

Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial

Seyed Mansoor Rayegani,¹

Seyed Ahmad Raeissadat,²

Morteza Sanei Taheri,³ Marzieh Babaei,¹

Mohammad Hassan Bahrami,¹

Dariush Eliaspour,¹ Elham Ghorbani¹

¹Physical Medicine and Rehabilitation Department, Shohada-e-Tajrish Hospital,

²Physical Medicine and Rehabilitation Department, Shahid Modarres Hospital,

³Radiology Department, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

We designed a randomized clinical trial with control group, to investigate the effects of platelet rich plasma (PRP) on pain, stiffness, function and quality of life in patients with knee osteoarthritis. Patients were randomly divided in two groups. For both groups of participants, therapeutic exercise was prescribed. In the PRP group, two courses of leukocyte rich PRP (5.6 fold higher platelet concentration) with a 4-week interval was injected. For each participant, Western Ontario and McMaster University's Arthritis Index (WOMAC) and the SF-36 questionnaire (Farsi version) were filled at the baseline and 6 months after treatments. Thirty-one patients in the PRP group and 31 patients in the control group were studied. Mean changes of total WOMAC, physical component summary and mental component summary of Short Form-36 in PRP group showed better improvement than control group ($P < 0.05$). This study showed that intra articular PRP knee injection combined with therapeutic exercise can be more effective in pain reduction and improvement of stiffness and quality of life, compared with therapeutic exercise alone.

Introduction

Approximately 11% of women and 7% of men older than 60 years present some degrees of knee osteoarthritis (OA).¹ Osteoarthritis is a chronic disease defined by progressive degradation of the joint as well as loss of cartilage on joint surfaces. The degeneration that occurs in

the joint leads to changes in the catabolic and anabolic activity of chondrocytes. As a result, other components of the joint get compromised which may lead to meniscus degeneration, bone deformity, sclerosis as well as subchondral tissue edema and intermittent synovial inflammation. This condition impairs functional capacity and decreases quality of life (QOL) in patients by producing pain, stiffness and limitation in range of motion of the joint.²

The weak potential of joint cartilage for repair which is related to its avascular nature has resulted in numerous researches focusing on cartilage repair processes during the last two decades. Common treatments for cartilage tissue repair procure relative satisfaction, but rarely achieve an ideal level of functional capacity for the patient.³ Recently, innovative treatments for cartilage tissue repair have been introduced, including mesenchymal stem cell therapy, autologous chondrocyte implantation, use of matrix metalloproteinase inhibitors, gene therapy and growth factors.^{4,5}

In 1970, various studies were performed on different platelet concentrations in plasma. This was followed by work on the higher amounts of growth factors present in platelets, and from those years the first clinical applications of platelet rich plasma (PRP) were investigated.⁵ Classically, PRP is considered as a volume of plasma containing higher concentrations of platelets compared to blood base line level.⁶ In fact, this definition includes plasma and platelets. Platelets contain different growth factors and cytokines, and plasma is a liquid without cells containing proteins and bioactive molecules which play an important role in the cellular repair process.⁷ Today, the generic term PRP has progressed and includes various products. These products are categorized based on the PAW classification system (platelet concentration, white blood cells and activation method).⁸ Because PRP contains growth factors and plasma proteins, it can regulate anti-inflammatory signals and equilibrate angiogenesis.^{9,10} Based on this, its use in order to reduce the progression of OA has been suggested in some studies.^{11,12}

Presently, different researches including systematic reviews have been performed on the effects of PRP on knee OA.¹³⁻¹⁵ In the majority of these studies, the effects were assessed as follow ups for different periods of time and in a number of these studies the effects were compared to intra articular hyaluronic acid.¹⁶⁻¹⁸ The discrepancies in patients' response in different studies can be related to PRP specificities (according to PAW classification system) and the conditions of the patient population. Although, those studies have showed some improvement in functional capacity and QOL, but the majority of these studies have no control group.^{4,19,20} Despite the growing application

Correspondence: Marzieh Babaei, Physical Medicine and Rehabilitation Department, Shahid Beheshti University of Medical Sciences, 1989934148 Tehran, Iran.
Tel/Fax: +98.212.273.1112.
E-mail: rambabaei@yahoo.com

Key words: platelet rich plasma, therapeutic exercise, knee osteoarthritis.

