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ORIGINAL ARTICLE

Efficacy of Intra-Articular Autologous Platelet Rich Plasma Application in Knee Osteoarthritis

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Objectives: This study aims to evaluate the efficacy of autologous platelet rich plasma applications on pain, functional status, and cartilage regeneration in advanced knee osteoarthritis.

Patients and methods: A total of 82 patients (13 males, 69 females; mean age 63.5±9.3 years; range 40 to 88 years) with chronic knee pain for the last one year, who had grade 3-4 knee osteoarthritis according to Kellgren-Lawrence Scale and visual analog scale value of higher than 5, who did not receive physical therapy for the last six months, and did not respond to treatment despite use of nonsteroidal antiinflammatory drugs and analgesics at least for the last three months were enrolled in the study. Totally 103 knee joints of 82 patients were applied intra-articular platelet rich plasma in the beginning, and first and second weeks of treatment. Platelet rich plasma was applied to both knees in 20 patients. Patients were evaluated clinically with visual analog scale, functionally with Western Ontario and McMaster Universities Osteoarthritis Index, and six-minute walk test before application and after application at first and second weeks, and third and sixth months. Cartilage thicknesses were measured by ultrasound before treatment and at third and sixth months after treatment. Obtained results were compared.

Results: Compared to values before treatment, patients' visual analog scale values were significantly decreased at third and sixth months after treatment ($p<0.001$). When compared according to Western Ontario and McMaster Universities Osteoarthritis Index, all values improved significantly after treatment ($p<0.001$). Results of six-minute walk test improved at third and sixth moths after treatment compared to results before treatment ($p<0.05$). Cartilage thicknesses increased significantly after treatment at third and sixth months compared to before treatment ($p<0.05$).

Conclusion: We believe that platelet rich plasma treatment is an effective, reliable, easily applied and low cost application in terms of pain, functional status as well as cartilage regeneration even in patients with advanced osteoarthritis.

Keywords: Intra-articular injections; knee osteoarthritis; platelet rich plasma.

Osteoarthritis (OA) is a chronic, non-inflammatory rheumatologic disease which affects the synovial joints. It is characterized with joint cartilage degeneration, subchondral bone changes, and synovitis.[1] Nonsteroid antiinflammatory drugs, glucosamine, chondroitin sulfate and hyaluronic acid are generally used for reducing inflammation and relieving pain in patients with OA. However, these have limited effect on reducing chondrocyte degeneration and improving regeneration.[2] Medications protecting or healing the cartilage are still at experimental stage. These include applications of cytokine inhibitors, gene therapy, artificial chondrocytes, and growth factor (GF).[3]

Growth factor increases the synthesis of chondrocyte matrix and stimulates chondrogenic cell proliferation.[4] It reduces the activation of nuclear factor kappa B which has an important role in the pathogenesis of OA, by inhibition of inflammatory process which is induced by interleukin-1 beta.[5] Platelet alpha granules contain

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significant amount of GF.[6] For this reason, autologous platelet rich plasma (PRP) application has emerged as a treatment option for OA. PRP also includes plasma proteins that act as mesenchymal cell adhesion molecules like fibrin, fibronectin and vitronectin. It is known that these molecules appear during recovery process following a trauma in the human body.[7]

Growth factor is easily provided in the intended concentration by centrifuging the whole blood taken from the patient and forming PRP. Obtaining it from the patient's own blood after a simple centrifuging is an advantage.

Platelet rich plasma contains a mean of three to five fold higher platelet counts compared with whole blood. There are no widely accepted and quantified values of platelet concentrations in PRP. Number of platelets which exist in whole blood ranges from 150,000/µl to 350,000/µl, while the aim is to maintain the concentration of platelets in PRP at least 200% compared with whole blood.

There is no standard technique for the preparation of PRP. While it can be prepared manually, there are also various commercial PRP preparation kits approved by United States Food and Drug Administration. PRP substrates consisting of different concentrations and counts of platelets are obtained by these kits using different clothing activators. It has been reported that platelet concentrations in PRP varies according to the preparation method, ranging from 2.5 to 8 fold higher compared to whole blood.[8,9] Therapeutic effects of PRP may vary due to different preparation techniques. Also high-cost of these commercial kits are disadvantages to be used frequently.[10] In this study, we aimed to evaluate the efficacy of autologous PRP applications on pain, functional status, and cartilage regeneration in advanced knee OA.

