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ORIGINAL ARTICLE

Evaluation of the results of intra-articular platelet-rich plasma injections in patients with knee osteoarthritis

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ABSTRACT

Objective: Osteoarthritis (OA) is the most common form of arthritis, resulting from the degradation of articular cartilage, degradation and proliferative reformation of subchondral bone and a low degree of synovitis that leads to a reduced quality of life. There is no established cure for knee OA. Treatment modalities which have an effect on the underlying biological processes responsible for OA pathogenesis may have potential. One such modality drawing attention is platelet-rich plasma (PRP) injections. In this study, we aimed to evaluate the effects of PRP injections retrospectively in patients with knee OA and the outcomes of two different volume injections.

Materials and Method: A total of 314 patients were included in the study. After baseline physical examination, each patient was evaluated with VAS score and WOMAC before the procedure. All the patients received two intra-articular injections one month apart with autologous PRP and were followed up for a minimum period of 1 year (range, 12-34 months). Two weeks after the injections, the physical examinations of the patients and their evaluations with VAS scores and WOMAC criteria were repeated.

Results: Both VAS scores and WOMAC scores showed significant differences after the first injection ($p<0.05$). Although both scores increased after the second injection, the differences were not significant ($p>0.05$). We also showed that as BMI increased both VAS scores and WOMAC scores increased.

Conclusion: Although our study showed that PRP injections have favorable improvements in the management of knee OA such as reducing the pain and decreasing joint stiffness, PRP injections in the treatment of knee OA needs more standardized research.

Keywords: osteoarthritis, osteoarthritis PRP, PRPVAS, VASknee osteoarthritis, knee osteoarthritis.

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INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, resulting from the degradation of articular cartilage, degradation and proliferative reformation of subchondral bone and a low degree of synovitis that leads to a reduced quality of life [1,2]. According to the results of Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability and 38th highest in disability-adjusted life years [3,4]. Knee OA accounts for approximately 85% of the burden of OA worldwide [5]. The global burden of knee OA is comparable with that of patients with cardiac dysrhythmias, liver cirrhosis or stage IV kidney disease [6]. Moreover, with the aging of the population and increase in obesity throughout the world, it is expected that the burden of OA will become a major problem for healthcare systems globally [2].

There is no established cure for knee OA. Knee OA management strategies include improvement in function, reduction in disability, pain relief and hence, improved quality of life (QoL). Recommended medical therapies like analgesics and anti-inflammatory agents have short-term clinical benefits with small to moderate effect [7]. Intra-articular hyaluronic acid (HA) is controversial with inconsistent recommendations [8]. Intra-articular corticosteroids are generally recommended and their short-term effects were found to be significantly greater than those of intra-articular hyaluronic acid [9]. However, they have short-term pain relief ability [8]. Although arthroplasty is a common and effective procedure for advanced hip or knee OA, there is a risk of serious medical and surgical complications [5]. This is important especially when you take into account the fact that the patients needing surgery are older.

Treatment modalities which have an effect on the underlying biological processes responsible for OA pathogenesis may have potential. One such modality drawing attention is platelet-rich plasma (PRP) injections. PRP is an autologous fraction of human blood and has a greater concentration of platelets than baseline levels of whole blood [10]. PRP functions through platelet degradation products, including multiple growth factors, which have well-defined roles in a range of critical tissue healing processes such as chondrocyte apoptosis inhibition, bone and vessel remodeling, inflammatory modulation and collagen synthesis [11].

In this study, we aimed to evaluate the effects of PRP injections retrospectively in patients with knee OA and the outcomes of two different volume injections.

PATIENTS AND METHODS

The present study was conducted according to the Helsinki Declaration of 1975. All patients signed a written informed consent following a full explanation of the treatment protocol. We recorded patients' demographics and pre-injection data, including age, sex, body mass-index (BMI), visual analogue scale (VAS) pain score and Kellgren-Lawrence classification (Table 1). BMI was calculated as weight in kilograms divided by the square of height in meters. Only the patients between 50-70 years of age who had Kellgren-Lawrence grade 2-3 OA and fulfilling American College of Rheumatology (ACR) criteria of OA were included. Patients were excluded if they had severe OA, glucocorticoid or hyaluronic acid injections in the past 6 months, ongoing anticoagulation therapy.

The primary outcome was the VAS pain score. Secondary outcome includes Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). After baseline physical examination, each patient was evaluated with VAS score and WOMAC before the procedure.

