The Short-term Effect of Consecutive Platelet-rich Plasma Injections on Chronic Pain in Knee Osteoarthritis

Kronik Ağrılı Diz Osteoartritinde Ardışık Plateletten Zengin Plazma Enjeksiyonunun Kısa Dönem Etkileri

 Ülkü DÖNMEZ

İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İzmir, Turkey

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ABSTRACT

Objective: Osteoarthritis (OA) is a joint disease that occurs because of various reasons that cause the imbalance between destruction and repair in the joint cartilage and subchondral bone. The purpose of platelet-rich plasma (PRP) in knee OA is to increase cartilage regeneration owing to the growth factors it contains. This study measured the short-term efficacy of consecutive PRP injections in patients with OA of the knee.

Methods: Patients with Kellgren-Lawrence (KL) stage 2-4 knee OA were included in the study. Three sessions of PRP injections at 2-week intervals were applied to 78 knees of 55 patients. The visual analog scale was used on day 0, week 4 and week 16 to assess pain. Additionally, the functional status was measured by Western Ontario and McMaster Universities OA index which contains pain, stiffness and disability sub-scores.

Results: Of the 55 patients, 45 were female. The mean age was 59.4±9.4 years. A total of 22 patients had bilateral knee involvement, and 51 of the 78 knee joints were classified as KL grade 3-4 OA and the other 27 knee joints were classified as KL grade 2.

Conclusion: It was shown that PRP injection was effective on pain and limitation of movement in knee OA for 16 weeks. Also, it has been noted that early injections provide a more significant reduction in pain in knee OA.

Keywords: Chronic pain, knee osteoarthritis, platelet-rich plasma

ÖZ

Amaç: Osteoartrit (OA), eklem kıkırdağı ve subkondral kemikte yıkım ve onarım arasındaki dengesizliğe neden olan çeşitli nedenlerle ortaya çıkan bir eklem hastalığıdır. Diz OA'sında trombositten zengin plazmanın (PRP) amacı, içerdiği büyüme faktörleri sayesinde kıkırdak rejenerasyonunu artırmaktır. Bu çalışma, diz OA'sı olan hastalarda ardışık PRP enjeksiyonlarının kısa vadeli etkinliğini ölçmüştür.

Yöntem: Kellgren-Lawrence (KL) evre 2-4 diz OA'sı olan hastalar çalışmaya alındı. Elli beş hastanın toplam 78 dizine 2 hafta ara ile 3 seans PRP enjeksiyonu yapıldı. Ağrıyı değerlendirmek için 0. gün, 4. hafta ve 16. haftada görsel analog skala kullanıldı. Ayrıca ağrı, tutukluk ve engellik alt skorlarını içeren Western Ontario ve McMaster Universities OA indeksi kullanılarak fonksiyonel durum ölçüldü.

Bulgular: Elli beş hastanın 45'i kadındı. Ortalama yaş 59,4±9,4 yıl idi. Toplam 22 hastada bilateral diz tutulumu vardı ve 78 diz ekleminin 51'i KL derece 3-4 OA, diğer 27 diz eklemi KL derece 2 olarak sınıflandırıldı.

Sonuç: Diz OA'sında takip eden 16 hafta boyunca, yapılan PRP enjeksiyonunun ağrı ve hareket kısıtlılığı üzerine etkili olduğu gösterildi. Ayrıca diz OA'sında erken enjeksiyonların ağrıda daha belirgin bir azalma sağladığı kaydedilmiştir.

Anahtar Kelimeler: Kronik ağrı, diz osteoartriti, plateletten zengin plazma

Corresponding Author/ Sorumlu Yazar:

Ülkü DÖNMEZ MD,

İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İzmir, Turkey

Phone: +90 535 644 46 58

 drulkudonmez@hotmail.com

ORCID: 0000-0002-0007-1517

INTRODUCTION

Osteoarthritis (OA) is a multifactorial disease characterized by degenerating the joint cartilage with an unknown etiology. Also, it is the most common joint disease in the world and has gained importance especially with the increase in the elderly population.[1] Although OA can damage any joint, the disorder most commonly affects joints in the hands, knees, hips and spine. OA symptoms can usually be managed, although the damage to joints can't be reversed. Staying active, maintaining a healthy weight and receiving certain treatments might slow the progression of the disease and help improve pain and joint function.[1] Conservative methods (physical therapy practices, topical or oral non-steroidal anti-inflammatory drugs and intraarticular injections) are applied primarily for treating the disease and give beneficial results in the early stage.[2-6] New treatment modalities are being emphasized as the side effects of these non-surgical treatment methods may be avoided. Therefore, studies have focused on the effect of cytokines on cartilage degeneration and repair.[2-9]

