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## The Efficacy of Platelet Rich Plasma and Prolotherapy in Chondromalacia Patella Treatment

### *Kondromalazi Patella Tedavisinde Trombositten Zengin Plazma ve Proloterapinin Etkisi*

Aydan Örsçelik<sup>1</sup>, Serkan Akpancar<sup>2</sup>, Mehmet Murat Seven<sup>3</sup>, Yusuf Erdem<sup>4</sup>, Kenan Koca<sup>5</sup>






<sup>1</sup> Sports Medicine Department, Gülhane Medical Faculty, Health Sciences University, Ankara, Turkey

<sup>2</sup> Orthopedics Surgery Section, Tokat State Hospital, Tokat, Turkey

<sup>3</sup> Sports Medicine Section, Special Command Forces, Ankara, Turkey

<sup>4</sup> Orthopedics Surgery Section, Gülhane Training and Research Hospital, Ankara, Turkey

<sup>5</sup> Orthopedics Surgery Department, Gülhane Medical Faculty, Health Sciences University, Ankara, Turkey

A. Örsçelik   
0000-0002-8610-8869  
S. Akpancar   
0000-0001-6673-1082  
M. M. Seven   
0000-0002-9894-9788  
Y. Erdem   
0000-0002-8685-2356  
K. Koca   
0000-0001-7051-8628

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*Yazışma Adresi /  
Corresponding Author:*  
Aydan Örsçelik  
Sağlık Bilimleri Üniversitesi,  
Gülhane Tıp Fakültesi, Spor  
Hekimliği, Ankara, Turkey

*E-mail:*  
aydanozcan@yahoo.com

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#### ABSTRACT

**Objective:** Chondromalacia patella (CMP) is a frequently seen musculoskeletal disorder. Platelet-rich plasma (PRP) is considerably useful in sports injuries. Prolotherapy (PrT) is a regenerative injection technique used in chronic musculoskeletal disorders. The aim of this study is to compare PRP and PrT therapies in CMP treatment.

**Materials and Methods:** Seventy five patients with CMP symptoms refractory to three months of conservative treatment methods were included in this study. The patients were divided into PRP (n=38) and PrT (n=37) groups. A questionnaire has been applied, VAS scores, Tegner and Lysholm knee scores (TLS) were obtained. They were repeated three, six weeks after the beginning of treatment, and 12 months following the treatment. A standard 12-week exercise program was prescribed to all of the patients.

**Results:** Pain and knee functions improved significantly after a minimum one year of follow-up in both groups (p<0.05). However, PRP was superior to PrT in terms of pain level during exercise, range of motion, crepitus, total number of medications, VAS and TLS (p=0.004, p=0.038, p<0.001, p=0.003, p=0.001 and p=0.026 respectively).

**Conclusions:** PRP and PrT therapies applied with exercise were shown to be effective in CMP treatment; however PRP therapy seems to be more effective than PrT.

**Keywords:** Platelet rich plasma, patellofemoral pain syndrome, prolotherapy

#### ÖZ

**Amaç:** Kondromalazi patella (CMP), sık görülen bir kas-iskelet sistemi hastalığıdır. Trombositten zengin plazmanın (PRP), spor yaralanmalarında önemli ölçüde faydalı olduğu bilinmektedir. Proloterapi (PrT) ise, kronik kas-iskelet sistemi hastalıkları için kullanılan rejeneratif bir enjeksiyon tekniğidir. Bu çalışmanın amacı, CMP tedavisinde PRP ve PrT tedavilerinin etkinliğini karşılaştırmaktır.

**Gereç ve Yöntemler:** Üç ay süren konservatif tedaviye dirençli yetmiş beş CMP hastası çalışmaya alındı. Hastalar randomize olarak PRP veya PrT grupları olarak iki gruba ayrıldı. Hasta sorgulama anketi, VAS, Tegner ve Lysholm diz skorları (TLS) uygulandı. Bunlar tedavinin başlangıcından üç, altı hafta sonra ve tedaviden 12 ay sonra tekrarlandı. Tüm hastalara 12 haftalık standart egzersiz programı verildi.