Acknowledgements: the authors would thank Hakim Pharmaceutical Company for providing acetaminophen to patients free of charge for this clinical trial. We appreciate the help of Mr. Naser Aghayi, technical manager of Shahid Modarres hospital laboratory and Dr. Mohamad Hosein Mohammadi, laboratory hematologist, for providing necessary laboratory equipment and information. We also thank Mrs. Zahra Maleki and Mrs. Fatemeh Rahimifard, managers of Shohada-e-Tajrish and Shahid Modarres hospital libraries, and Mrs. Zahra Razzaghi, the epidemiologist, for having high cooperation with us in this study.

Contributions: SMR, SAR, MB, EG, following up the patients, gathering the data of patients, writing and editing the article; MHB, DE, following up the patients, editing the article; MST, radiologic investigation, editing the article.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 25 March 2014.

Revision received: 3 July 2014.

Accepted for publication: 14 July 2014.

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

©Copyright S.M.Rayegani et al., 2014
Licensee PAGEPress, Italy
Orthopedic Reviews 2014; 6:5405
doi:10.4081/or.2014.5405

of PRP, a high level of evidence for its use on patients suffering from knee OA has not been provided.²

In this study we tried to design a randomized clinical trial with control group, to investigate the effects of PRP on pain, stiffness, function and quality of life of patients suffering from knee osteoarthritis.

Materials and Methods

In this clinical trial, patients with knee OA referring to the physical medicine and rehabilitation clinics of Shahid Modarres and Shohada-e-Tajrish medical centers from 2012 to 2013 were evaluated. This study was not blinded. Inclusion criteria were arthralgia from the past 3 months with radiologic evi-

dence of articular damage (grade 1-4 of Kellgren-Lawrence scale) based on knee OA criteria of American College of Rheumatology (ACR).^{21,22} Exclusion criteria included, age over 75 years, history of diabetes mellitus, immunosuppressive and collagen vascular disorders, history or presence of cancer or malignant disorders, any infection or active wound of the knee, recent history of severe trauma to the knee, autoimmune and platelet disorders, treatment with anticoagulant and anti-platelet medications 10 days before injection, use of non-steroidal anti-inflammatory drugs (NSAIDs) 3 days before injection, history of knee articular injections of corticosteroids during previous 3 weeks or use of systemic corticosteroids 2 weeks before PRP injections, hemoglobin measures of less than 12 g/dL and platelet counts of less than 150,000 per micro liter, history of vasovagal shock, pregnancy or breastfeeding and genu valgum/varum greater than 20 degrees.

After selecting patients, they were briefed by one of the author physiatrists describing the aim and method of conduction while presenting scientific evidence, benefits and possible complications of participating in the study and written information about the probable issues was also presented. After signing the consent form (approved by the ethics committee of Shahid Beheshti university of medical sciences), patients were enrolled in the study. Patients' personal information such as age, gender, height, weight, Body Mass Index (BMI), educational level, physical activity, symptom duration and the grade of OA (based on Kellgren-Lawrence grading scale in simple radiographs) were recorded. Then, for each participant the native (Farsi) versions of the Short Form-36 (SF-36) questionnaire for assessment of quality of life (QOL) and Western Ontario and McMaster University's Arthritis Index (WOMAC) questionnaire for evaluation of patients' functions were filled by a physical medicine and rehabilitation resident. Patients were randomly divided into two groups (based on the table of random numbers). For both groups of participants, exercise and acetaminophen 500 mg without codeine (PRN according to the patient needs up to 2 g/day) were prescribed. In the test group (PRP), in addition to these prescriptions, PRP was injected. Exercise was taught and demonstrated to all patients in the two groups by a physical medicine and rehabilitation resident. The exercise protocol was composed of multi angle isometric exercises of muscles around the knee (quadriceps muscle, adductors and abductors of the thigh) as well as stretching of the hamstring 3 times a day and every move lasting 10 seconds and repeated 10 times. And after 4 weeks, concentric exercises of the quadriceps, adductors and abductors were taught to the patient. For the process of PRP

