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The Effects of Intra-articular Platelet-Rich Plasma Injection on Severity of Knee Osteoarthritis

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Abstract:
Introduction: The prevalence of osteoarthritis (OA) continues to rise along with the increase in life expectancy. When orally administered drugs are ineffective, intra-articular injection (IA) is the next treatment of choice. Intra-articular injection therapy with platelet-rich plasma (PRP) has emerged as a conservative treatment for knee osteoarthritis. This study aims to investigate the effect of IA-PRP on the severity of knee OA.
Methods: This study is a clinical trial conducted at Puri Raharja Hospital Bali from January to June 2022. Fifty-three patients with knee OA grades 2-3 Kellgren-Lawrence were injected with 2 ml PRP for each intra-articular injection. Two injections were done at one-week intervals. The severity of knee OA was determined by Western Ontario and McMaster's University Osteoarthritis Index (WOMAC) score.
The score was assessed before injection and two weeks after the first injection.
Results: The mean age of the subjects was 64.79 years, dominated by females (64.2%), normal body mass index (35.8%), suffering from OA grade II (56.6%) based on radiographs, grades I and III on ultrasound of osteophyte size (34%), and grade 2A on ultrasound of cartilage (39.6%). After PRP injection, there was a decrease in the WOMAC score of pain (Mean Difference (MD) 4.77 ± 4.98, $p<0.001$), stiffness (MD 1.71 ± 2.2, $p<0.001$), functional disability (MD 16 .75 ± 14.4, $p < 0.001$), and total WOMAC (MD 24.77 ± 16.6, $p < 0.001$).
Conclusion: Intra-articular injection of PRP 2 times in 1-week intervals can reduce the level of pain, stiffness, and functional disability in patients with knee OA grade 2-4.

Keywords (11Bold) - *PRP, intra-articular injection, genu, OA, WOMAC*

I. INTRODUCTION

Osteoarthritis (OA) of the knee is one of the leading causes of musculoskeletal disability. Osteoarthritis is characterized by gradual abrasion of the articular cartilage, osteophyte formation, subchondral bone sclerosis, and arthritis.[1] The number of people with osteoarthritis continues to rise along with the increase in life expectancy. The estimated global prevalence of knee OA in people over 15 years old was 16%, while in people over 40 years old, it was 22.9%. There were approximately 86.7 million new cases of knee OA worldwide in 2020.[2]

Clinical guidelines recommend a variety of non-surgical procedures to treat knee osteoarthritis. Non-pharmacological treatments include patient education and self-management with exercise, weight loss, use of crutches and supports, shoe and insole modifications, and local cooling. Pharmacological therapy consists of the

use of acetaminophen, non-steroidal anti-inflammatory drugs, and opioids.[3],[4],[5] If orally administered drugs are ineffective, intra-articular corticosteroid (IA) and hyaluronic acid (AH) injections are the next non-operative treatment of choice.[6]

The IA-AH is widely used in Japan because it is highly recommended in the guidelines for the management of knee osteoarthritis published by the Japanese Orthopedic Association (JOA).[7] However, the IA-AH is not recommended in the related guidelines published by the American Academy of Orthopedic Surgeons.[5] Currently, the efficacy of the IA-HA for knee osteoarthritis is considered controversial.

Therapy with platelet-rich plasma (PRP) has emerged as a biological conservative treatment for knee osteoarthritis. PRP is broadly defined as the plasma fraction containing abundant platelets, although there is no clear definition in terms of platelet count or platelet concentration. PRP has high concentrations of autologous growth factors and secretory proteins, which can enhance the cellular-level healing process.[8]–[10] PRP has been used in clinical settings to promote healing. Several studies have shown that treatment involving IA-PRP is superior to the use of IA-HA in terms of improving the total score of The Western Ontario and McMaster's Universities Osteoarthritis Index (WOMAC) and other parameters.[6] However, these studies were conducted in Europe and the United States, while the therapeutic efficacy of IA-PRP has not been adequately evaluated in Indonesian patients with knee osteoarthritis. Recent studies have shown that platelet function differs between ethnicities. Therefore, we aim to investigate the effect of IA-PRP on the severity of knee OA.