**Bulgular:** Her iki grubun da ağrı ve diz fonksiyonları bir yıllık izlemiden sonra belirgin olarak düzeldi ( $p < 0.05$ ). Ancak PRP; egzersiz sırasındaki ağrı düzeyi, eklem hareket açıklığı, krepitasyon, toplam ilaç sayısı, VAS, TLS açısından PrT'den üstündü (Sırasıyla  $p = 0.004$ ,  $p = 0.038$ ,  $p < 0.001$ ,  $p = 0.003$ ,  $p = 0.001$  ve  $p = 0.026$ ).

**Sonuç:** Egzersiz ile uygulanan PRP ve PrT tedavilerinin CMP'de etkin olduğu gözlemlendi; bununla birlikte PRP tedavisi PrT'den daha etkin bulundu.

**Anahtar sözcükler:** Trombositten zengin plazma, patellofemoral ağrı sendromu, proloterapi

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## INTRODUCTION

Chondromalacia patella (CMP) is a frequently seen disease of the knee with chronic pain and dysfunction symptoms. The degeneration and thinning of the patellar cartilage is described as CMP. Disruption of cartilage and eventually resultant osteoarthritis could be seen in the progression (1). Conservative therapy is the first option in CMP treatment (2). A considerable ratio of patients may benefit of conservative methods; however, some are resistant to these therapies, and eventually undergo surgery (3). Individualized treatments should be used according to the underlying cause of disease and functional status of the patients (4,5).

Platelet-rich-plasma (PRP) is a plasma component with high platelet concentration (6). It is obtained from autologous blood samples by centrifugation (7). Platelets include various growth factors. These factors stimulate growth and development of the cartilage tissue in osteoarthritis. Thus, PRP treatment is commonly used in knee joint damage. (8-12).

Proloterapy (PrT) is a regenerative injection technique used in chronic musculoskeletal disorders (13-16). PrT can be classified in three groups according to injection location: enthesofascial, myofascial and neurofascial. The most well-known and applied PrT type is enthesofascial/intra-articular PrT; known as the classical type, where (17) irritant solutions are injected into the enthesis of the ligament and/or tendon of the bone, adjacent joint spaces (18), and into the joints (17). The degeneration of these structures often results in chronic musculoskeletal pain and disability, and PrT heals this degeneration at the tissue level (18). Hypertonic dextrose

and sodium morrhuate are the most common used solutions (15,19). Hypertonic dextrose can cause osmotic rupture of cells and induce production of growth factors. Furthermore, a hypertonic environment can lead to the release of DNA-encoding growth factors (20).

CMP was assessed similar to osteoarthritis due to cartilage defects. It has been shown that dextrose PrT is superior to exercise, local anesthetics and corticosteroids in six months follow-up in the treatment of knee osteoarthritis (17). It has also been documented that it provided better improvement in pain reduction, function and stiffness than saline injections and exercise. Similar success has been demonstrated in studies with knee osteoarthritis in which only intraarticular PrT was preferred (17). Treatment modalities are not enough for some patients, and new treatment methods are necessary. Our aim in the present study is to compare PRP and PrT therapies in CMP treatment, as a seldom addressed approach.

## MATERIALS AND METHODS

### Research Design

A prospective double-blind, randomized controlled study was designed. The Ethics Committee of the Gülhane Medical Faculty, Health Sciences University, Ankara, Turkey (E. Kurul-E-15-386/29.01.2015) approved the study protocols. Informed consent was signed by patients enrolled in the study.

### Subjects

Patients with chronic knee pain applied to the orthopedics and sports medicine departments

between January 2015 and July 2016. One hundred twenty four patients were evaluated for eligibility. Forty six of them were excluded for not meeting the inclusion criteria and 3 rejected to participate in the study. Seventy five patients who were aged 21 to 66 years old and diagnosed as chronic CMP were included in the study.