Platelet-rich plasma (PRP) is defined as the volume of plasma with a platelet concentration higher than the average in peripheral blood. Many basic, preclinical and even clinical case studies and trials report PRP's ability to improve musculoskeletal conditions, including OA.[2-10] PRP injection is often preferred for treating knee OA because it is safe and effective.[8-10]

Anti-inflammatory effect of PRP occurs through the release of many cytokines.[10] It provides cartilage regeneration by affecting the stimulation of chondrocyte differentiation and proliferation.[11-13] Studies recently have emphasized that PRP has an important place for treating OA due to its regenerative and anti-inflammatory effects.[14-17]

From this perspective, firstly we showed the effect of consecutive PRP injections on pain and functionality in patients with chronic knee pain. Secondly, we also evaluated the results of the effects of the injections at the following 16th week.

Thirdly, we also compared whether the PRP injection applied was different between early and advanced OA.

METHODS

Patients who were diagnosed with OA according to the American College of Rheumatology criteria, who had knee pain for at least 3 months and who were admitted to our hospital's outpatient clinics were included in the study.[18] And, the age range of these volunteers, whose knee radiographs were compatible with OA Kellgren-Lawrence (KL) grade 2-4.[19] Patients who applied to our hospital between December 2019-October 2020 were included in the study. Initially sixty patients with chronic knee pain were assessed in our study. Only 5 patients who did not come to the third control were excluded from the study. As a result, the PRP injection was applied to 55 patients (78 knees) at the end of the study. Although the number and frequency of PRP injections on OA are still under discussion, we performed a total of three intraarticular PRP injections with two weeks intervals to 55 patients.[8,10,17] Ethics committee approval was received from İzmir Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee (date: 24.02.2021, protocol no: 2-10).

The exclusion and inclusion criteria are provided in Table 1. Our youngest patient was 30 years old and he had KL stage 2 OA due to overweight without any additional disease. Moreover, the reason for planning the PRP injection in patients with advanced stage and age was; they did not benefit from the medical treatment they used and they did not want to have a prosthesis operation.

Table 1. Inclusion and exclusion criteria
Inclusion criteria - Age between 30 and 80 years - OA Kellgren-Lawrence grade 2-4 - Pain that was present for more than 3 months - Patients who completed all injections were controlled
Exclusion criteria - Active infection, inflammation or a cancer diagnosis - A history of trauma to the affected knee in the past year - Critical systemic disorders (rheumatoid arthritis, coagulopathies, severe cardiovascular/neurological diseases or immunodeficiencies) - Hemoglobin values lower than 11 g/dL or platelet counts lower than 150.000/mL - Knee instability - Pregnancy and lactation - Recent intra-articular injections in the past 6 months - Patients who did not complete all controls
OA: Osteoarthritis

The medical treatment (oral analgesics, myorelaxans) taken by these patients throughout the study continued without changing. It was also noted that the patients included in the study did not receive additional injection treatment in their knees during the study period. All patients were informed about the study and a signed consent form was obtained.

Interventions

Approximately 10-mL blood was drawn from patients for each injection into vials containing sodium citrate. A double centrifugation process was carried out, first at 3200 rpm for 10 min, then the buffy coat and upper plasma layers were re-centrifuged for another 5 min at 3200 rpm. By doing so, approximately 4 mL of leukocyte-poor PRP was obtained. The prepared PRPs were injected into the joint within twenty minutes. Injections were performed while the patients were lying down with their knees at approximately 70-80 degrees of flexion. The injections were applied to the knee joint space anterolaterally under aseptic conditions. Needle would be readjusted if too much resistance or pain was encountered. Patients were recommended to apply cold packs to the injection area for 20 min during the first 3 days after the procedure. They were also advised not to engage in strenuous activities on the first day.

