Orijinal Araştırma / Original Investigation
Aegean J Med Sci 2020;1:13-19

The Effect of Platelet Rich Plasma Frequency On Early Stage Knee Osteoarthritis

Plateletten Zengin Plazma Uygulama Sıklığının Erken Evre Diz Osteoartriti Üzerine Etkisi

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ÖZET

AMAÇ: Plateletten zengin plazma (PRP) erken evre diz osteoartritinde (OA), özellikle genç hastalarda ağrıyı azaltıp fonksiyonu arttırarak iyi sonuçlar sağlamaktadır. Ancak ideal dozun ne olduğu ve kaç kere yapılması gerektiği, farklı OA evrelerindeki etkinliği tartışılagelen konulardır. Literatürde uygulama sıklığı ile PRP etkinliğini karşılaştıran az sayıda çalışma vardır. Bu çalışmanın amacı, primer diz OA hastalarında PRP uygulama sıklığının etkinliğini kıyaslamaktır.

GEREÇ ve YÖNTEM: Ocak 2016 ile Nisan 2017 arasında kriterlere uygun 174 hasta geriye dönük olarak incelendi. Hastalar uygulama doz sayılarına göre 3 gruba bölündü. Tedaviden önce ve tedaviden sonraki 6. ve 12. aylarda Western Ontario and McMaster University Arthritis Index (WOMAC) skorları, International Knee Documentation Committee (IKDC) skorları ve 100 mm Visual Analogue Scale (100 mm VAS) skorları ölçüldü. Hastaların memnuniyet durumu ve tedaviye bağlı komplikasyonlar 12. ayda değerlendirildi.

BULGULAR: Takip sonunda her 3 grupta tedavi öncesi değerlere göre iyileşme görüldü (p<0,05). Ağrı skorlarında (p<0,001) ve fonksiyonel skorlarda (p<0,001) her 3 grupta da önemli gelişme vardı. Tedavi öncesi ve sonrası değerlendirildiğinde iki ve üç doz uygulana gruplar arasında istatistiksel anlamlı bir fark yoktu (p>0,05). Tek doz grubunun klinik ve fonksiyonel sonuçları diğer iki gruptan kötüydü (p<0,05).

SONUÇ: Tek doz PRP uygulamasının yeterli etkinliği sağlamadığı, bu sebeple tedavide uygun metodun en az 2 doz PRP uygulaması olduğu kanaatindeyiz.

Anahtar Kelimeler: plateletten zengin plazma, PRP, diz, osteoartrit, doz, sıklık

ABSTRACT

OBJECTIVE: Platelet rich plasma (PRP) revealed quite satisfying results for early knee osteoarthritis (OA) especially in younger ages by decreasing pain and improving function and quality of life. However, what becomes the ideal dose and how often it should be performed, the effectiveness of intra-articular PRP injection in different stages of OA are the main topics discussed. There are few studies in the literature comparing the efficacy of PRP with the administration dose. The primary aim of this study was to compare the efficacy of different doses of PRP in primary knee OA and to determine the ideal treatment modality.

MATERIALS AND METHODS: 174 patients who met the criteria were evaluated retrospectively between January 2016 and April 2017. The patients were divided into 3 groups according to doses. Western Ontario and McMaster University Arthritis Index (WOMAC) scores, International Knee Documentation Committee (IKDC) scores and 100 mm Visual Analogue Scale (100 mm VAS) scores were calculated before treatment, 6 months and 12 months after treatment. Satisfaction status and treatment-related complications were examined at 12 months after treatment.

RESULTS: At the end of the follow-up, a significant improvement was observed in all three groups compared to the pre-treatment values (p <0.05). Significant improvement was observed in pain scores (p <0.001) and functional scores (p <0.001) in all three injection groups. No significant difference was observed between twice or thrice injections (p >0.05). The clinical and functional results of one injection was significantly lower than the other groups (p <0.05).

CONCLUSION: We think that single dose therapy is less sufficient in effect, thus the appropriate method of treatment is at least 2 doses of PRP.