Patients with at least six months of symptoms, persistent to at least three months of conservative therapy, with positive MRI findings and grade II-IV lesions according to Mc Cauley et al. (21) were included in the study. Diagnosis of the patients were clinically confirmed upon physical examination (22,23).

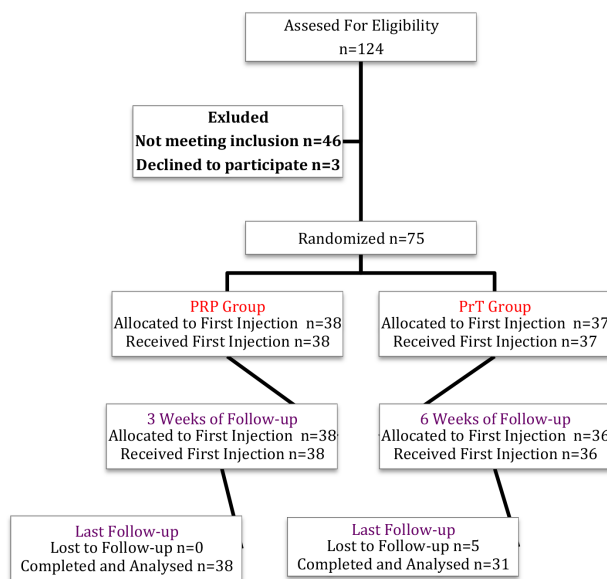
Patients with systemic inflammatory diseases, active/chronic infection or history in the knee area, previous knee operation, corticosteroid injection within previous 12 weeks, bleeding tendency, pregnancy, and condition other than CMP on MRI were excluded from the study.

Seventy five patients met the inclusion criteria. Patients were divided into PRP (n=38) and PrT (n=37) groups using computer-derived random charts. Only one researcher could reach group assignments, the patients and the remaining researchers were not allowed to reach these throughout the study. This researcher was not allowed to assess patient, drew 72 ml of blood from all patients, and prepared 7.0 ml solutions of either PrT or PRP, and covered the solutions using an opaque band. Anyone other than this researcher remained blinded to the injection content. Each group of patients received triple intraarticular injections with three week intervals. A patient from the PrT group refused treatment after the first injection session, and five from the same group were not available at last-follow-up, therefore 69 patients (PrT group: n=31) completed the study (Figure 1).

**Intervention**

Each protocol consisted of three sessions. A 27 G, 1.5” needle was used for delivering an intra-articular 7.0 ml solution in each session. All the injections were performed with USG-guidance,

under aseptic conditions. Solutions were slowly infiltrated from the lateral aspect of the knee next to the patella, while it was mildly subluxated and the knee flexed. After injections, knee range of motion (ROM) exercises in flexion-extension direction were prescribed to patients. All participants were reminded to avoid non-steroidal anti-inflammatory drugs (patients could use 500 mg of acetaminophen up to four times/day if only the pain was unbearable) and to limit overuse of the knee for the first three days during the treatment period.



**Figure 1.** Flowchart of patient selection, treatment application and follow-up.

**Exercise Program**

After the first three days, a standard exercise program consisting of three sessions/wk (30 min/session) was applied to all patients under the supervision of same physiotherapist for 12 weeks. Range of motion and stretching exercises were given for the first 3 weeks. After three weeks, standard isotonic strengthening exercises were added (Table 1). All exercises were performed bilaterally. Patients were also recommended to continue the same exercises after 12 weeks of the rehabilitation program.