Outcome Measures

Recorded age, gender, physical examination findings, duration of pain, medications, comorbid diseases, surgical history and KL classification of all patients were collected. As a result, 3 groups, grades 2, 3, and 4 were evaluated. Data analysis was also performed according to these groups. Patients' pain was assessed by an independent researcher on day 0 (before first injection), week 4 (after third injection) and week 16 using visual analog scale (VAS). We used the 10-centimeter VAS, the most widely used in the literature, for pain assessment.[20] VAS assessment was done with the help of a scale of "0" to "10," equidistantly marked on a 10-cm line with 0, 5, and 10 cm marks corresponding to no pain, moderate pain and unbearable pain, respectively. The Western Ontario and McMaster Universities OA index (WOMAC) is a scale that evaluates the activities of daily living in patients with knee OA.[21] It includes 24 items for evaluating pain, assessing stiffness and difficulty in some daily living activities. The questions were scored on a scale of 0-4, which corresponds to: none (0), mild (1), moderate (2), severe (3), and extreme (4). The sum of the scores for all three subscales gives a total WOMAC score. The scores from 0-8 for stiffness, 0-20 for pain and 0-68 for physical function are recorded. A high WOMAC score indicates that patients are adversely affected. In the follow-up controls after PRP injections, it was questioned whether the patient had any adverse effects (pain, swelling etc.).

Statistical Analyses

All statistical analyses were performed using Statistical Package for the Social Sciences 27.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics). A power analysis was carried out to determine the minimum required sample size. Sample size was calculated as 45 with a significance value of 0.5, medium effect size and 95% power for our primary outcome, VAS. The normality of the data was assessed using the Mardia (Dornik and Hansen omnibus) test. While Jonckheere-Terpstra test was used to compare more than two groups of quantitative data and Dunn's test was used for Post-hoc analysis. Friedman's Two-Way test (Monte Carlo) was used to compare dependent quantitative variables with more than two repetitive measurements, while the Stepwise step-down comparison test was used for Post-hoc analysis. Quantitative variables were expressed as mean (standard deviation), median (minimum/maximum) and median (percentile 25/percentile 75), while categorical variables are shown as n (%). For all analyses, a value of $p\ 0.05$ was considered to indicate statistical significance.

RESULTS

Initially sixty patients with chronic knee pain were assessed in our study. Five patients who did not come to the third control were excluded from the study. In this study, 55 patients (78 knees) underwent 3 sessions of PRP injection. No side effects related to the injection were observed in any of our patients.

The mean age of 55 patients, of which 45 were female was 59.4±9.4/years. Fifty-one of the 78 knee joints were observed to have KL grade 3-4 OA (Table 2). In the 78 knee joints of 55 patients, mean VAS scores on day 0 and at 4, 16 weeks were 7, 5 and 4, respectively (Table 3). In patients

Table 2. Clinical and demographic characteristics of the subjects	
Total number of patents (n)	55
Gender Male, n (%) Female, n (%)	10 (18.2) 45 (81.8)
Age, mean±SD	59.4±9.4
Injection side n (%) Right Left	38 (48.7) 40 (51.3)
Injected total number of knee joints, n	78
Kellgren-Lawrence grade Grade 2, n (%) Grade 3, n (%) Grade 4, n (%)	27 (34.6) 35 (44.9) 16 (20.5)
SD: Standard deviation, n: Number of patients	

with all KL grades, there was a meaningful decrease in the VAS score at the fourth and 16th week compared to the baseline. But when the scores between the 4th and the 16th weeks were compared, no significant difference was found (p>0.05). The variation in the VAS score between different stages of KL is shown in Table 4. The improvement in pain response of patients with early-stage knee OA was more significant than in other stages. Changes in the VAS score are shown in Figure 1.