PATIENTS AND METHODS

The patients who admitted to Kayseri Training and Research Hospital between September 2012 and April 2013 were enrolled in the study. A total of 82 patients (13 males, 69 females; mean age 63.5±9.3 years; range 40 to 88 years) with chronic knee pain for the last one year, grade 3-4 degenerative OA according to Kellgren-Lawrence scale, no response to NSAIDs or analgesics, knee pain in most of the day for the last month, and visual analog scale (VAS) score higher than 5 were enrolled. Totally 103 knee joints of 82 patients were included. Twenty patients received injection in both knee joints. Meanwhile, patients with thrombocytopenia and anemia, hematological disorder and malignancy, active use of anticoagulant therapy, severe cardiovascular and infectious disease, insulin-dependent or uncontrolled diabetes were not included. Also, patients who had received intra-articular injection (glucocorticoid, hyaluronic acid etc.) and physical therapy for the last six months were not included to eliminate the synergistic effects. Before the study, informed consent forms were obtained from all patients. The local ethics committee approval was obtained and World Medical Association, Declaration of Helsinki, 2008, was signed by the investigators.

Kellgren-Lawrence scale, which was shown to be concordant for the clinical status, was used for the radiologic grading of knee OA.[11] The severity of pain was evaluated by using VAS. The patients were asked to score their pain on a scale of 0 (no pain) and 10 (worst pain).

Use of NSAIDs was not allowed before and after seven days of PRP application. Only use of paracetamol up to 4 g/day was permitted for pain before and after the injection.

Intra-articular PRP was applied in the beginning, and at first and second weeks of treatment. Functional levels of the patients were assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and six-minute walk test before the application and at first and second weeks, and third and sixth months after the application. Cartilage thicknesses were measured radiologically by ultrasound before and at third and sixth months after treatment. The results were compared before and after treatment.

Western Ontario and McMaster Universities Osteoarthritis Index, which is recommended for OA studies by Outcome Measures in Rheumatology Clinical Trials, is a reliable and valid method for the assessment of patients with knee and hip OA.[12] In our country, the reliability and validity studies for Turkish translation of WOMAC

was performed by Tüzün et al.[13] WOMAC OA index which assesses pain, stiffness and physical function using a Likert pain scale is composed of three sections and 24 questions. High WOMAC scores show increased pain and stiffness, and impaired physical function.[13,14]

Six-minute walk test was performed at a 30-meter long patient corridor to evaluate physical performance. The patients were asked to walk up and down the corridor without stopping for six minutes. At the end of the test, the distance walked in six minutes was recorded as meters.[15,16]

Cartilage thicknesses were measured with ultrasound by an experienced radiologist. Sonographic examinations of related knee joints were taken with a Toshiba PLT- 704 SBT Linear 7.5 MHz Ultrasound Transducer (Toshiba Medical Systems Co. Ltd, Otawara, Japan) in sitting position with flexed knees. Linear transducer was oriented perpendicular to the axial plane of medial tibiofemoral joint in its long axis. Articular cartilage of medial femoral condyle was evaluated with a starting point at the level of intercondylar notch to the medial border of medial condyl. Articular cartilage thickness was measured as a distance that perpendicular to the articular surface of medial condyl at the level of which we have differentiated the cartilage well in described anatomic location. Differentiated articular cartilage was seen as isoechoic-mildly hyperechoic band like structure bordered with thin, medial condylar cortex. Since the majority of patients had wide articular cartilage defects, the most appropriate tissue was used for measurement.

Twenty-four milliliter blood sample was obtained from each patient from blue intravenous cannula. Two milliliter anticoagulant citrate dextrose solution filled injector added with 8 mL blood sample was transferred to a 10 mL red top sterile science lab vacutainer. Three tubes, each containing 10 mL, were centrifuged at 160 rpm in a Hettich Universal 320 equipment (Hettich GmbH Co. KG., Tuttlingen, Germany) for 20 minutes. After centrifuge, whole blood was separated into three layers: plasma (upper layer), buffy coat (leucocytes mixed with platelets), and erythrocytes (lower layer).

