO, MSA, OSY. Literature Review; CT, EO, MSA, OSY. Critical Review; CT, EO, MSA, OSY. Final approval of the version to be published; CT, EO, MSA, OSY.

Ethical Approval
Ethics committee approval was received from the ethics committee of Ataturk University Medical Studies Department Head on 04.10.2018 at the 6th meeting with regards to the document written on 04.10.2018 with number 25.

Data sharing statement
None

Consent to participate
Informed consent was obtained from the patients

Informed Consent
The study complies with the Declaration of Helsinki. Consent of all patients was obtained before the article.

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