**Table 1.** Exercise program

Period	Exercises	Recommendations
<b>First 3 weeks</b>	ROM and stretching exercises; Stretching of iliotibial band, rectus femoris, hip rotators, hamstring, gastrocnemius and soleus muscles.	Daily ROM exercises: 3 sets of 10-20 repetitions Stretching exercises: 3 repetitions of 30 s
<b>After 3 weeks</b>	Continue stretching exercises. Progressive resistance cycling (slow to moderate) Strengthening exercises: knee extensors and flexors, hip abductors and adductors, hip extensors, hip external rotators	Daily Strengthening exercises: 3 sets of 10-20 repetitions
<b>After 6 weeks</b>	Continue stretching exercises Continue strengthening exercises. Continue strengthening with ankle weights; 90° squats, step-up progressions, closed chain hip strengthening	Daily
<b>After 9 weeks</b>	Continue stretching exercises Continue strengthening exercises Static lunge, lateral lunge, progressive single leg strengthening (squats, dead-lifts)	Daily

### PRP and PrT Preparation

The GPS III Platelet Separation System (Biomet Biologics, Warsaw, Indiana) was used for PRP preparation according to system instructions. Venous blood (72 ml) drawn from all the patients was mixed with 8.0 ml of citrate. The 80 ml solution was centrifuged for 15 min at 3200 rpm, and 8.0 ml of PRP solution was obtained. A 7.0 ml portion of PRP was used for intraarticular injection and 1.0 ml was used to calculate platelet concentration. For the PrT intervention, 7.0 ml of 25% dextrose solution without any activating agent was used.

### Assessment and Outcomes

A patient questionnaire designed by Hauser et al. (24) has been applied, VAS, and the Tegner and Lysholm knee scores were used for assessing knee pain and function in the beginning, three and six weeks after the beginning of the treatment, and 12 months after the treatment. Patients were questioned about side effects in all rounds.

**Patient questionnaire:** Each patient's clinical outcomes were evaluated by a 32-item questionnaire (24). The first 12 questions were related with average daily pain level at rest, dur-

ing daily activity, and exercise on a scale of 0-10 (0: no pain, 10: severe pain). Range of motion, level of stiffness and crepitus, walking ability, exercise ability were assessed on the scale by physical examination, set of questions, walking distance or improvement rate. The amount of medications which the patient took was also evaluated in this questionnaire. The recommended dose of 500 mg acetaminophen was considered as 1 medication and half dose of it - 250 mg- as 0.5 medication. According to this calculation, taking none or only one medication per day was evaluated as 10 points on the scale, 1.5-2 medications as 8 points, 2.5-3 medications as 5 points, and 3.5-4 medications as 3 points. Patients who took more than four medications were excluded from the study for not obeying the recommendations and prescriptions.

**Tegner and Lysholm knee score:** Each patient's clinical outcomes were also self-evaluated using a 100-points questionnaire. The questionnaire involved assessment of severity of support, pain, swelling, instability, limp, locking, stair climbing, squatting on a scale. Outcomes were defined as <65 poor, 65-83 fair, 84-90 good, >90 excellent. Turkish translation of this questionnaire was found to be valid and reliable (25).

**VAS score:** The patient’s subjective self-assessment of his/her pain level was scored between 0 and 10 points (0: no pain, 10: severe pain) by using a visual analog scale.

**Statistical analyses**

Statistical analysis was performed with SPSS 22.0 (Statistical Package for Social Science) for Windows. Descriptive statistics were identified as mean ± standard deviation (SD), minimum-maximum, case number (n) and percentage (%). Normal distributions of continuous variables were analyzed with the Shapiro-Wilk test. It was determined that variables were distributed non-normally. For the inter-group comparisons, chi-square test was used for discrete variables. The Mann-Whitney U test was used for continuous variables. The Friedman test was used for intra-group intermittent measurement comparisons. The Mann-Whitney U test with Bonferroni correction was used as post hoc test. Spearman's

rank order correlation test was used for examination of the linear relationship between platelet variables. Values were considered as statistically significant with a p<0.05.