Under the Nuve 120 laminar flow, plasma and buffy coat above the platelet and leukocyte layer and the erythrocyte layer border were transferred with green tip injectors to empty 10 mL red top tubes. Three tubes were centrifuged at 400 rpm for 15 minutes. After the centrifuge, the tube was divided into two layers consisting of an upper layer of platelet poor plasma and lower layer of PRP. Under the laminar flow, platelet poor plasma layer was emptied until 1.5 mL remained in the tube. Tube was slightly shook for the PRP which was in the bottom of the tube to be released. Two tubes containing PRPs were taken into two injectors. Two injectors each containing 1.5 mL PRP were prepared. Under sterile conditions, 3 mL of PRP was injected intra-articularly to the patient. The third tube containing 1.5 mL PRP was secured for hemogram blood count. All the prepared PRP was confirmed to contain two fold to eight fold higher platelet counts compared with whole blood.

After the application, platelets excreted 70% of deposited GF in the first 10 minutes and approximately 100% in the first one hour. Still, a slight amount of GF excretion lasted for eight days until the death of the platelets. Since in normal conditions the lifetime of platelets is 8-10 days, PRP injections were applied with one week intervals.

After the preparation of PRP, injection was applied as soon as possible by lateral approach following skin disinfection of knee joint. No exercise protocol was applied after the injection. To eliminate synergistic effects, patients did not receive any physical therapy or intra-articular injection after the treatment.

Statistical analysis

SPSS version 15.0 software program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Quantitative data were defined as mean ± standard deviation. Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Repeated variant analysis was performed for the time variance of the variables. Bonferroni method was used for multiple comparison tests. Statistical significance value was accepted as $p<0.05$.

RESULTS

Mean body mass index was 33.5±4.6. PRP was applied to 61 knee joints with grade 3 OA, and

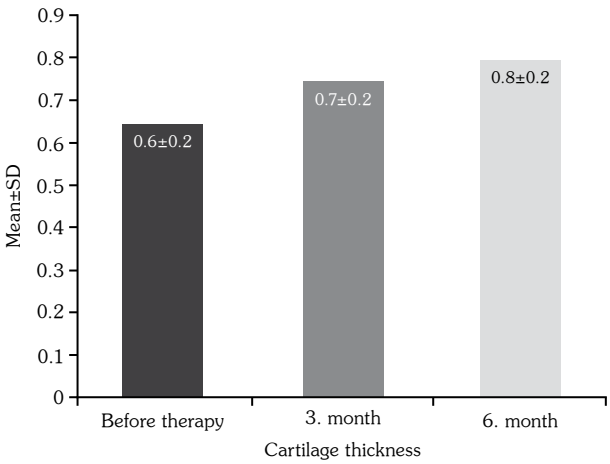

Figure 1. Ultrasound guided cartilage measurement values.

41 knee joints with grade 4 OA. PRP was applied in 56 right and 47 left knee joints. Mean platelet counts were 2512.1±1716, $7x10^3$ in the PRP which we prepared. VAS levels of the patients decreased statistically significantly three and six months after treatment compared to before treatment ($p<0.001$).

All values of WOMAC scale improved significantly compared to before treatment ($p<0.001$). Six-minute walk test results improved in the third and sixth months of treatment ($p<0.05$). Cartilage thicknesses increased significantly three and six months after treatment compared to before treatment ($p<0.05$) (Figure 1).

As an adverse event, synovitis was detected in six patients, which resolved in a few days. Synovitis developed by the first injection in three patients, by the second injection in two patients, and by the third injection in one patient. In 18 patients, temporary and mild or moderate pain developed following the injection. In one patient, severe pain developed and resolved in two days following the first injection. Still, these patients completed the second and the third injections, and pain or synovitis did not repeat. A 67-year-old patient suffered heart attack three months after the injection, so he was delayed for the follow-ups. This patient completed the follow-ups later.