II. METHODS

Sample Selection

This study has been approved by a local ethical committee with ethics number 01_028/UNBI/EC/V/2021. A clinical trial was conducted at Rheumatology Clinic in Puri Raharja Hospital, Bali, Indonesia, in January-June 2022. All patients signed an informed consent form. Inclusion criteria were patients with knee pain for at least three months, aged between 40 and 80 years old, and the results of radiological examination of the knee obtained OA grade 2-4 based on the Kalgreen Lawrence classification. Exclusion criteria were polyarticular rheumatic disease; knee arthroscopy <1 year; intra-articular injection of hyaluronic acid (HA) or steroids in the past three months; current infection, diabetes metabolic disease, rheumatoid arthritis disease, coagulopathy disorders, anticoagulant or antiplatelet aggregation therapy, immunodeficiency disease, taking nonsteroid anti-inflammatory drugs (NSAIDs) 2 weeks before the procedure, knee trauma; inflammation; and tumors around the knee.

PRP Preparation

The PRP was prepared according to the manufacturer's (T_Biyoteknoloji LTD, Turkey) guidelines. To avoid the influence of dietary intake on purified PRP, patients were instructed to fast for 4 hours prior to blood collection on the day of injection. Water intake was not restricted. Using an aseptic technique, approximately 36 mL of venous blood was drawn from the antecubital vein in an effort to avoid irritation and trauma to the platelets. Blood is drawn in 1-2 extraction tubes containing 3.8% sodium citrate as an anticoagulant. Next, the tubes were centrifuged at 2400 rpm for 8 minutes at room temperature to separate the blood in each tube into plasma, buffy coat, and remaining red blood cells. The procedure was carried out entirely in a biosafety cabinet. Platelet-poor plasma (PPP), which represents the top 2 mL fraction in each tube, was aspirated and discarded. Platelet-rich plasma (PRP), which is located above the deposited red blood cells but excludes the buffy coat layer, was carefully aspirated from each tube using a pipette. For each patient, 2 mL PRP was used for intraarticular injection.

Injection Procedure and Follow-Up

The patient was placed in a supine position with the knee in 20° flexion. Under aseptic conditions, 2 mL of PRP was injected into the suprapatellar bag via a superolateral approach using a 21 gauge needle. No local anesthetic was used. Blood pressure, heart rate, and body temperature were measured before and 30 minutes after the injection. After injection, patients were instructed to refrain from physical exercise for at least 24 hours, but no

restrictions were set regarding activities of daily living. Two intra-articular injections of PRP were given at 1-week intervals. Injections were administered by the same physician involved in the recruitment and assessment of participants (IARWM).

To assess the safety of IA-PRP, adverse events that occurred during treatment and the follow-up period were documented at each visit. The onset, duration, and severity of events such as knee pain, stiffness, swelling, and burning sensation near the injection site were recorded in detail. The only drug that was allowed during clinical trials was acetaminophen. To assess the feasibility of IA-PRP in managing knee osteoarthritis, all patients were evaluated at baseline (before the IA injection procedure) and at two weeks after the first injection. The following measures were assessed: NRS pain score, change in ROM using a goniometer, and WOMAC score.

Statistical Analysis

Differences between outcome measures were evaluated by using paired t-tests. P value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS Statistics 21.0 for Windows (IBM Corp, New York)

III. Result

Our study included 53 patients. The mean age of the subjects was 64.79 ± 8.61 years, dominated by female gender (64.2%), normal body mass index (35.8%), and suffering from OA grade II (56.6%) based on Kellgren-Lawrence radiographs, grades I and III on ultrasound of osteophyte size (34%), and grade 2A on ultrasound of cartilage (39.6%). The characteristics of the study are shown in **Table 1.**

Table 1. Characteristics of The Study

Characteristics	n=53
Age	64,79 ± 8,61
Gender, n (%)	
Female	34 (64,2)
Male	19 (35,8)
Body Mass Index, n (%)	
Normal	19 (35,8)
Overweight	16 (30,2)
Obesitas I	15 (28,3)
Obesitas II	3 (5,7)
VAS, mean ± SD	4,5 ± 0,77
Extension ROM, mean ± SD	170,83 ± 6,66
Flexion ROM, mean ± SD	55,15 ± 13,43
OA grades based on Kellgren-Lawrence, n (%)	
II	30 (56,6)
III	23 (43,4)
OA grades based on osteophyte USG, n (%)	
1	18 (34)
2	17 (32,1)
3	28 (34)

OA grades based on cartilage USG	
1	5 (9,4)
2	3 (5,7)
2A	21 (39,6)
2B	14 (26,4)
3	10 (18,9)

PRP injection twice can significantly reduce the total WOMEC score and WOMAC subscale for pain, stiffness, and impaired functional activity (**Table 2**).