**RESULTS**

Both groups had similar characteristics (Table 2). Despite the randomization of the groups, there were statistically significant differences in pain during exercise, exercise ability, crepitus, total number of medications and VAS between the PRP and PrT groups before the treatments (p=0.014, p=0.001, p=0.042, p=0.003 and p=0.029 respectively). Regarding the improvement from pre- to a year post-treatment, there were statistically significant differences in pain during exercise, crepitus, ROM, total number of medications, VAS and the Tegner and Lysholm knee scores (p=0.004, p<0.001, p=0.038, p=0.003, p=0.001 and p=0.026 respectively) (Figure 2).

**Table 2.** Characteristics of the patients

	<b>PRP group</b>	<b>PrT group</b>	<b>p</b>
<b>N</b>	38	37	
<b>Age (yr)</b>	44.5 ± 10.3	39.0 ± 11.8	> 0.05
<b>Gender</b>	22 males (57.9%) 16 females (42.1%)	20 males (64.5%) 11 females (35.5%)	> 0.05
<b>Duration of symptoms (mo)</b>	17.4 ± 8.2	14.5±7.7	> 0.05
<b>Side (right/left)</b>	20/18	19/12	> 0.05
<b>Follow-up (mo)</b>	17.1 ± 5.4	17.0 ± 3.8	> 0.05
<b>Grade of lesion</b>	Grade II: 15; Grade III: 16; Grade: IV: 7	Grade II: 13; Grade III: 17; Grade: IV: 6	

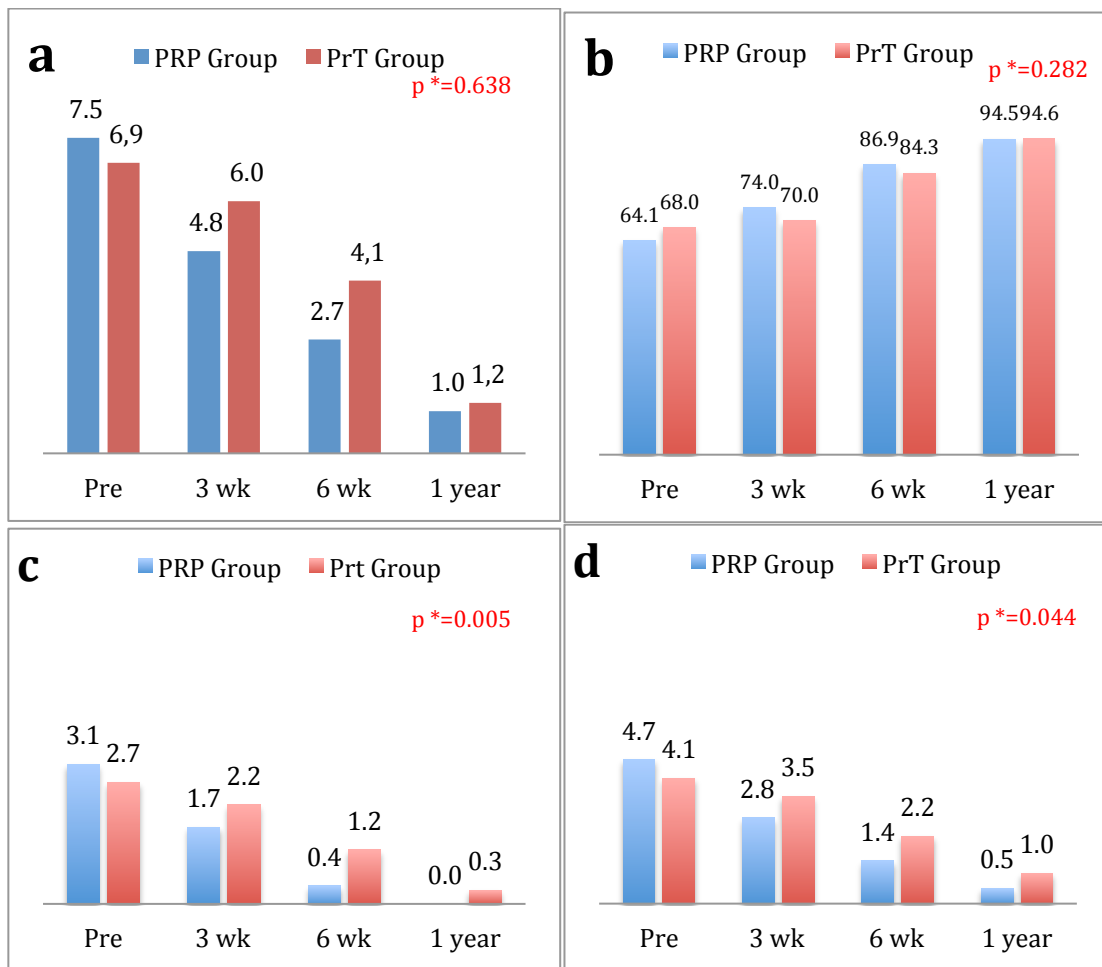
PRP: Platelet rich plasma; PrT: Prolotherapy; yr: years; mo: months; Values as mean ± SD