All the patients received two intra-articular injections one month apart with autologous PRP

Table 1. Preinjection demographic findings.

Variables	Unilateral Knee Injection	Bilateral Knee Injection
Male (number of patients)	71	51
Female (number of patients)	65	127
Age (mean)	52.9	57.6
BMI (kg/m^2)	29.2	30.4
Kellgren and Lawrance -II (number of patients)	53	76
Kellgren and Lawrance -III (number of patients)	83	102

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Table 2. VAS Scores and WOMAC Scores before and after injections.

Variables	Preinjection	After the First Injection	After the Second Injection
Unilateral Knee Injection			
VAS Score	5.44 (± 2.1)	2.72 (± 0.67)	3.14 (± 1.12)
WOMAC Score	63.93 (± 7.3)	39.67 (± 3.2)	41.72 (± 4.5)
Bilateral Knee Injection			
VAS Score	5.36 (± 2.2)	3.11 ± (0.71)	3.47 ± (1.24)
WOMAC Score	67.41 (± 9.1)	41.52 (± 4.5)	43.25 ± (6.1)

and were followed up for a minimum period of 1 year (range, 12-34 months). Two weeks after the injections, the physical examinations of the patients and their evaluations with VAS scores and WOMAC criteria were repeated (Table 2).

PRP preparation

A peripheral venous blood sample of 15 mL was obtained from the upper extremities of the patients, and 1.5 mL of the sample was used for a platelet count. The remaining 13.5 mL was mixed in a 15-ml sterile centrifuge tube containing 1.5 mL of 3.2% sodium citrate and centrifuged at 1800 rpm for 10 minutes in a centrifuge (Digisystem, New Taipei City, Taiwan). After centrifugation, 6 mL of PRP was obtained from the middle fraction of the blood sample between the erythrocytes and the plasma.

Intra-articular PRP injection

Lateral to patellar tendon, a 25-gauge needle was slowly inserted into inferior lateral aspect of the patella at a 45-degree angle with the knee flexed to 90 degrees. The injection was stopped if the patient experienced pain or a sensation of pins and needles. For unilateral knee OA, 5 ml PRP was administered. For bilateral knee OA, 3 mL of PRP was administered into each knee joint. The patient was discharged after the injection. Limited movement was allowed in the knee for 24 hours, and resting was recommended in the case of pain. Non-steroidal inflammatory drug use was restricted in both groups because of the possibility of platelet function inhibition. Intermittent icepack compression was recommended to relieve discomfort in the knee.

Statistical analysis

The data were analyzed using SPSS version 23.0 (IBM statistics for Windows version 23, IBM Corporation, New York, NY). A Shapiro-Wilk test revealed that VAS scores and WOMAC scores were normally distributed. Paired sample t-tests were used to examine changes within the groups. Pearson's correlation test and Spearman's rho test were used to determine whether any correlation existed between variables. Quantitative variables were indicated as mean and standard deviation (±). The results were considered statistically significant when the p-value was < 0.05.

RESULTS

A total of 314 patients were included in the study. Of them, 192 was female, 122 was male. 178 patients had bilateral knee OA injections at the same time. The remaining patients had unilateral injections.

Both VAS scores and WOMAC scores showed significant differences after the first injection ($p<0.05$). Although both scores increased after the second injection, the differences were not significant ($p>0.05$).

The mean platelet count of the PRP was 1.681×10^6 ($\pm 3.53 \times 10^5$) and that of whole blood was 2.41×10^5 ($\pm 4.67 \times 10^4$). We were not able to show a significant correlation between the mean platelet count in the PRP and outcomes (Pearson's correlation coefficient $r = 0.192$). The mean BMI was 29.8 kg/m^2 (±4.15). On the other hand, as BMI increased both VAS scores and WOMAC scores increased. (Pearson's correlation coefficient $r = 0.872$).

DISCUSSION

Our study demonstrated that PRP injections into the knee joint in patients with mild to moderate knee OA proved to be effective in reducing pain, as shown by the improvement in the VAS scores 3 months after the injections. This could be due to the immediate and sustained release of growth

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factors over a prolonged period, which enhances healing resulting in sustained clinical effects [12]. Nevertheless, we believe that PRP has modulatory effects on synovial cavity that cannot be explained merely by the effects of the one specific growth factor that it contains. PRP use has been advocated as a treatment option in all stages of knee OA [1]. Intra-articular PRP injections in patients with knee OA show significant improvements in pain reduction, improved symptoms and QoL [13,14].