DISCUSSION

Osteoarthritis is a chronic, degenerative disease characterized by progressive cartilage damage. Knee is the most commonly affected joint in OA.[1,2] The aim of management of knee OA is to reduce pain and stiffness, protect or regain range of motion and muscle strength, and decrease dependence in daily living activities. Thus, in recent years, cartilage supporting or improving medications have been investigated. Application of PRP, which consists of GF, appears to be an effective treatment option in the management of degenerative OA.[6]

Platelet rich plasma is known to be used for the last 20 years.[17] However, in musculoskeletal conditions and particularly in OA, GF application has been started to be used in recent years.[18] In 2008, Sánchez et al.[19] compared 60 patients treated with PRP intra-articular injections to 30 patients treated with hyaluronic acid injections for knee OA. They showed that application of GF rich PRP was more effective than hyaluronic acid injections on pain management. Furthermore, in a prospective study, Wang-Saegusa et al.[20] demonstrated significantly improved WOMAC, VAS, Lequesne Index, and Short Form-36 values at the six months follow-up in 261 patients with unilateral or bilateral knee OA. Kon et al.[21] reported 91 patients receiving PRP injections in one week intervals. They noted that 80% of patients were satisfied with the treatment. Moreover, in a systematic review and meta-analysis, Chang et al.[22] reported that PRP applications were more effective in functional improvement in patients with degenerative knee joint pathology compared to hyaluronic acid administration.

In our study, we aimed to show the efficacy of PRP application on functional outcomes and cartilage repair in knee OA. We observed that PRP application improved pain and clinical outcomes which was correlated with the results from the studies of Sampson et al.,[23] Sánchez et al.,[19] Kon et al.,[21] VAS scores and six-minute walk test results improved statistically significantly in the third and sixth months after treatment compared to before treatment. Also, WOMAC scores improved significantly. These results were meaningful with regard to the symptomatic and functional recovery in six months after PRP application (Table 1).

Table 1. Clinical values of patients before and after prp therapy

	Before therapy	1. week	2. week	3. month	6. month	*p*
VAS	8.1±2.1[‡§†¶]	6.2±2.4[*§†¶]	4.6±2.4[*‡§†]	3.9±2.3[*‡]	4.4±2.9[*‡]	<0.05
Walking distance	345.8±75.9[†¶]	350.4±79.1[§¶]	365.4±67.0	369.8±68.6[*]	375.6±84.9[*‡§]	<0.05
WOMAC	16.6±3.1[‡§†¶]	14.4±3.5[*§†¶]	12.4±3.3[*‡]	11.6±4.1[*‡]	12.5±4.6[*‡]	<0.05
WOMAC stiffness	5.8±2.4[‡§†¶]	5.0±2.3[*§]	4.4±2.1[*‡]	4.3±2.1[*]	4.6±2.0[*]	<0.05
WOMAC function	58.9±11.0[‡§†¶]	52.4±12.1[*§†¶]	48.3±12.3[*‡†]	43.9±13.6[*‡§]	45.1±13.5[*‡]	<0.05
WOMAC total	81.5±14.5[‡§†¶]	72.3±16.6[*§†¶]	65.6±15.7[*‡†]	60.2±18.1[*‡§]	62.2±18.5[*‡]	<0.05

VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; * Shows group which is different compared to before treatment; ‡ Shows group which is different compared to first week; § Shows group which is different compared to second week; † Shows group which is different compared to third month; ¶ Shows group which is different compared to sixth month.

Concentration of chondroprotective anabolic cytokines is high in PRP compared to whole blood.[24] They enhance synthesis of type II collagen and chondrocyte by stimulating the proliferation of chondrocytes and pluripotent mesenchymal stem cells.[25] Based on potential benefits of these biological factors, it is hypothesized that PRP may have positive effects on cartilage regeneration. For this reason, *in vivo* and *in vitro* animal studies about pluripotent mesenchymal stem cells and chondrocytes have been continued for the treatment of local cartilage defect and knee OA. Results are promising in terms of macroscopic, histologic, and biomechanical outcomes.[25,26] However, studies on the treatment of human degenerative cartilage lesions with PRP mostly focus on pain, stiffness, functional state, and radiologic outcomes. Such as, Halpern et al.[27] applied a single dose of PRP in 22 patients between the ages of 30-70 with grade 0-3 early knee OA diagnosed by magnetic resonance imaging. Fifteen subjects underwent clinical assessments at baseline, one week, and one, three, six, and 12 months, and evaluated by magnetic resonance imaging at one year. As a result, pain scores significantly decreased, whereas functional and clinical scores increased at six months and one year from baseline. Qualitative magnetic resonance imaging demonstrated no change per compartment in at least 73% of patients at one year.[27]