preparation and injection, participants were referred to Shahid Modarres hospital laboratory. The PRP processing was done using the Rooyagen kit (made by Arya Mabna Tashkis Corporation, RN:312569). For preparing 4-6 mL of PRP with concentration of 4-6 times the average normal values, 35-40 mL of blood was first collected from the patient's upper limb cubital vein using an 18G needle. Then 5 mL of ACD-A was added to the sample as an anticoagulant. 1 mL of the blood sample was sent for complete blood count. The rest of the sample passed two stages of centrifuge (first with 1600 rpm for 15 minutes for separation of erythrocytes and next with 2800 rpm for 7 minutes in order to concentrate platelets). The final product was 4-6 mL of PRP containing leukocytes. The PRP quantification and qualification procedure was performed using laboratory analyzer Sysmex KX 21 and swirling and if approved, the injection would proceed. As it was stated in some resources that anesthetic agents could not only have toxic effects on chondrocytes but could also influence the activation of platelet by changing the pH of the environment, therefore no local anesthetic agent was injected.²³ Instead, patients were given a single dose of acetaminophen-codeine 2 hours before injection. It was also indicated in some studies that a factor helpful for the activation of platelets is contact with endogenous collagen.^{8,23} We did not use exogenous factor for the process of activation but let the platelets be in contact directly with the joint collagen to become active. The skin of the injection site was prepped and draped and the liquid PRP was injected in a sterile condition using a 22G needle through the classic approach for intra articular injection (suprapatellar or medial). After 15-20 minutes of rest, patients were asked to actively flex and extend their knees so that the PRP could spread evenly across the joint space before changing into gel. Then participants were sent home with a written order regarding the following issues. They were recommended to have relative rest 24 to 48 hours post-injection and limit weight bearing on the injected joint. Meanwhile for reducing pain and inflammation they were instructed to use cold therapy three times a day each time for 10 minutes. In the case of pain onset they had permission to use 500 mg of acetaminophen and if persistent, acetaminophen-codeine could be used PRN. However, they were strictly prohibited to take NSAIDs, Aspirin or any steroids. Generally participants were recommended to have mild to moderate levels of activity and increase it as tolerated. They could resume their usual activities of daily living (ADL) one week after injection. For the PRP group, exercise was started a week after injection with lower intensity in the first days and then it increased progressively to be continued on a normal level. In the control

group, exercise was prescribed immediately after entrance in the study. It was said to patients in control group to use only acetaminophen without codeine if they felt pain, and changing to Acetaminophen codeine in case of persistent pain.

There is no consensus about the standard regimen of PRP treatment in musculoskeletal disorders. In different study protocols, the average series of injections is two to three times at two to six week intervals.²⁴ Because the inflammatory process and patient's symptoms usually subside in 2 weeks,²⁴ we chose 2 series of injections with 4 weeks interval in order to have enough time to pass patient's symptoms. In our study the second injection was performed 4 weeks after the first. All of the participants were visited consecutively at 4, 8 and 24 weeks after treatment. Meanwhile they were evaluated for the amount of acetaminophen consumption, pain, joint swelling and stiffness. 6 months from first injection, SF-36 and WOMAC questionnaires were filled again. Participants were informed about the necessity of following the instructions, avoiding medications influencing platelet activity and having communication with the project executor in the case of any problem.

Final data before and after the treatment were imported and analyzed by SPSS version 16. Normality of the data was described by mean and variance was evaluated using Kolmogorov-Smirnov Test. For comparing variables with normal distribution, paired t-test, independent t-test and ANOVAs tests were used. To evaluate non-normal variables, non-parametric tests of Wilcoxon on signed rank and Mann-Whitney were applied. Qualitative variables were expressed with frequency and percentage. For evaluating the relationship between quantitative variables, correlation coefficients of Pearson and Spearman were used. P value below 0.05 was meaningful.

