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The effect of platelet-rich plasma on chronic pain in osteoarthritic knees

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Abstract

Platelet-rich plasma (PRP) is an autologous blood product with widespread use in recent years to increase regeneration in many joints and tissues. Knee osteoarthritis is a degenerative process increasing with age and causing chronic pain. Therefore, the aim of the study was to investigate the short-term effectiveness of intra-articular PRP injection, used to provide cartilage regeneration, on chronic pain in osteoarthritic knees. 60 patients with stage 1-4 knee osteoarthritis according to the Kellgren-Lawrence grading scale (K-L) were included in the study. Three doses of PRP were injected into the knee joint once every three weeks. All three initial measurements were made before injection. Chronic pain of the patients was evaluated using visual analog scale (VAS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) scales on Day 1, Week 3, Week 6, Week 12, and Month 6. 6 months of follow-ups for all 60 patients were completed. Mean baseline values were measured as follows: VAS 8.63 ± 1.0 , and KOOS Pain 22.11 ± 13.7 , KOOS Sympt 24.80 ± 18.3 , KOOS Function 24.90 ± 15.7 , KOOS Sport 13.00 ± 11.6 , KOOS QoL 16.16 ± 10.2 . Mean values measured during the last follow-up were as follows: VAS 2.30 ± 1.0 , and KOOS Pain 81.20 ± 11.7 , KOOS Sympt 81.78 ± 12.5 , KOOS Function 78.08 ± 10.9 , KOOS Sport 73.58 ± 11.7 , KOOS QoL 68.91 ± 10.7 values. Significant improvements were observed in VAS and KOOS values after injection compared to the baseline values ($p = 0.001$ for all). Treatment of knee osteoarthritis (OA) with PRP injection is safe in terms of adverse reactions. PRP seems to be effective in managing pain and improving quality of life in all osteoarthritis stages, especially in patients with K-L grade 1-2 knee OA.

Keywords: Gonarthrosis, platelet-rich plasma (PRP), kellgren-lawrence grading scale, the knee injury and osteoarthritis outcome score (KOOS), injection.

Introduction

Osteoarthritis (OA) is a slow-progressing joint disease that can cause loss of function after degeneration of the joint cartilage and chronic pain. Prolonged life expectancy has increased the incidence of OA. It is an important cause of morbidity, especially after the 5th decade. Even though significant progress has been made regarding the pathophysiological process of OA, most of the existing treatments today are symptomatic approaches [1,2]. Osteoarthritis is a degenerative disease of the synovial joints that progresses with the loss of articular cartilage. It occurs mainly due to primary (intrinsic defect) or secondary (trauma, infection) causes. It begins with the degradation of the load-bearing joint cartilage surface and subsequent osteophyte formation. The late period of the degenerative disease is characterized by cartilage breakdown that exposes the bone surface.

Biochemically, there is increased water content (decreases with aging), changes in proteoglycans (decrease in content and increase in chondroitin/keratin sulphate ratio). This leads to a decrease in cartilage stiffness and fibrillation of the cartilage surface. The cartilage begins to wear, deep clefts in the cartilage and morphological changes in the subchondral bone occur during the same process. As the synovial fluid infiltrates these clefts, subarticular cyst formation also occurs in the subchondral bone. Furthermore, there is an increase in metalloproteinases and IL-1, which can lead to cartilage degeneration and can have a catabolic effect. Histologically, there is cartilage destruction with loss of the superficial layer of the superficial chondrocyte and eburnation in the subchondral bone [3,4].

There is no definitive treatment for preventing the progression of OA. However, a number of treatment modalities, including modification of daily activities, medical therapy, physical therapy, intra-articular injections, and joint replacement, are used to relieve pain and increase joint function [5]. Among these treatment methods, one of the effective treatment methods preferred before surgical options is usually intra-articular injections.