The ideal PRP volume has not been studied enough yet. Most of the studies have focused on the number of platelets in PRP rather than its volume, or how often to apply it. Spakova et al., [15] and Paterson et al., [16] have used 3 ml PRP whereas Patel et al., [17] and Sanchez et al., [18] have used 8 ml PRP. Our previous clinical experience was that PRP injections of more than 6 ml were found to be uncomfortable by patients because they were painful.

There have been lots of randomized controlled trials in knee OA mostly comparing PRP to intra-articular injection of HA. All studies are of low to moderate methodological quality and use variable PRP protocols. In general, results showed that PRP is a safe treatment with potential to provide symptomatic benefit for OA at least in the short term. The enhanced effectiveness of PRP for pain treatment and knee joint function in comparison to HA or placebo and positive outcomes in all stages of knee OA have all been reported [19-21]. It has also been shown in a few in vitro as well as clinical studies that combination of PRP with HA may exert a synergistic effect [22].

In knee OA, PRP injections aim to stimulate cartilage repair and offer relief to other osteoarthritic symptoms, potentially delaying the need for joint replacement surgery. PRP injections have shown to influence the entire joint environment, leading to a short-term clinical improvement [23]. Recently a randomized clinical trial has shown that knee injections of PRP did not significantly improve knee pain or reduce medial tibial cartilage volume loss at 12-month follow-up, compared with placebo saline injections, in people with symptomatic mild to moderate radiographic knee OA [24]. However, Lin et al showed that intra-articular injection of PRP can significantly reduce the subchondral bone marrow edema and the level of biomarkers in synovial fluid of the symptomatic knee osteoarthritis [25].

Intra-articular glucocorticoid injections are efficacious for short-term pain relief, commonly lasting a few weeks, and may be a useful adjunct therapy, particularly for an upcoming life event [26]. Regular injections are not recommended; in patients with symptomatic knee OA, 2 years of treatment with triamcinolone, administered intra-articularly every 3 months, resulted in greater loss of cartilage volume than saline injections [27].

There are many controversies with regard to the best volume and formulation of PRP, the number and frequency of injections, the need for ultrasound guidance, the speed and duration of spins to isolate the PRP, whether an activating agent is necessary and co-administration with a local anesthetic. The variety of PRP application process, including PRP collection volumes and preparation protocols, reflects an absence of consistency among trials. Cell membrane receptors are limited, so very high concentrations of growth factors probably have no beneficial effect on cell stimulatory processes [28]. Different preparation methods are known to yield different PRP product in the same donor [29]. Intra-individual variation in the PRP product with the same technique at different time frames is also noted [30]. The ideal PRP needed for treatment of knee OA is not clearly defined and requires further standardization [22].

The ACR strongly recommends weight loss and exercise as non-pharmacological cures for knee OA. Oral and topical non-steroidal anti-inflammatory drugs and intra-articular glucocorticoid injections are strongly recommended, whereas there is no recommendation about PRP injections [31]. In a recent randomized clinical trial, intra-articular injection of PRP, compared with injection of saline placebo, did not result in a significant difference in symptoms or joint structure at 12 months among patients with symptomatic mild to moderate radiographic knee OA 24. Although the authors reported that that the PRP preparation used in their study contained elevated concentrations of growth factors and cytokines that promote tissue healing and inhibit inflammatory processes, we strongly believe that it is not the concentration that shows the benefit, but the effect of the content.

High BMI or BMI ≥25 kg/m^2 is one of the most critical risk factors of OA and needs to be included in global- and national-level prevention policies. The increasing prevalence of overweight and obesity is

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contributing to the increasing burden of OA [32]. Consistent with this fact, the study population consisted of a large proportion of overweight patients. We also found that PRP application was less effective in obese patients in our study.

Although our study showed that PRP injections have favorable improvements in the management of knee OA such as reducing the pain and decreasing joint stiffness, PRP injections in the treatment of knee OA needs more standardized research. Stronger medical evidence is required, because of confusing literature.

Author contribution

Study conception and design: ÖU; data collection: ÖU; analysis and interpretation of results: ÖU; draft manuscript preparation: ÖU. The author reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee (Protocol no. E2-22-2001 / 22.06.2022).

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Conflict of interest

The authors declare that there is no conflict of interest.

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