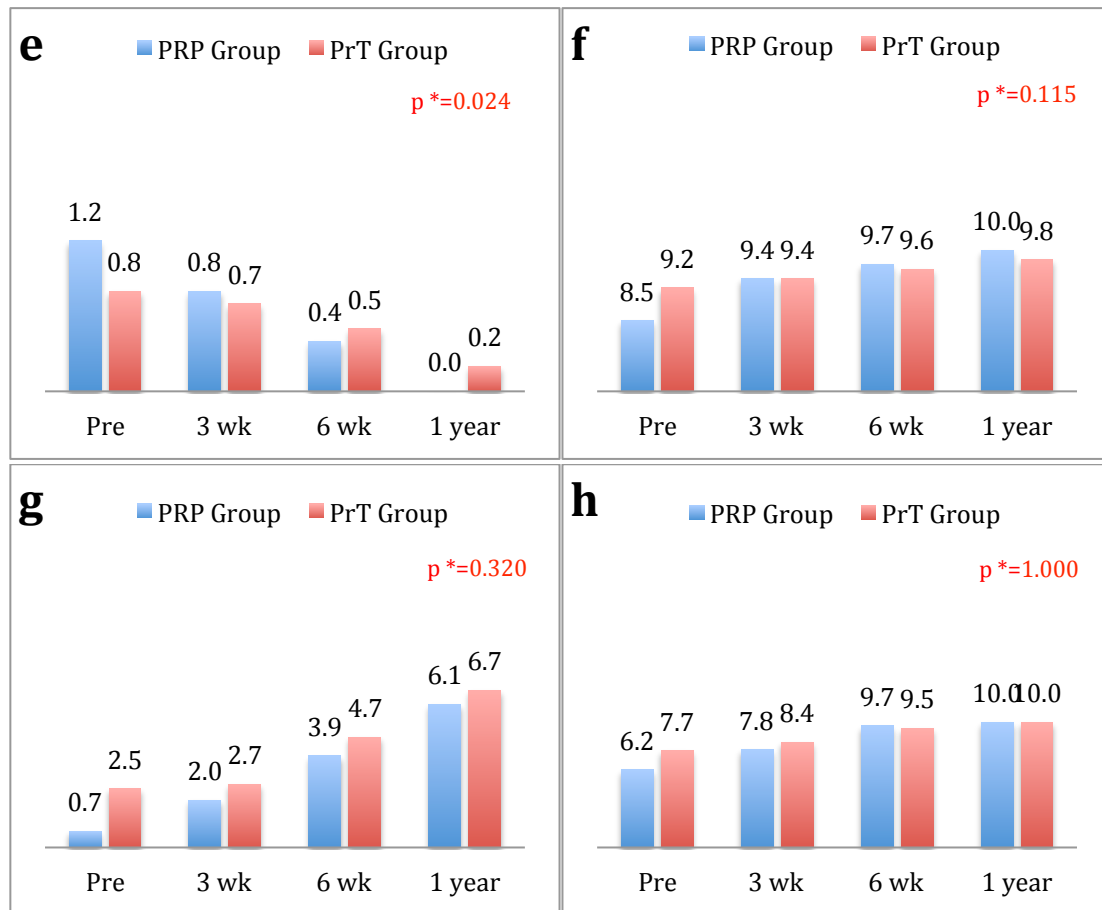
Using within-group comparison, statistically significant differences in pain at rest/during daily activities/during exercise, stiffness, crepitus, VAS and Tegner and Lysholm knee scores were found in both groups at each control (p<0.001). The stiffness, crepitus, range of motion, walking ability, exercise ability, number of medications, VAS and Tegner and Lysholm knee scores are shown in Figure 2. There was statistically significant differences in ROM and exercise ability for