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Pharmacological treatments (analgesics, non-steroidal anti-inflammatory drugs and intraarticular steroid injection) are only symptomatic, not curative. In addition, these treatments have systemic adverse reactions, especially gastrointestinal side effects [6,7]. Due to its structure, cartilage does not have direct blood supply. Since cartilage receives its blood supply through diffusion from the joint, chondro-protective intra-articular applications with high concentrations have become increasingly common [8]. The popularity of Platelet-Rich Plasma (PRP) among injection products for both relief of symptoms and functional improvement of patients with knee OA has been increasing in recent years [9,10]. PRP is a blood extract obtained by centrifugation of autologous blood. Many studies have revealed that PRP has a chondroprotective effect. Many growth factors with regenerative capacity such as Transforming growth factor beta (TGF- β), Epidermal growth factor (EGF), Platelet-derived growth factor (PDGF), Fibroblast growth factor (FGF) and Insulin-like growth factor (IGF) are present in a-granules of platelets [11-13]. Along with growth factors, other cytokines contained in PRP such as Nuclear factor-kappa B (NF-K B), Interleukin-1 (IL-1) and Nitric oxide (NO) inhibit the inflammatory effects on chondrocytes [14,15].

Various reports including in systematic reviews and meta-analyses have concluded that PRP is an effective and safe bio-approach in the treatment of knee OA compared to other intra-articular injections [16-22].

In studies on PRP, there are usually single or two-dose applications. There are quite few studies in which 3 doses have been administered 3 weeks apart. In our study, we aimed to reveal the reduction in knee pain and increase functional capacity with comprehensive scales such as KOOS and VAS after three doses of PRP application with an interval of 3 weeks to knees with osteoarthritis.

Patients and Methods

This study was carried out with the approval of the local ethics committee of clinical research with the decision numbered 2020/143. Our study was conducted retrospectively with 85 patients between May 2019 and May 2020. 15 patients were excluded because they could not meet the inclusion criteria. 10 of the patients lost during the follow-up.

The complete workflow is shown in Figure 1. Patients aged 32-86 years who applied to the orthopedics and traumatology outpatient clinic of Malatya Training and Research Hospital and had knee pain for more than 6 months were included in the study. Inclusion criteria were visual analog scale (VAS) > 4/10 and stage 1-4 primary knee OA according to the Kellgren -Lawrence (K-L) scale [23].

Exclusion criteria were as follows; any previous knee surgery, acute knee trauma, unstable knee, presence of active infection, diabetes, rheumatic diseases, immunodeficiency, blood diseases causing coagulation disorder (hemophilia, etc.) (Table 1). Anteroposterior and lateral knee X-rays were taken under load for pre-treatment classification. Three doses of PRP were injected into the knee joint at 3-week intervals. Chronic pain of the patients was evaluated using VAS and KOOS Turkish version scales on Day 1, Week 3, Week 6, Week 12, and Month 6 [24].

Table 1. Patient screening criteria

Inclusion Criteria	Exclusion Criteria
1. Patients aged 32-86 years	1. Unstable knee (multiple ligament injury etc.)
2. Stage 1-4 primary knee OA according to the Kellgren -Lawrence (K-L) scale	2. Presence of active infection
3. Knee pain that lasts longer than 6 months	3. Systemic disorders (rheumatoid arthritis, diabetes, immunodeficiency and coagulopathy)
4. Patients with VAS score > 4/10	4. Acute and severe knee trauma
5. Didn't benefit from medical treatment	5. Pregnancy and those with suspicion of pregnancy
	6. Any previous knee surgery

Interventions

PRP preparation was performed as follows. 20 ml venous blood was taken from each patient for each knee and centrifuged at 3200 rpm for 12 minutes in an S&M system (Nevaya medical and health products, Istanbul, Turkey). After this procedure, the average amount obtained for intra-articular application was 2 mL PRP. The process from patient preparation to completion of the injection took approximately 30 minutes.

The patient sat on the edge of the examination stretcher with the knee flexed at 90 degrees and the feet not touching the ground. Injection area on the knee was disinfected with Batticon® (Adeka İlaç Sanayi ve Ticaret A.Ş., Istanbul, Turkey) from the center to the periphery. The PRP portion of the centrifuged liquid was sterile taken into the injector, and then the tip of the injector was changed. PRP was injected into the entire knee joint very slowly under sterile conditions using a 22 gauge needle at a 45° angle through the anterolateral "soft spot". After the application, passive knee flexion and extension exercises were performed. After the injection, the patients were laid on the stretcher on their back and monitored for possible early complications and hypotension for 15 minutes. A single intra-articular PRP injection was performed to all knees in each session. None of our patients received physical therapy and pain-relieving medical therapy (NSAIDs) after injections.