Results

In this study, 31 patients in the PRP group and 31 patients in the control group were finally investigated. The mean age of the patients was 56.19 ± 10 and the mean BMI 27.77 ± 3.61 . Characteristics of the two groups are presented in Table 1. Figure 1 shows the consort flow diagram.

Platelet rich plasma preparations in this study contained leukocytes (LR-PRP). Table 2 demonstrates the mean platelet concentrations and white blood cell in PRP and the mean platelet concentrations at base (whole blood); PRP concentration had no significant relation to the response to treatment ($P > 0.05$).

Mean total WOMAC score from base to 6 months follow up improved in the two groups

with a $P=0.01$ (Figure 2A). Also mean total WOMAC changes between the two groups had a significant difference with $P=0.03$ (Figure 2A). Changes of all 3 WOMAC parameters in the two groups showed improvements. The mean difference of WOMAC subgroups between the two groups was significant only for pain ($P<0.05$) Table 3.

Analysis of the two main domains of SF-36 showed that mean changes of PCS in the PRP and control groups were significant with respective P values of 0.001 and 0.015. But the MCS domain change was not significant in either of the groups (P value in PRP group =0.135 and P value in control group =0.262). Comparing the two groups, the mean changes of the PCS and MCS domains were significant with P values of 0.05 for both domains (Figures 2B,C). Mean changes of significant parameters of WOMAC and SF36 with demographic information (age, gender, BMI, education level, regular exercise, family history, duration of symptoms, patellofemoral osteoarthritis grade and tibiofemoral osteoarthritis grade) were analyzed for the two groups. In the PRP group, the amount of improvement of the stiffness (WOMAC) parameter in the patients with symptoms lasting less than a year was higher in comparison to patients with symptoms lasting more than a year ($P=0.01$). In the control group, improvement in MCS in patients with preceding symptoms of less than a year was better compared to patients with symptoms lasting more than a year ($P=0.001$). For the PRP group, the amount of improvement of PCS for patellofemoral and tibiofemoral grade 3 was superior to grade 2 ($P=0.037$). This difference did not exist with age and BMI adjustments by the linear regression test ($P>0.05$).

Weight changes were not significant between the two groups ($P=0.083$). But the amount of acetaminophen consumption was significantly different in the two groups ($P=0.012$). In the PRP group, mean acetaminophen 500 mg consumption was 64 ± 11.8 and in the control group 31.45 ± 36.52 . The effect of acetaminophen consumption was assessed using the General linear model multivariate on SF36 and WOMAC subgroups as well as the total. And it was observed that this variable was not effective in the amount of response to treatment ($P>0.05$).

Discussion

In our study after 6 months, pain, stiffness, functional capacity and QOL in the domain of PCS of patients improved in both PRP and control groups. Comparing with control group, reduction in pain, total WOMAC score and improvement of PCS and MCS domains of SF-36 were higher in the PRP group.

Table 1. The two treatment groups are homogeneous for all the parameters evaluated.