the PRP group, and total number of medications for the PrT group at each control (p<0.001). There was statistically significant difference in ROM between pre- and minimum a year post-treatment for the PrT group (p<0.001). There were no statistically significant differences in walking ability between pre- and beyond a year post-treatment, and three weeks from the beginning and minimum a year post-treatment for the PrT group (p>0.05).

There were no statistically significant differences in walking ability and total number of medications between six weeks from the beginning and beyond a year post-treatment for the PRP group ( $p>0.05$ ). There were no statistically significant differences in exercise ability between pre-treatment and three weeks from the beginning; walking ability between pre-treatment and both three and six weeks of treatment, between three and six weeks of

treatment, and between three weeks from the beginning of treatment and last follow-up (minimum a year); range of motion between pre-treatment and both three and six weeks of treatment, between three and six weeks of treatment, between three weeks from the beginning of treatment and last follow-up, and between six weeks of treatment and last follow-up for the PrT group ( $p>0.05$ ). No side effect was reported except for locally increased pain.





**Figure 2:** Progression of PRP and PrT groups at pre-, 3 weeks, 6 weeks and 1-year post treatment follow-up **a:** VAS scores **b:** Tegner and Lysholm scores **c:** Stiffness **d:** Crepitus **e:** Range of Motion **f:** Walking ability **g:** Exercise ability **h:** Number of pain medications **Pre:** pre-treatment; **wk:** week; **PRP:** Platelet rich plasma; **PrT:** Prolotherapy \***:** 1-year post treatment comparison of PRP and PrT groups

**DISCUSSION**

CMP is a common cause of knee pain; it considerably decreases patient’s satisfaction and comfort. Numerous treatment methods have been proposed but an optimal process has not been identified yet. (1,10,20).

PrT is being used widely in the treatment of musculoskeletal disorders as a regenerative injection therapy (16). Unfortunately, its action mechanisms for pain relief and regeneration are not yet precisely understood. By injecting various irritant solutions, fibroblastic stimulation occurs. These activated fibroblasts secrete new collagen fibrils, required to heal the damaged tissues and healing is encouraged (26).

The effect of PrT in CMP treatment was previously reported in the literature. Hauser et al. reported significant improvement (24). Both intra- and extra-articular injections were done. They used 40 ml of PrT solution (15% dextrose, 0.1% procaine and 10% sarapin). Yildiz et al. applied 10 ml of 15% hypertonic dextrose solution extraarticularly, and 5 ml of 25% as intraarticular injection, and demonstrated that knee function, balance and coordination were improved significantly (19). In our study, we used a total of 7.0 ml 25% dextrose solution for intraarticular injection, and obtained statistically significant difference in pain level at rest/during daily activities/exercise, stiffness, crepitus, VAS



and the Tegner and Lysholm knee scores in the PrT group. However; range of motion, walking and exercise abilities were not significantly improved. Lacking of extraarticular injections might be the reason for this limited improvement.