Table 2. Comparison of WOMAC Before and After PRP

Variable	Mean Difference ± SD	95% Confidence Interval	P value
Total WOMEC	24,77 ± 16,6	20,19 - 29,35	<0,001
WOMEC Pain	4,77 ± 4,98	6,14-3,4	<0,001
WOMEC Stiffness	1,71 ± 2,2	2,32-1,1	<0,001
WOMEC Functionality	16,75 ± 14,4	20,72-12,7	<0,001

IV. DISCUSSION

This study reported that intra-articular injection of PRP twice in intervals of 1 week can reduce the severity of knee OA measured by WOMAC score. This study was supported by a similar study by Sampson et al., where thrice IA-PRP at 4-week intervals promotes favorable outcomes at 12-month follow-up measured by visual analog scale (VAS) and Knee Injury and Osteoarthritis Outcome Scores (KOOS).[11] A study by Kon et al. revealed that 5 ml PRP thrice daily for 21 days created significant improvement in VAS and International Knee Documentation Committee (IKDC) scores.[12] A study by Patel et al. reported significant improvement in WOMAC score after twice PRP injections in a 3-week interval. Napolitano et al. reported that 5 ml PRP thrice weekly improved NRS and WOMAC scores at one-week and six-month follow-up.[13] A retrospective study in Turkey stated that the administration of 4 ml PRP once or thrice in a 1-week interval significantly reduced total WOMAC score and all WOMAC subscale scores at 6-month and 12-month follow-ups.[14] A clinical trial in Japanese society reported that 6 ml of IA-PRP thrice in 1-week intervals can decrease VAS pain scores and Japanese Knee Osteoarthritis Measure (JKOM) scores on 1-month and 6-month follow-ups.

In a meta-analysis of 10 RCTs, IA-PRP injections were found to be more effective than placebo and IA-HA injections in reducing NRS pain scores.[15] Different results were found in a randomized clinical trial that compared IA-PRP vs. placebo injection in knee OA, which revealed that there was no significant difference in knee pain score and medial tibial cartilage volume as assessed by magnetic resonance imaging (MRI) on 12-month follow-up.[16] The difference with this study is probably due to the difference in outcome parameters. Even though there is already a meta-analysis of RCT, the outcome parameter was using NRS pain score, while this study used WOMAC, which is more objective and specific to knee OA.

There is variability in PRP dosage, amount of injection, and outcome parameters across the study. This study used 2 ml PRP twice in 1-week intervals. A survey by Atik et al. revealed that a PRP injection twice is better than a single injection to decrease WOMAC score, but there was no significant difference between twice and thrice PRP injections.[14] A study by Patel et al. reported no difference between a single PRP injection and twice PRP injection. The dosage of PRP in the previous study was ranging from 2 ml-8 ml,[17] Most studies use 5 ml of PRP.[12], [13] A clinical trial in Japan used 6 ml PRP,[8] Clinical trial in Australia used 5 ml PRP, [16] While in Turkey, used 4 ml PRP. [14] Injection intervals were varied from 4 weeks,[11] Three weeks,[18] 21 days, [12] And one week, with most studies using a weekly interval. When there is no difference between twice-

injected and a greater number of injections, it's preferable to use the less amount of injection and shortest interval for patient comfort and compliance. Further study is needed regarding how many injections are required, the interval of injections, and the PRP dosage in each infusion.

The limitation of this study is there is no control subject using a placebo or other treatment such as hyaluronic acid. This may create bias with the effect of self healing on knee OA. Another limitation is this study only evaluates WOMAC scores in a short follow-up period. Different results might occur over a long period. In addition, this is a single-center study with a small number of samples. The inclusion criteria of our research are Kellgren Lawrence, grades 2-4, but we only found patients with grades 2-3.

V. CONCLUSION

Intra-articular injection of PRP twice in 1-week intervals can reduce the level of pain, stiffness, and functional disability in patients with knee OA grade 2-4 Kellgren-Lawrence based on WOMAC score. To elucidate this topic, randomized controlled trials with longer follow-ups are needed. Further studies regarding PRP dosage and amount of injection are also needed.

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