Variables	PRP group	Control group	P
Age, mean \pm SD	58.07 \pm 8.95	54.68 \pm 10.83	0.18
BMI, mean \pm SD	28.23 \pm 4.1	27.30 \pm 3.27	0.33
Sex (%)			
Male	2 (6.5)	2 (6.5)	0.97
Female	29 (93.5)	29 (93.5)	
Educational level (%)			
Below high school diploma	15 (48.4)	10 (32.3)	0.19
Diploma and higher	16 (51.6)	21 (67.7)	
Dominant knee involvement (%)			
Right	11 (36.7)	15 (48.4)	0.44
Left	19 (63.3)	16 (51.6)	
Grade of tibiofemoral osteoarthritis (%)			
Grade 1	1 (3.3)	3 (10)	0.11
Grade 2	15 (50)	21 (70)	
Grade 3	10 (33.3)	6 (20)	
Grade 4	4 (13.3)	0 (0.0)	
Grade of patellofemoral osteoarthritis (%)			
Grade 1	2 (6.7)	0 (0)	0.06
Grade 2	13 (43.3)	15 (51.7)	
Grade 3	9 (30)	13 (44.9)	
Grade 4	6 (20)	1 (3.4)	
Regular Physical activity (3 times a week, for at least 30 minutes every time) (%)			0.79
Regular active	15 (48.4)	14 (45.2)	
Not active	16 (51.6)	17 (54.8)	
Symptom period (%)			
3-12 months	5 (16.7)	8 (25.8)	0.53
More than 12 months	25 (83.3)	23 (74.2)	
Family history (%)			
Positive	20 (66.7)	26 (83.9)	0.11
Negative	10 (33.3)	5 (16.1)	

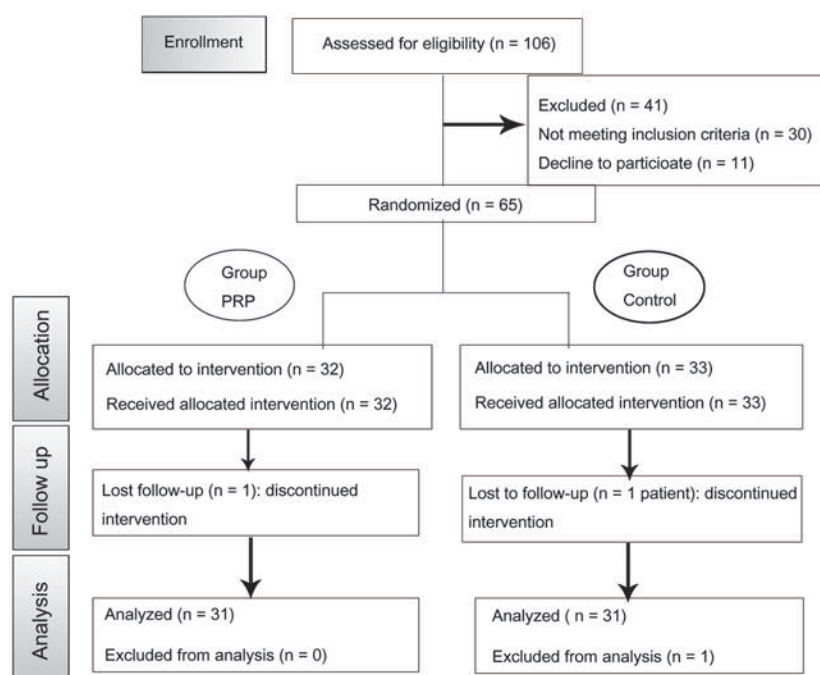


Figure 1. Consort flow diagram.

Table 2. Platelet rich plasma cytologic findings (mean±SD).

Parameters	Platelets concentration in whole blood*	Platelets concentration in PRP*	Platelets concentration in whole blood/PRP°	WBC count in PRP*
First injection	218643.80±85715.72	1346060.00±523291.05	5.68±1.17	240.00±203.65
Second injection	241166.14±51168.98	1367833.33±364955.38	5.62±1.65	388.89±489.76

*Per mL; °fold increase in platelet concentration.

Table 3. Score changes of Western Ontario and McMaster University's Arthritis Index sub-groups at baseline and after 6 months follow up in both groups.

Parameters	Baseline	6 months	P (intra group)*	P (between groups)
Pain				
PRP	9.13±3.72	4.2±3.08	0.001	0.006
Control	7.12±3.67	5.16±4.5	0.007	
Stiffness				
PRP	2.3±1.76	0.83±1.28	0.001	0.17
Control	1.67±1.64	0.83±1.31	0.014	
Functional capacity				
PRP	31.86±9.81	14.1±9.12	0.001	0.09
Control	25.03±17.25	13.93±13.4	0.001	

*Paired T test is used.