Keywords: platelet rich plasma, PRP, knee, osteoarthritis, dose, frequency

INTRODUCTION

Joint cartilage pathologies tend to increase recently due to many factors like higher prevalence of obesity, increased rate of sport activities and increased average-life expectancy [1, 2]. Osteoarthritis (OA) is the most commonly seen joint disorder in all around the world especially over

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Received/Geliş Tarihi: 13 Jan 2020 || **Accepted/Kabul Tarihi:** 25 Feb 2020

60 years of age [3]. In 1986, The American Rheumatism Association made a definition and classified the diagnostic and therapeutic criteria of OA. According to this definition; OA includes heterogeneous group of symptoms and signs caused by joint cartilage disorders, and carries on with periarticular and bony changes [4].

In early stages of OA, joint pain and stiffness are predominant than other symptoms. Therefore, the primary objective in the treatment to be applied is to reduce the joint pain and stiffness, and also to increase the functional capacity. In addition, the long-term treatment plan should aim to reduce joint damage and improve the quality of life [5].

Multiple treatment modalities can be combined simultaneously, according to the risk factors and symptoms. Patient-based treatment usually begins with topical agents and nonsteroidal anti-inflammatory drugs (NSAIDs), but the therapeutic efficacy of these drugs is particularly limited in advanced stage osteoarthritis with well-known side effects especially in elderly ages. Intraarticular steroid injections can provide short-term pain control and functional gain, but its harmful effects are still on debate thus prevents continuous use [6, 7]. There have been several studies on the beneficial effects of intraarticular hyaluronic acid (HA) injections [8-10]. It may increase the range of motion by lubricating the joint surfaces, and provides long-term pain control [11]. All these therapeutic modalities can success in some manners but may not cease natural progress of the disease.

First studies about platelet rich plasma (PRP) revealed quite satisfying results especially in younger ages by decreasing pain and improving function and quality of life. Some studies comparing PRP and HA, concluded in favor of PRP [12-14]. However, what is the ideal dose and how often it should be performed, the effectiveness of intra-articular PRP injection in different stages of OA are the main topics discussed. There are few studies in the literature comparing the efficacy of PRP with the administration dose. The primary aim of this study was to compare the efficacy of different doses of PRP in primary knee OA and to determine the ideal treatment modality.

MATERIAL AND METHOD

In this study, 174 patients who met the criteria were evaluated retrospectively between January 2016 and April 2017. Local ethical committee has approved the study (ethical approval number: 94025189-050.03). All patients signed informed consent forms, and all administrations were performed by the same surgeon (AA). Patients were selected seriatim for administration dose. Treatment inconsistency and lose of follow-up figured out the total patient numbers after applying exclusion criteria.

Inclusion criteria were; intraarticular autologous PRP injected symptomatic early stage (Kellgren Lawrence [KL] stage 1-2) primary knee OA, at least 1-year follow-up, absence of any cognitive disease and systemic disorders such as diabetes. Exclusion criteria were; rheumatic disease, axial deformity (varus/valgus > 5°), hematological diseases (coagulopathy) or therapy with anticoagulants / antiaggregant, severe cardiovascular diseases, immunocompromised patients, and patients with Hb values < 11 g/dl and platelet values < 150,000/mm^3.

KL stages of all patients were determined by radiographic x-ray and KL stage 1 and 2 patients were included in the study. The patients were divided into 3 groups according to doses: PRP1 (single-dose PRP), PRP2 (2-dose PRP) and PRP3 (3-dose PRP). Western Ontario and McMaster University Arthritis Index (WOMAC) scores, International Knee Documentation Committee (IKDC) scores and 100 mm Visual Analogue Scale (100 mm VAS) scores were calculated before treatment, 6 months and 12 months after treatment. Satisfaction status and treatment-related complications were examined at 12 months after treatment.