Currently a specific PrT guideline does not exist (18,27). Different concentration dosages and combinations of PrT were used in studies. Rabago et al. advocate 25% dextrose to joint space and 15% dextrose to extra-articular soft tissue attachments for better clinical outcomes (28). Reeves et al. declared that significant results were obtained after application of 25% dextrose for the treatment of ACL laxity (29). We used 7.0 ml 25% dextrose of PrT as recommended in most of the studies, and obtained successful clinical results only with intraarticular injections to an extent.

Intra-articular PRP injection has been progressively preferred for osteoarthritis and is considered as one of the worthy treatment options. PRP provides essential growth factors. These stimulate the mesenchymal stem cells to differentiate into chondrocytes. PRP created favorable improvement of cartilage stiffness and displayed higher International Cartilage Repair Society scores in an experimental animal study on chondral defects (30). Too many clinical studies have been conducted about the effects of PRP in the treatment of chronic knee problems; however, there is lack of PRP standardization and high level of evidences to encourage the clinical use of PRP as a treatment modality in most orthopedic problems. Kon et al. found that PRP injections gave better results in terms of pain reduction and articular function recovery in degenerative knee cartilage lesions or osteoarthritis treatment, compared to hyaluronic acid (31).

Unlike this study, Filardo et al. declared that PRP and hyaluronic acid injections had similar results (8). Orsçelik et al. found that single and triple PRP injections were both effective and had similar effects in the treatment of CMP (10). Different than the mentioned studies, a kit system was used for PRP preparation, which was mentioned to provide highest platelet concen-

tration when compared with other systems, thus higher platelet counts were obtained in PRP samples (32,33). Triple injections of PRP were preferred for each patient (34). Injections were made USG-guided; hence security and effectiveness were increased. These might have been effective for the better clinical outcomes of the present study.

The participants were randomly divided; however, there were significant differences in some of the parameters between the groups at the beginning of the study. Patients of the PRP group were worse than the PrT group; however, last follow-up (minimum a year) values of pain levels during activity, stiffness, crepitus and range of motion were significantly better in the PRP group than those in the PrT group. Regarding these results, PRP can be considered more successful. Because of these different parameters at the beginning, we also used the difference between last follow-up and pre-treatment values for between-group comparisons. Parameters of pain level during exercise, range of motion, total number of medications, crepitus, VAS and the Tegner and Lysholm Knee Scores improved significantly.

In within-group comparisons there was significant difference in most of the parameters (pain level, stiffness, crepitus, VAS and functional knee score) at each control in both groups. However, there was no change in walking ability and total number of medications between six weeks and beyond a year of treatment for the PRP group ( $p>0.05$ ). Walking ability was improved and patients needed less medications as they healed after six weeks of treatment.

There was no change in range of motion, walking ability and exercise ability in some follow-up periods for the PrT group ( $p>0.05$ ). PrT did not improve exercise and walking ability in initial applications. There was significant difference between only pre-treatment and after last follow-up in range of motion. Therefore, intra-articular PrT provides slow progress in range of motion.

Both injection groups had significant clinical improvements after a minimum year of treat-

ment. Those similarities can be related to exercise. The positive effects of exercise in CMP are known widely (35-37). Exercise treatment may have increased PRP and PrT efficiency; however, the considerable amounts of the healing effect were believed to be due to injection therapies.

Small sample size is a limitation of this study. Another point is that, in both groups, the mechanical effect of needles used in injection causes focal bleeding and might stimulate inflammatory processes and increase healing (38). Solutions caused distension into the joint space, and this might stimulate the process (39). Only exercise implementation and placebo injections besides PRT and PrT injections should be researched for better understanding of these common interventions.

## CONCLUSION

We suggested PRP and PrT applications with exercise in the treatment of CMP. PrT and PRP ameliorate symptoms and improve physical ability. PRP and PrT injections applied with exercise were shown to be effective in CMP treatment; however PRP was superior to PrT.

## Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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