Presently, various studies, including systematic reviews, have reported the effects of PRP on knee OA, and obtained results similar to our study.^{2,6} Patel *et al.* study, by comparing the effects of single injection or double injections of PRP and injection of normal saline (as a control group) in patients suffering from knee arthritis, showed that single injection was as effective as two times injections and both had better effects than normal saline injection. In their study, PRP obtained was lacking leukocytes with concentration of 2.5 million per micro litter with a single centrifuge turn.²⁵ In our study, PRP used contained leukocytes after 2 turns of centrifuge with a platelet concentration of 5.6 times.

The results of the present study are similar to those of Wang-Saegusa *et al.*⁴ They evaluated the effects of PRGF (rich growth factor plasma) on functional capacity and QOL of patients suffering from knee OA. In their study the amount of mean WOMAC and its components as well as mean changes of physical parameters of SF36 questionnaire were significant.

Kon *et al.* during a two year study investigating the short term (6 and 12 months) and long term (24 months) effects of PRP in knee osteoarthritis. In their studies using the IKDC questionnaire and VAS evaluation to assess patients' condition, results similar to our study were reported.²⁶⁻²⁸

Sanchez *et al.* showed short term signs and symptoms improvement was correlated with severity of osteoarthritis (radiologic grading).¹⁶ In our study also, PRP had better short term results compared to the control group even if in our study this finding didn't show any difference in various grades of OA. A rea-

son for this difference may be related to fewer recruited patients in grades 1 and 4 compared to grades 2 and 3, exclusion of patients with severe genu varum and valgum and the small size of the sample.

In our study, there was no correlation between the amount of improvement of functional capacity and QOL of patients with weight changes and BMI. On the contrary, in the Filardo and Kon study in patients with higher BMI and higher grades of OA, the amounts of improvement were lower.^{26,27} The reason for lack of correlation with BMI in our study can be explained by the positioning of its mean in the overweight category. In our study there was no correlation between age, OA grade and gender with the amount of response to treatment. In some studies better responses have been reported in younger ages, lower grades and male gender.^{3,27} This difference between our study and other studies can be related to lack of control group in previous studies, small number of male patients in comparison to female patients in our study, small number of patients with grades 1 and 4 in our study, selection of patients (primary and secondary OA) as well as primary BMI and age of patients investigated. Although, observing lower response to PRP injection in older ages, with fewer active and living cells for better response to growth factors is something expectable and explainable.

The total amount of acetaminophen consumption during the 6 months follow up was higher in the PRP group than in the control group. By questioning patients, it appeared that in the PRP group due to prescription of before injection acetaminophen and because of intermittent pain 3 to 7 days after injection

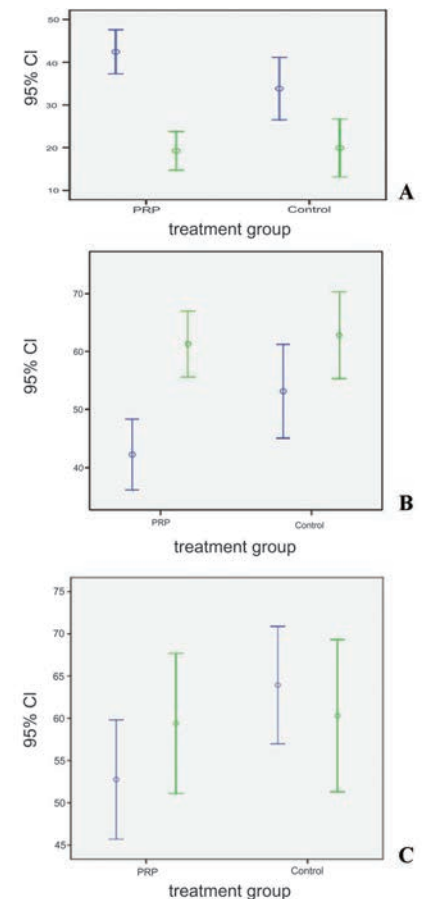


Figure 2. A) Score changes of WOMAC between 2 groups. B) SF-36 test: pre and post-treatment for the physical health domain in both groups. C) SF-36 test: pre and post-treatment for the mental health domain in both groups. Statistical between and inter-group difference was observed (P<0.05). Blue lines: values at baseline; green lines: values after 6 months.