PRP Preparation Protocol

A 40-mL venous blood sample was taken in aseptic conditions from antecubital region in 6 vacutainer tubes with 3.2% sodium citrate. Samples were gently turned upside down to ensure mixing of the anticoagulant with the blood. One of the tubes was sent to the laboratory for complete blood count. Blood samples were centrifuged for 10 min at 1800 rpm to separate the erythrocyte layer. The upper plasma layer was carefully collected in a new sterile propylene tube while attempting not to remove the leukocyte layer. The plasma from all tubes was centrifuged again for 12 min at 3400 rpm to obtain a two-part plasma, with the upper part consisting of platelet-poor plasma and the lower part consisting of leukocyte-poor, platelet-rich plasma (LP-PRP). The platelet-poor plasma was taken out to

obtain a final volume of 4 ml. This LP-PRP was mixed carefully by absorbing with pipets to resuspend the platelets, and it was then transferred to a new tube. A separate part of the final LP-PRP was sent to the laboratory for platelet count. Before the injection %10 of Ca-chloride was added to the PRP unit to activate platelets.

Injection Procedure and Follow-up

The knee region was prepared with povidone iodine solution application in sterile conditions. Injection was performed with a 22-g needle from the superolateral knee region. After injection, the knee was immobilized for 10 minutes and the patient was observed for 1 hour. Application of ice around the joint and paracetamol was prescribed for pain control. The patients were reevaluated at the 6th and 12th months after the total treatment dose preferred and the side effects were recorded, besides satisfaction status was questioned at the end of 12 months.

Statistical Analysis

All analyzes were performed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) Data was reported as standard deviations (SDs) or frequencies. Normality was confirmed using the Shapiro-Wilk test. The quantitative data was investigated with one-way analysis of variance (ANOVA), and then when the variances were homogeneous the Bonferroni test or when the variances were not homogeneous the Tamhane T2 test were used for comparison. Qualitative data were analyzed using Pearson's Chi-square test. In each group, knee scores at 6-month and 12-month follow-up were compared with repeated one-way ANOVA and then with Bonferroni test and $p < 0.05$ values were considered significant.

RESULTS

64 patients (98 knees) received a single-dose of PRP, 52 patients (78 knees) received two doses of PRP with 1-month interval, and 58 patients (84 knees) received 3 doses of PRP with 1-month intervals. Age, sex, body mass index (BMI), lesion side, and duration of symptoms were analyzed in all 3 groups (Table 1).

Table 1. *Demographic Data*

	PRP1	PRP2	PRP3	Total	P value
Patient/Knee	64/98	52/78	58/84	174/260	0.985
Age					
Mean±SD	60.9±13	57.8±16.1	63±11.6	60.8±13.1	0.226
Distribution	21-83	15-81	31-85	15-85	
Sex(Male/Female)	27/37	30/22	28/30	85/89	0.105
BMI					
Mean	27.2±5.5	25.4±4.2	25.7±4.9	26.4±5.1	0.305
Distribution	16-49.8	20-35.2	17.4-36.7	16.4-49.8	
Lesion Side					
Right/Left	47/51	36/42	38/46	121/139	0.804
Bilateral	34	20	21	75	
Symptom Duration (Months)					
Mean±SD	22.6±18.6	23.8±22.6	19.9±16.3	21.8±18.4	0.882
Distribution	1-120	3-72	3-60	1-120	
Follow-up Time (Months)					
Mean.±SD	14.8±3.2	16.4±4.8	13.6±4.6	14.0±4.6	0.642
Distribution	12-18	12-20	12-18	12-20	
Kellgren Lawrence Stage					
Stage 1	38	30	40	108	0.686
Stage 2	50	48	44	142	0.702