For the whole of the 55 patients, the WOMAC scores (median) on day 0 and at 4,16 weeks were 63.54, 45.83 and 38.54 (Table 3). In all KL grade groups, there was a significant decrease in the WOMAC scores at the fourth and 16th week compared to baseline (Table 4). But, it appears that the WOMAC score change between week 4 and 16 is not significant for the KL grade 4 group (Table 4). Compared with grades 3 and 4, the WOMAC score decrease of grade 2 patients was significantly more. When KL grade 3 and 4 patients were compared, it was observed that the change in the WOMAC score was not significantly different (p>0.05). All changes in the WOMAC scores are shown in Figure 2.

DISCUSSION

PRP is often preferred for treating knee OA because it is safe and effective.[22] It has been observed that the results of PRP injections performed at different stages of OA are also different.[9,23-25] However, today it is argued that PRP treatment at the early stages is more effective.[3,8,9] Factors such as decrease in subchondral bone density, weakening of the joint capsule and weakening of the ligaments around the knee could reduce the effectiveness of PRP.[7,26] In our study, PRP performed in early-stage patients with OA compared to advanced stage patients; a positive change was observed in VAS and WOMAC scores. This may be attributed to the lower initial scores in early-stage patients and the fact that these patients are more physically active in daily life compared to advanced stages.

In a systematic review that included 14 randomized controlled trials (RCT), the effect of PRP was compared with other injections (saline, hyaluronic acid, ozone, and corticosteroids).[27] It has been stated that PRP is more effective on pain and functionality and its effect continues after 12 months of treatment. In another study by Taniguchi et al.[28] it was reported that 6-mL PRP injections to the knee joint three times at 1 week intervals, in mild -to- moderate knee OA, decreased VAS pain scores at 6 months follow up.

Similar to literature, in our study, at the 4th week after the injection and at the 16th week of the follow-up; a significant decrease was observed in both VAS and WOMAC scores in all stages. But, it appears that the WOMAC score change between week 4 and 16 is not significant for the KL grade 4 group. This may be attributed to the severe limited of functionality in grade 4 patients and the weakness of the muscles around the knee.

In another systematic review by Meheux et al.[29] the effect of PRP was compared with hyaluronic acid injection. They reported that PRP was more effective in WOMAC and pain scores and showed that this significant effect continued at the 3rd and 12th months after injection. Also, in our study, there was a significant improvement in VAS and WOMAC scores at the end of the 16th week compared to the baseline. But compared to grades 3 and 4, the WOMAC score decrease of grade 2 patients was significantly more. This can be attributed to the fact that early grade patients with OA are younger and more active in daily life than advanced stage patients. It is also a factor that the initial WOMAC scores of patients with early stage OA are lower than those in other stages.

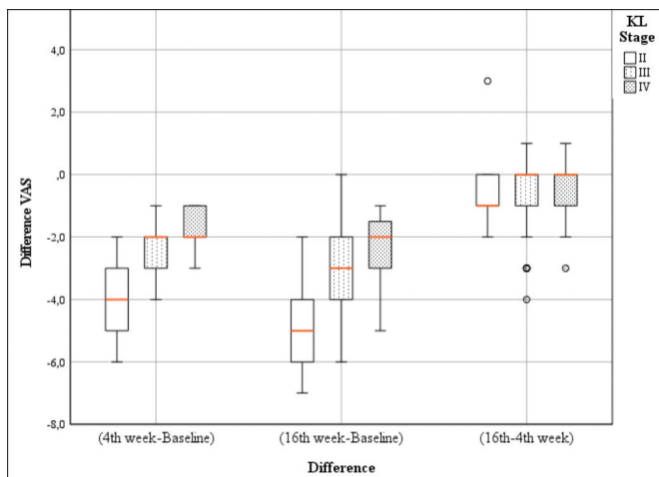| Table 3. VAS and WOMAC scores change from the baseline			
Time		**VAS**	**WOMAC**
		Median (Q1/Q3)	**Median (Q1/Q3)**
0. day	**A**	7 (7/8)	63.54 (56.25/72.91)
4. week	**B**	5 (3/6)	45.83 (30.2/56.25)
16. week	**C**	4 (2/6)	38.54 (16.66/53.12)
p value		**<0.001**	**<0.001**
Pairwise comparisons of time	**A→B**	**<0.001**	**<0.001**
	A→C	**<0.001**	**<0.001**
	B→C	0.039	**<0.001**
Friedman test (Monte Carlo); Post-hoc test: Stepwise step-down comparisons, Q1: Percentile 25, Q3: Percentile 75			