(because of the inflammatory process which is part of the PRP mechanisms), the highest amount of acetaminophen consumption occurred around the time of injection, but in the control group this amount was spread along the treatment period. Unfortunately, data regarding distribution of the time of acetaminophen consumption are unavailable to us. In further analysis, it appeared that there was no correlation between the amount of acetaminophen consumption and the amount of response to treatment. In the Patel et al. study, it was stated that increase in amount of platelet concentration in PRP leads to an increase in patient's pain after injection which can explain the increased consumption of pain killers the first few days after injection.²⁵

Cellularity is one of the main aspects of PRP evaluation in different clinical applications. In our study the mean platelet concentration obtained for PRP in the first and second injection was 3-7.8 and 3.2-8.6 times respectively. No relation was found between improvement of pain, stiffness, functional capacity and QOL of patients and the platelet concentration. Some studies have indicated a positive effect of PRP in musculoskeletal diseases subject to concentrations of 4-6 times and others believe that concentrations higher than 8 times can jeopardize the repair process and induce an inhibitory effect on cellular proliferation.^{8,28} Up to now, we haven't been able to find a published study about the effect of PRP in knee OA based on platelet concentration.^{2,6,17} Also, in our study, the obtained PRP contained WBCs with a mean of 10-20% of blood white cells. Some believe, in the process of PRP preparation not only platelet but also monocytes as well as white cell stem cells become present. Some studies only consider PRP to be appropriate when it is free of leukocytes. In their opinion, leukocyte secretion of proteases and reactive oxygen are unwanted.⁸ But certain researches mention the secretion of substances such as cytokines and enzymes to be effective in the processes of repair, platelet activation, prolonging the duration of growth factor release and prevention of infection (*Staphylococcus aureus* and *Escherichia Coli*).^{8,29} Up to now very few human studies have been published which had mean WBC of PRP in mind.^{2,6} In other studies it was also stated that presence of leukocytes increases pain after injection.

The most important positive point of our study was the presence of a control group and the cytology assessment of PRP. Our study limitations included: relative small sample size, use of subjective evaluation, inexistence of blinding conditions and predominance of female patients.

No significant complication (such as infection, atrophy, deep vein thrombosis, fever, hematoma and tissue hypertrophy) was

observed except for transient increase in local pain and swelling. Other studies had the same reports. The most frequent patient complaint was injection site pain. In some cases pain lasted up to 10 minutes post injection, decreased gradually and continued as a dull pain at the injection site which lasted from 3 days to 2 weeks. Some patients complained of transient knee stiffness and even local pelvic pain and feeling of swelling. In most cases pain was improved by following the instructions and acetaminophen consumption.

Overall, our study and other studies proposed the short term efficiency of PRP injection in comparison to control group in the treatment of patients suffering from OA. Details considered while choosing this treatment take into account age, gender, grade of arthritis and the duration of complaint from symptoms. These can affect the decision on the characteristics and best concentration of PRP, number of injection, their intervals as well as patient selection. The reduction of PRP effect with time indicates the lack of role of chondral remodeling alone. Therefore more studies are suggested to determinate PRP treatment patients' eligibility conditions, assessment of PRP real effects in the short and long term, and PRP cost benefit nature in a comprehensive and unique protocol. Also performing objective investigations such as MRI, arthroscopy and pathology to assess the effects of PRP specially for changes in meniscus, bone subchondral edema and synovial intermittent inflammation accompanying knee OA, could be beneficial in patients suffering from arthritis.

Conclusions

Results obtained from this study showed that intra articular PRP knee injection can be effective in reduction of pain, stiffness and QOL improvement of patients in comparison to the control group in the short term.