Table 2. *Functional Scores*

	PRP1 (n=89)	PRP2 (n=78)	PRP3 (n=72)	P Value[1]
WOMAC stiffness				
Basal				
Mean ± SD	2.5±0.8	2.6±0.8	2.5±0.8	0.624
Range	(1-5)	(2-4)	(2-4)	
6. months				
Mean ±SD	1.8±0.9 a,b	1.1±0.6	1.2±0.8	<0.05
Range	1-5	0-4	0-4	
P value[2]	<0.05	<0.05	<0.05	
12 months				
Mean.±SD	1.9±0.9 a,b	1.3±0.7	1.4±0.9	<0.05
Range	0-5	0-4	1-4	
P Value[3]	<0.05	<0.05	<0.05	
WOMAC Pain				
Basal				
Mean.±SD	7.1±1.2	7.2±1.3	7.2±.1.1	0.728
Range	5-12	5-9	5-10	
6 months				
Mean.±SD	6.0±1.6 a,b	4.9±1.6	5,1±1.4	<0.05
Range	1-11	3-9	4-12	
P Value[2]	<0.05	<0.05	<0.05	
12 months				
Mean.±SD	6.3±1.8 a,b	5.3±1.8	5.4±1.9	<0.05
Range	2-11	1-9	4-9	
P Value[3]	<0.05	<0.05	<0.05	
WOMAC function				
Basal				
Mean±SD	20.6±2.9	20.7±2.8	21.3±2.8	0.912
Range	16-39	17-28	17-35	
6 months				
Mean.±SD	18.0±1.8 a,b	15.4±2.2	15.2±1.9	<0.05
Range	4-38	4-26	10-30	
P Value[2]	<0.05	<0.05	<0.05	
12 months				
Mean.±SD	19.1±4.6 a,b	16.8±4.2	16.6±3.5	<0.05
Range	6-37	4-25	14-25	
P Value[3]	<0.05	<0.05	<0.05	
WOMAC total				
Basal				
Mean.±SD	30.2±4.2	30.5±4.3	31.0±3.9	0.682
Range	23-55	24-40	24-49	
6 months				
Mean.±SD	25.8±6.7 a,b	21.4±5.8	21.5±5.4	<0.05
Range	6-46	5-52	8-32	
P Value[2]	<0.05	<0.05	<0.05	
12 months				
Mean.±SD	27.3±6.[9] a,b	23.4±5.9	23.4±5.7	<0.05

P value[1]: Comparison of data between groups and among PRP1, PRP2 and PRP3

P value[2]: Comparison of data between groups and among pretreatment and post treatment 6 months

P value[3]: Comparison of data between groups and among pretreatment and post treatment 12 months

a Significantly between groups and among group PRP1 and group PRP2.

b Significantly between groups and among group PRP1 and group PRP3

c Significantly between groups and among group PRP2 and group PRP3

There were 27 male 37 female patients in the PRP1 group and the mean age was 60.9 (30-75) years. Average BMI was calculated 27.2 (19-34.8). In PRP1 group, there were 47 right and 51 left knees while 34 being bilateral. The mean symptom duration was 22.6 months (1-120) and the mean follow-up period was 12.8 months (10-13). According to KL classification, 38 knees were stage 1 and 60 knees were stage 2.

There were 30 male 22 female patients in the PRP2 group and the mean age was 57.8 (28-72). Average BMI was calculated 25.4 (20.4-35.2). In PRP2 group, there were 36 right and 42 left knees while 26 being bilateral. The mean symptom duration was 23.8 months (3-72) and the mean follow-up period was 16.4 months (12-20). According to KL classification, 30 knees were stage 1 and 48 knees were stage 2.

There were 28 male 30 female patients in the PRP3 group and the mean age was 63 (31-73). Average BMI was calculated 25.7 (17.4-36.7). In PRP3 group, there were 38 right and 46 left knees while 26 being bilateral. The mean symptom duration was 19.9 months (3-60) and the mean follow-up period was 13.6 months (12-18). According to KL classification, 40 knees were stage 1 and 44 knees were stage 2.

There was no statistically significant difference between the three groups in terms of patient demographic information (p> 0.05). WOMAC score values before and after treatment are shown in table 2. At the end of 6 and 12 months follow-up, a significant improvement was observed in all three groups compared to the pre-treatment values (p <0.05). Significant improvement was observed in pain scores (p <0.001) and functional scores (p <0.001) in all three injection groups. No significant difference was observed between PRP2 and PRP3 groups before and after the treatment. (p =0,258). The clinical and functional results of PRP2 and PRP3 patients were significantly better than PRP1 group (p <0.05) (Table 2).