With the development of musculoskeletal ultrasound in recent years, there are studies using ultrasound to evaluate the quantitative thickness of joint cartilage.[28] Sampson et al.[23] applied three PRP injections at one month intervals to 14 patients with primary or secondary knee OA. They demonstrated statistically significantly improved pain scores during physical activity and at rest at one year follow-up. Besides, they reported eight patients who expressed full satisfaction after the first year of treatment. Sampson et al.[23] measured the medial condyle, intercondylar notch and lateral femoral condyle cartilage thickness of 13 patients by ultrasound. Of these patients, 12 were males older than 18 years old and with a mean body mass index score of 25.0. However, the authors did not record the grade of degeneration. They demonstrated improvement, although not statistically significant, in the cartilage thickness on sonography at lateral condyle and intercondylar notch during the first six months follow-up. They attributed the insignificant statistical results to the limited number of patients.[23] Number of patients in our study was higher than the study of Halpern et al.[27] and Sampson et al.[23] Also, all of our participants were 40 years of age and older with advanced degenerative OA. Mean body mass index of our patients was 33.5 and female-male ratio was 69/13. This may suggest that our study represents better the population with

Table 2. Cartilage thickness measurements with ultrasound

	Before therapy	3. month	6. month	*p*
Cartilage thickness	0.6±0.2[‡§]	0.7±0.2[*§]	0.8±0.2[*‡§]	<0.05

* Shows group which is different compared to before treatment; ‡ Shows group which is different compared to third month; § Shows group which is different compared to sixth month.

degenerative OA. Since the improved thickness of cartilage was preserved statistically significantly at sixth-month follow-ups, we suggest that PRP can be effective in long-term cartilage repair as well (Table 2).

It was shown that the efficacy of PRP changes according to environmental pH and addition of activator like bovine thrombin or calcium chloride before the application. Indeed, 70% of GF in the alpha-granules were released in 10 minutes and nearly all in one hour.[20] It is also estimated that, without this preactivation, pure PRP is activated slowly with the contact of type I collagen when applied to the tissue.[29] There are studies which demonstrate that non-active PRP increases proliferation of the mesenchymal stem cells five fold.[30] Also, in another study, it was reported that activated PRP inhibited chondrogenesis and osteogenesis while inactivated PRP improved cartilage and bone formation *in vivo* and *in vitro*.[31] For this reason, we preferred to use inactivated PRP in our study.

Different manual centrifugation techniques are used to obtain the intended platelet concentration. Food and Drug Administration approved commercial PRP kits are used for some studies. In our study, we prepared PRP manually. To be clinically efficient, PRP platelet concentration was aimed to be at least two fold higher compared to peripheral blood, even though a wide range such as eight fold was reported in the literature.[32] The therapeutic effects are considered to be various due to the standardization and optimization deficiency in the PRP preparation. In our clinic, we prepared a cost-effective protocol. To standardize this protocol, we ensured that platelet counts were 2-8 fold higher compared to whole blood. Thus, we managed a reliable and cost-effective application.

There are studies reporting that PRP is effective in the management of early degenerative OA. Kwon et al.[33] showed that PRP was efficient in all stages of degeneration; but PRP injections had stronger regenerative effects in mid- or mild-mid level OA. Kon et al.[34] compared PRP and hyaluronic acid injection in early degenerative knee OA and demonstrated that PRP injections were more efficient compared to hyaluronic acid injections in the long-term decreasing of pain and symptoms and improving articular functions. They achieved better results in younger patients and patients with lower cartilage degeneration. However, in our study, we included patients with advanced OA (grade 3-4). We showed short and long term clinical, functional and radiological improvement in our patients compared to before treatment. To the best of our knowledge, there is no another study on a homogenous population which includes patients of 40 years of age or older with advanced degenerative OA. Our results support the regenerative effect of PRP injections in patients with advanced degenerative OA. However, a limitation of our study is the lack of a control group.

In conclusion, we demonstrated PRP injections to be a safe, efficient, minimally invasive, and cost-effective method in terms of clinical and functional outcomes and cartilage repair even in patients with grade 3-4 OA. Still, further studies are required with larger sample sizes and control groups including longer follow-ups.

Declaration of conflicting interests

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