Assessment

All patients were followed clinically by a physician who was not involved in the PRP injection process. All patients were evaluated by VAS and KOOS Turkish Version on Day 1, Week 3, Week 6, Week 12, and Month 6 [24]. The demographic characteristics of the patients and complications and side effects during treatment were recorded.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences version 22.0) was used for all analyses. Quantitative variables were presented with mean $\pm$ standard deviation, and qualitative variables were presented with number and percentage. Kolmogorov Smirnov test was used to check for conformity to normal distribution. One Way

Repeated Measures Analysis of Variance (RM ANOVA) test was used in the evaluation of quantitative data. Bonferroni was used as a post hoc test. $P < 0.05$ was considered statistically significant in all analyses.

Results

49 women (81.7%) and 11 men (18.3%) with a (58.93 ± 12.82) years (range, 32 to 86) were included in the study (Table 2). Preoperative plain radiography detected primary OA in 14 K-L grade-1 patients (23.3%), 14 K-L grade-2 patients (23.3%), 20 K-L grade-3 patients (33.3%), and 12 K-L grade-4 patients (20.0%), respectively (Table 3). All patients were evaluated by Visual analog scale (VAS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) Turkish version before 1st, 2nd, and 3rd injections, and in the 3rd and 6th months. Mean values before first injection were KOOS Pain 22.11 ± 13.7 , KOOS Sympt 24.80 ± 18.3 , KOOS Function 24.90 ± 15.7 , KOOS Sport 13.00 ± 11.6 , KOOS QoL 16.16 ± 10.2 and mean VAS was 8.63 ± 1.0 . The last values at six month follow-up were KOOS Pain 81.20 ± 11.7 , KOOS Sympt 81.78 ± 12.5 , KOOS Function 78.08 ± 10.9 , KOOS Sport 73.58 ± 11.7 , KOOS QoL 68.91 ± 10.7 , and mean VAS was 2.30 ± 1.0 . The improvements in KOOS and VAS scores were statistically significant ($P = 0.001$) (Table 4).

Although the measurements improved significantly after the first injection, positive improvement continued after repeated injections. No adverse effects were observed in patients following PRP injections.

Table 2. Distribution of the sociodemographic characteristics of the patients

Sociodemographic characteristics	n	%
Gender		
Female	49	81.7
Male	11	18.3
Age		
55 age and younger years	25	41.7
56 age and older years	35	58.3

Table 3. Distribution of knee osteoarthritis stage of patients (k-l)

Stage	n	%
Stage 1	14	23.3
Stage 2	14	23.3
Stage 3	20	33.3
Stage 4	12	20.0

K-L :Kelgren-Lawrence

Table 4. Scores of Patients VAS and KOOS Values in Repeated Measures

	First Measurement (Mean±SD)	Second Measurement (Mean±SD)	Third Measurement (Mean±SD)	Fourth Measurement (Mean±SD)	Last Measurement (Mean±SD)	P*
VAS	8.63± 1.0	6.15± 2.2	3.10± 1.0	2.73± 0.9	2.30± 1.0	0.001
KOOS Pain	22.11± 13.7	52.16± 14.0	66.80±11.1	76.35±10.9	81.20±11.7	0.001
KOOS Sympt	24.80±18.3	55.11±15.9	68.41±12.9	78.01±12.0	81.78±12.5	0.001
KOOS Function	24.90±15.7	51.26±15.3	65.75±12.6	73.21±11.5	78.08±10.9	0.001
KOOS Sport	13.00±11.6	44.66±11.6	59.08±11.7	69.25±11.4	73.58±11.7	0.001
KOOS QoL	16.16±10.2	44.98±14.3	55.91±13.0	63.31±12.1	68.91±10.7	0.001

*:One way Repeated Measures Analysis of Variance (RM ANOVA). VAS: Visual Analog Scale. KOOS :The Knee Injury and Osteoarthritis Outcome Score . SD: Standard Deviation.