IKDC scores were significantly higher in all three groups at 6 months and 12 months after treatment than before treatment. However, there was no difference between the PRP2 and PRP3 groups, but in the PRP1 group, the results of the 6th and 12th months were significantly worse than the other 2 groups (p <0.05) (Figure 1).

100 mm VAS scores were significantly higher in all three groups at 6 months and 12 months after treatment than before treatment. However, there was no difference between the PRP2 and PRP3 groups, but in the PRP1 group, the results of the 6th and 12th months were significantly worse than the other 2 groups (p <0.05) (Figure 2).

Figure 1. *IKDC scores of the groups pre- and post-treatment*

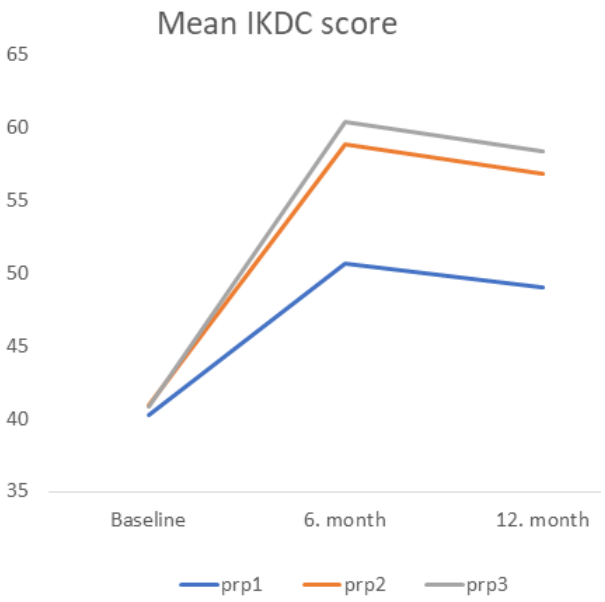
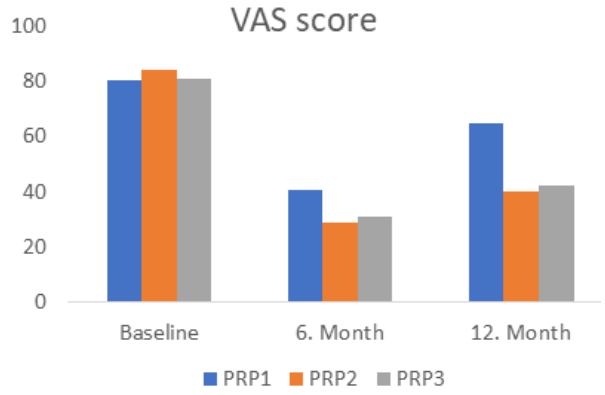


Figure 2. *100mm VAS scores of the groups pre- & post-treatment*



The platelet concentration in peripheral blood and PRP were 237,73 ± 111,23 x10³/ µL and 689,68 ± 178,80 x10³/ µL in the PRP1 group; 245,73 ± 108,38 x 10³/ µL and 708,44 ± 110,80 x10³/ µL in the PRP2 group; 262,73 ± 119,42 x10³ / µL and 692,68 ± 114,80 x10³ / µL in the PRP3 group respectively. There was no statistically significant difference between groups (p =0.462).

The leukocyte concentration in peripheral blood and PRP were 7,25±2,49 x 10³ / µL and 1,68±0,26 x 10³ / µL in the PRP1 group; 7,38±2,58 x10³ / µL and 1,52±0,37 x10³/ µL in the PRP2 group; 7,23±2,24 x10³ / µL and 1,32±0,34 x10³ / µL in the PRP3 group respectively. There was no statistically significant difference between groups (p=0.344).

In terms of patient satisfaction after twelve months, 78.2% of the patients in the PRP1 group were highly satisfied, 14.6% were satisfied and 7.2% were not satisfied with the treatment. 81.4% of the patients in the PRP2 group were highly satisfied, 11.2% were satisfied and 7.4% were not satisfied. 77.9% of the patients in the PRP3 group were highly satisfied, 11.8% were satisfied and 10.3% were not satisfied with the treatment. No statistical difference was observed in patient satisfaction (p=0.268).