Figure 1. Differences in VAS scores in all the groups

VAS: Visual analog scale, KL: Kellgren-Lawrence

Table 4. Intragroup and intergroup comparisons of VAS and WOMAC scores

			KL grade			p value[j]	Pairwise comparisons of KL grades		
			II	III	IV		II→III	II→IV	III→IV
	Time		Median (Q1/Q3)	Median (Q1/Q3)	Median (Q1/Q3)				
VAS									
	0. day	A	7 (6/7)	7 (7/8)	9 (9/9)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	4. week	B	2 (2/3)	5 (5/6)	7 (6/8)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	16. week	C	1 (1/2)	5 (3/5)	7 (5.5/7)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Difference VAS									
	(B-A)		-4 (-5/-3)	-2 (-3/-2)	-2 (-2/-1)	**<0.001**	**<0.001**	**<0.001**	0.156
	(C-A)		-5 (-6/-4)	-3 (-4/-2)	-2 (-3/-1.5)	**<0.001**	**<0.001**	**<0.001**	0.193
	(C-B)		-1 (-1/0)	0 (-1/0)	0 (-1/0)	0.376	ns.	ns.	ns.
p value[f]			**<0.001**	**<0.001**	**<0.001**				
Pairwise comparison of time points A→C B→C	A→B		**<0.001**	**<0.001**	**<0.001**				
			<0.001	**<0.001**	**<0.001**				
			0.124	0.454	0.999				
WOMAC									
	0. day	A	55.2 (50/59.4)	64.6 (58.3/71.9)	90.6 (80.2/97.4)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	4. week	B	28.1 (21.9/32.3)	49 (41.7/54.2)	71.9 (60.4/83.9)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	16. week	C	10.4 (6.3/25)	44.8 (30.2/50)	70.3 (51/82.3)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Difference WOMAC									
	(B-A)		-28.1 (-32.3/-19.8)	-14.6 (-18.8/-9.4)	-16.6 (-21.9/-7.3)	**<0.001**	**<0.001**	**0.002**	0.999
	(C-A)		-39.6 (-44.8/-33.3)	-21.9 (-35.4/-12.5)	-17.2 (-31.8/-7.3)	**<0.001**	**<0.001**	**0.001**	0.625
	(C-B)		-10.4 (-18.8/-4.2)	-6.3 (-16.7/0)	-2.7 (-9.9/0)	**0.024**	0.264	**0.028**	0.526
p value[f]			**<0.001**	**<0.001**	**<0.001**				
Pairwise comparisons of time A→C B→C	A→B		**<0.001**	**<0.001**	**0.002**				
			<0.001	**<0.001**	**<0.001**				
			0.013	**0.026**	0.335				

[j]Jonckheere-Terpstra test (Monte Carlo); Post-hoc test: Dunn's test, [f] Friedman test (Monte Carlo); Post-hoc test: Stepwise step-down comparisons, Q1: percentile 25, Q3: percentile 75.

ns.: Not significant, VAS: Visual analog scale, KL: Kellgren-Lawrence, WOMAC: The Western Ontario and McMaster Universities OA index