Discussion

The main finding of the present study is that intra-articular PRP injection is an effective, protective and safe treatment for grade 1-4 knee OA according to the K-L classification in terms of functional improvement and pain reduction in patients in short-term follow-up. A wide range of methods, ranging from conservative approach to surgery, have been used in OA treatment until today. Today, biological applications respecting existing tissue and cost-effective treatment approaches have gained popularity for OA treatment.

Due to its structure, cartilage does not have direct blood supply. Since cartilage receives its blood supply through diffusion from the joint, chondroprotective intra-articular applications with high concentrations have become increasingly common [8]. Platelets are the main cells that reach the affected region first in tissue healing and organize the healing process via the growth hormones and other cytokines they secrete. For all these reasons, PRP acts through the presence of high-concentration growth hormones and inhibition of proinflammatory cytokines. Thus, intra-articular PRP application contributes to regenerative effects by acting against cartilage catabolism in OA pathogenesis.

In the study of Sundman et al., synovium and cartilage tissues obtained from patients who underwent total knee arthroplasty were cultured in two different media, PRP and high molecular weight hyaluronan (HA). Both PRP and HA treatments caused a decrease in cartilage catabolism in OA joint tissues, while PRP caused an increase in cartilage synthetic activity compared to HA. These results showed that PRP acts to stimulate endogenous HA production as well as reduce cartilage catabolism. The authors concluded that the antinociceptive and anti-inflammatory activities of PRP will be clinically beneficial in OA joints to reduce pain and modulate the disease process [12].

Since PRP is prepared from autologous blood, risks such as allergic reactions and disease transmission are not observed. There are no studies in the literature showing that PRP promotes hyperplasia, carcinogenesis, or tumor growth. Growth factors that are the mediators of PRP act on cell membranes rather than cell nuclei and activate normal gene expression [25]. PRP has shown promising results for the treatment of various musculoskeletal injuries and due to its ease of use, low cost and minimally invasive nature, has gained popularity in knee OA treatment [26,27]. The fact that it does not require hospitalization after the application is a very important gain for the healthcare workforce.

In a prospective study, three doses of intra-articular PRP injections were applied to 115 knee joints of 100 patients with knee joint degeneration. 12-month follow-up results showed that this procedure is safe and improves quality of life in young patients with low degree of joint degeneration [28].

In a study conducted by Filardo et al. (2010) on the duration of effect of PRP applied intra-articularly to knees with OA, a general decrease was observed in all evaluated parameters, although pain and functional results at 24 months remained above the baseline values compared to 12 months. These results indicate that the repetition of PRP at certain intervals decreases its effectiveness. In addition, in the same study, although the effectiveness of PRP decreased over time, it was observed that this decrease was minimal in young patients with less cartilage degeneration [29].

In a randomized controlled clinical study, 78 patients (156 knees) with knee osteoarthritis were divided into three groups, the first group was injected with two doses of PRP (administered 3 weeks apart), the second group was injected with a single dose of PRP, and the third group was injected with a single dose of saline. It was concluded that both groups that received intra-articular PRP injection had significantly better Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at 6 month follow-up compared to the saline group [30].

Clinically, the most significant findings of the present study are that there is a significant improvement in knee OA, especially in the symptoms related to pain, as shown by the VAS results. There is an increase in the quality of life and satisfaction of patients revealed by the KOOS questionnaire results. In addition, it has been observed that as the number of PRP applications increases, there is a positive effect on pain and functional outcome. In the short-term the advantage of this conservative treatment modality is that although the mechanisms leading to clinical effects are not fully understood, the current literature accepts PRP as a safe practice and does not report any serious complications and adverse

reactions [30, 31].

The present study covers a relatively short follow-up period that does not evaluate long-term outcomes of PRP. Therefore, long-term effects of PRP application on knee OA pain cannot be fully evaluated. Another limitation of the present study is the low number of patients. It is believed that the effect of PRP on pain and vital activities of patients with OA will be better understood through studies with larger samples and longer follow-up periods.

In conclusion, it has been noted that intra-articular PRP application in patients with stage 1-4 knee OA is an effective treatment during short-term follow-up, especially for reducing pain and improving the quality of life of patients.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

This study was carried out with the approval of the local ethics committee of İnönü University clinical research with the decision numbered 2020/143.

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