References

1. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1987;30:914-8.
2. Yuan M, Meng H, Wang A, et al. Basic science and clinical application of platelet-rich plasma for cartilage defects and osteoarthritis: a review. *Osteoarthritis Cartilage* 2013;21:1627-37.
3. Frizziero A, Giannotti E, Ferraro C, Masiero S. Platelet rich plasma intra-articular injections: a new therapeutic strategy

for the treatment of knee osteoarthritis in sport rehabilitation. A systematic review. *Sport Sci Health* 2012;8:15-22.

4. Wang-Saegusa A, Cugat R, Ares O, et al. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. *Arch Orthop Trauma Surg* 2011;131:311-7.
5. Napolitano M, Matera S, Bossio M, et al. Autologous platelet gel for tissue regeneration in degenerative disorders of the knee. *Blood Transfus* 2012;10:72.
6. Smyth NA, Murawski CD, Fortier LA, et al. Platelet rich plasma in the pathologic processes of cartilage: review of basic science evidence. *Arthroscopy* 2013;29:1399-409.
7. Metcalf KB, Mandelbaum BR, McIlwraith CW. Application of platelet-rich plasma to disorders of the knee joint. *Cartilage* 2013;4:295-312.
8. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. *Arthroscopy* 2012;28:998-1009.
9. Raeissadat SA, Sedighpour L, Rayegani SM, et al. Effect of platelet-rich plasma (PRP) versus autologous whole blood on pain and function improvement in tennis elbow: a randomized clinical trial. *Pain Res Treat* 2014;2014:8.
10. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Is platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: one year randomized clinical trial. *BMC Sports Sci Med Rehabil* 2014;6:12.
11. Civinini R, Nistri L, Martini C, et al. Growth factors in the treatment of early osteoarthritis. *Clin Cases Min Bone Metab* 2013;10:26.
12. Anitua E, Sánchez M, Orive G, Padilla S. A biological therapy to osteoarthritis treatment using platelet-rich plasma. *Expert Opin Biol Ther* 2013;1-12.
13. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol* 2013;9:721-30.
14. Park YG, Han SB, Song SJ, et al. Platelet-rich plasma therapy for knee joint problems: review of the literature, current practice and legal perspectives in Korea. *Knee Surg Relat Res* 2012;24:70-8.
15. Jang SJ, Kim JD, Cha SS. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. *Eur J Orthop Surg Traumatol* 2012;1-8.
16. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070-

- 8.
17. Spaková T, Rosocha J, Lacko M, et al. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehab* 2012;91:411-7.
18. Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis preliminary results in a group of active patients. *Sports Health* 2012;4:162-72.
19. Raeissadat SA, Rayegani SM, Babae M, Ghorbani E. The effect of platelet-rich plasma on pain, function, and quality of life of patients with knee osteoarthritis. *Pain Res Treat* 2013;2013:165967.
20. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy* 2011;27:1490-501.
21. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64:465-74.
22. Misso ML, Pitt VJ, Jones KM, et al. Quality and consistency of clinical practice guidelines for diagnosis and management of osteoarthritis of the hip and knee: a descriptive overview of published guidelines. *Med J Aust* 2008;189:394-9.
23. Allan M, James W, Amy V. Treatment of tendon and muscle using platelet-rich plasma. *Clin Sports Med* 2009;28:113-25.
24. Crane D, Everts P. Platelet rich plasma (PRP) matrix grafts. *Pract Pain Manage* 2008;8:12-26.
25. Patel S, Dhillon MS, Aggarwal S, et al. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis a prospective, double-blind, randomized trial. *Am J Sports Med* 2013; 41:356-64.
26. Kon E, Buda R, Filardo G, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc* 2010;18:472-9.
27. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2011;19:528-35.
28. Tate K, Crane D. Platelet rich plasma grafts in musculoskeletal medicine. *J Prolotherapy* 2010;2:371-6.
29. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 2001;10:225-8.