In terms of common complications; there was pain, swelling or feeling of burn in 8 knees (8,1%) of PRP1 group, 6 knees (7,6%) of PRP2 group, and 7 knees (8,3%) of PRP3 group. There was no statistically significant difference between groups (p>0.05). All of the patients recovered without any surgical or invasive intervention with rest, elevation and ice compression.

DISCUSSION

Intra-articular PRP injections may provide improvement in knee functions and symptoms for early-stage knee OA patients. What we saw in this study was that administration of multi-dose PRP was better to single-dose in terms of functional and clinical results.

PRP is described as autologous plasma containing higher concentrations of platelets and higher rates of growth factors than peripheral blood [15, 16]. Platelets undertake important tasks for the onset of healing process. They act as a scaffold for clot formation and provide chemotaxis for the collection of appropriate cytokines at the site of injury. Some studies have reported that PRP acts as a stem cell growth initiator and provides chondrocyte differentiation [16]. In a rabbit study with anterior cruciate ligament deficiency model, Saito et al. showed a significant reduction of OA progression in PRP-treated rabbits [17].

Discussions about the appropriate PRP preparation method, dose and frequency of administration have still been ongoing. Two previous studies have demonstrated the efficacy of single-dose PRP in the treatment of early knee osteoarthritis. In 2013, Jang et al. divided the patients into 3 groups according to the KL stage in a prospective

study of 90 knees of 65 patients and administered a single dose of 3 ml intraarticular PRP to each patient [18]. To evaluate the results, they used VAS and IKDC scales at 1, 3, 6, 9, and 12 months. All patients included in the study showed improvement in clinical scores at 6 months, but deteriorated at 12 months, although they were better than before treatment. In 2013, Halpern et al. published a series of 18 cases of 17 patients [19]. Magnetic resonance imaging was performed before and after treatment in 6 ml single dose intra-articular PRP in patients with CL stage 1-2 and VAS and WOMAC scores were calculated at 1,3,6 and 12 months. All patients had significant improvement in pain and function questions at 12 months compared to the pre-treatment level. In 73% of the patients, no radiological change was detected in MRI performed at 1 year. Apart from these two studies, most authors recommend multiple injections. Cerza et al. showed 4-times PRP injection is superior to HA injections [20]; therewithal Spakova et al. reported 3-dose PRP injection is more beneficial than 3-times HA injections [13]. However, these studies did not make a comparison about the frequency of PRP injections. In our study we found that PRP treatment improved results in patients with early stage knee OA independent of dose, and at the end of 12 months good results continued despite some decrease in scores.

Patel et al reported that, single dose was as effective as 2 doses of PRP [21]. Görmeli et al. found no difference between single dose and 3 doses in advanced OA patients, however they found that the clinical outcomes of patients who underwent 3 doses of PRP in patients with early stage OA were significantly better than those with a single dose [22]. In our study, we found that multi-dose of PRP treatment was significantly better than single dose. There have been few studies examined the effectiveness of PRP frequency in the treatment of early-stage knee osteoarthritis in current literature. In a retrospective study similar to ours, Huang et al. reported that 3 doses of PRP treatment were superior to single dose and 2 doses [23].

In our study we have used leukocyte-poor PRP. Although the complaints of knee swelling were found to be higher in three doses compared to the other groups, the results were similar with leukocyte-poor PRP studies in the literature.

We used the same PRP kit for all patients in our study to eliminate bias. The method of preparation, preactivation, and injection; platelet and white blood cell concentration, volume, pre and post injection protocols were the same in all patients. Nevertheless, retrospective nature, short follow-up period and lack of definitive research on all three stages of osteoarthritis are important limitations of this study

CONCLUSION

PRP is an autologous treatment method with low side effects which could be considered in early stages of knee OA. However, we think that single dose therapy is less sufficient in effect, thus multiple doses of PRP may be more effective. Moreover, the need for randomized controlled trials is clear to elucidate this topic.

Yazarlar arasında çıkar çatışması yoktur.

The author declares no conflict of interest.

Finansal Destek: yoktur / Funding: none

doi: https://doi.org/10.33713/egetbd.674135

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