Görmeli et al.[30] showed that especially in the early grade OA subgroups, significantly better clinical results were achieved in subjects treated with three PRP injections, than hyaluronic acid, or placebo. Another study reported that the improvement in pain scores in early-stage OA was found to be more significant.[31] Furthermore, Sucuoğlu and Üstünsoy[32], showed that 3 doses of PRP injections with intervals of three weeks apart, yielded a more significant reduction in pain observed in patients with early-stage knee OA (n=21 knees). Cerza et al.[33] compared 1 week apart four PRP injections with low molecular weight hyaluronic acid injections and observed a more significant improvement in WOMAC scores in the PRP group in the following 24 weeks. Considering these studies, although the dosage and frequency of PRP is still controversial, we performed a total of three intraarticular PRP injections
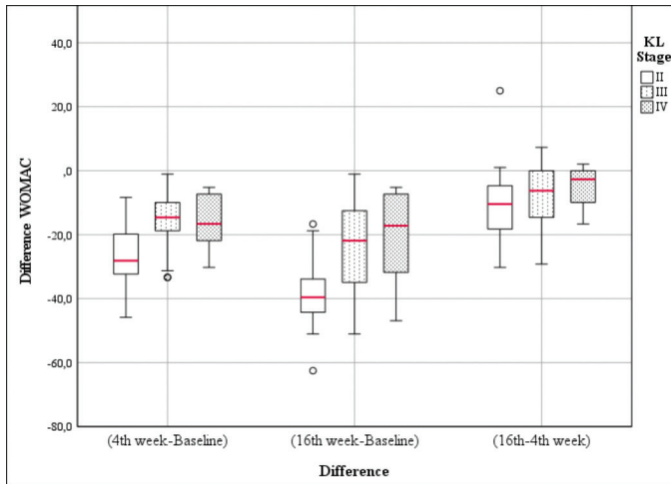
Figure 2. Differences in WOMAC scores in all the groups

WOMAC: The Western Ontario and McMaster Universities OA index, KL: Kellgren-Lawrence

with two weeks intervals to 55 patients, which is the most used in the literature.[29-32]

In our study, the patients with early-stage OA had lower baseline VAS scores. The decrease in VAS scores of early-stage patients was more significant than those of advanced-stage patients ($p<0.001$). Also, the decrease in the WOMAC scores of patients with stage 4 OA was not significantly different between the fourth and 16th weeks. We can attribute this to the advanced stage of the disease and more restrictions in daily life activities compared to other groups.

In another randomized controlled study by Sánchez et al.[34] in which 126 patients with different stages of OA participated, it was observed that the significant effect of PRP injection performed with a one-week interval on the WOMAC score lasted 24 weeks. In our study, although there was a significant decrease in WOMAC scores in patients in all groups compared to the baseline, the decrease in scores in patients who received early-stage injection was found to be more significant.

As a different opinion, in a study by Bennell et al.[35] in patients over 50 years of age with symptomatic knee OA; 3 sessions of weekly PRP and saline injections were compared. At the end of the 12th month, no significant difference was found between the groups in terms of knee pain and mean medial tibial cartilage volume. So they do not support the use of PRP for managing knee OA. We did immeasure the medial tibial cartilage volume in our study, but we found significant changes in VAS scores after PRP injections.

In another study comparing PRP, saline and plasma injection; 62 patients with knee OA were included and

VAS scores at 6, 12, and 24 weeks were compared.[36] There was no significant difference between the 3 groups in terms of knee pain. Therefore, they indicated that PRP and plasma was not superior to placebo for pain and function improvement in knee OA over 24 weeks. The PRP group showed a higher frequency of adverse events (65% versus 24% and 33% for plasma and saline, respectively). They attributed this to the fact that the PRP volume (1.4 mL) they injected was variable and less than in other studies.[28,29,33-35] They also concluded that saline may be effective as an analgesic. Such as the effect of saline; it may be related to the alteration of osmolality in synovial fluid and the possible involvement of sodium in the pathophysiology of OA. In our study, we injected 4 mL in each injection of PRP. And there was a significant decrease in the VAS score at both the 4th and 16th weeks; also no side effects related to the PRP injection were observed.

Study Limitations

Our study has some limitations. Firstly, it was an open-label study, we did not have a control group. Secondly, the effect of PRP on pain was not evaluated after 16 weeks; so our follow-up period was short. Furthermore, we used direct X-rays to evaluate the OA stages in our study. But magnetic resonance imaging is deemed a more sensitive and superior method for grading the level of synovitis and OA.[37]

CONCLUSION

PRP is an established injection option for treating OA. In this study, we have shown that consecutive PRP treatment is effective on pain and functionality in patients with knee OA, in line with the literature. As a secondary result, we have shown that it is more effective in early-stage OA patients than in advanced stage, again similar to the literature. Other studies are needed to evaluate the efficacy and optimum number of PRP treatments for patients with knee OA.

Ethics

Ethics Committee Approval: The study were approved by the İzmir Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research (date: 24.02.2021, protocol no: 2-10).

Informed Consent: All patients were informed about the study and a signed consent form was obtained.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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