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Research Article

A Comparative Study of Intra-Articular Knee Injection of Leukocyte-Poor Platelet-Rich Plasma Compared to Corticosteroids and Local Anesthetics in Patients with Knee Osteoarthritis

Abbas Ahmadi[1,2], Reza Atef Yekta[1,3], Alireza Khajeh Nasiri[1,3], Nader Ali Nazemian Yazdi[1,4], Mohsen Cheraghi[5], Mehdi Sanatkar[1], Ebrahim Espahbodi[1]*

[1]*Pain Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran.*

[2]*Department of Anesthesiology, Shahid Beheshti Hospital, School of Medicine, Qom University of Medical Sciences, Qom, Iran.*

[3]*Department of Anesthesiology, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.*

[4]*Department of Anesthesiology, Amir Alam Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.*

[5]*Physical Medicine and Rehabilitation Department and Research Center, Shohadaye Tajrishi Hospital, School of Medicine, Beheshti University of Medical Sciences, Tehran, Iran.*

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ABSTRACT

Background: Knee osteoarthritis (OA) is the most common reason for orthopedic secondary care referral. And it is one of the main causes of disability in adults worldwide. It is estimated to affect between 10 to 25% of patients over the age of 60. Intra-articular corticosteroid injection (IA CS) and physical therapy were the two choices in an attempt to provide symptomatic management or deferred surgery. There is a growing trend is intra-articular platelet-rich plasma (IA PRP) injection to reduce pain and improve function in OA patients. PRP is divided into two types: leukocyte-poor platelet-rich plasma (LP-PRP) and leukocyte-rich platelet-rich plasma (LR-PRP). It was shown that LR-PRP increases pro-inflammatory factors and also decreases anti-catabolic mediators, and LP-PRP has the opposite aspect.

Methods: In our research 40 patients were divided into two equal groups, IA corticosteroid and leukocyte-poor platelet-rich plasma (LP-PRP) 40 cc of blood from the basilic vein of the upper limb is used with two step centrifugation. The final samples were 4 millilitres product injected intra-articular. group two (corticosteroid (CS)) received an intra-articular injection of triamcinolone acetate (Kenalog) 40 mg/ml along with 4 ml of lidocaine 0.02% (Abureyhan Co.) for a total of 5 ml. The needle used is a 22-gauge pencil-point Quincke needle (Dr. Japan Co, Ltd), which is performed with the Sonosite Edge II ultrasound guide and in an anterior-lateral manner in the knee joint. Pain was assessed on a visual analogue scale (VAS range 0-10 points) before, one week, one month, two month and 3 months after the operation. The WOMAC questionnaire was also filled before injection and three months following injection and other variables were examined.

Results: There were no significant differences between the groups across all the baseline parameters including age, sex, body mass index and comorbidities including high blood pressure, diabetes and smoking. Both injection groups were effective in reducing patients' pain from one week to three months after injection. The level of pain in the first week after injection was significantly lower in the corticosteroid group than in the PRP group. In the first month and the third month after the injection, the pain reduction according to mean scores of VAS was the same in both groups.

Conclusion: In short, one injection of PRP can reduce the pain of patients with osteoarthritis of the knee as much as corticosteroids during a three-month treatment process. Considering the possible side effects of corticosteroids, this alternative treatment can be considered with further investigation.

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: eespahbodi@yahoo.com;

Introduction

A recent analysis of primary care referrals to secondary medical care indicates that knee osteoarthritis (OA) is the most common reason for orthopedic secondary care referral [1]. In addition, symptomatic OA disease is one of the main causes of disability in adults worldwide, which has a significant economic impact [2]. In addition, the incidence of knee OA continues to increase [3-4]. It is estimated to affect between 10 to 25% of patients over the age of 60 [5-6]. These findings emphasize the necessity of effective pain management options, including Intraarticular (IA) injections, physical therapy, medication and lifestyle modification, especially in the case of a long wait for surgical intervention [7-8]. Which negatively affects the patient's quality of life if treatment principles are not followed. Intraarticular corticosteroid (IA CS) injections are often prescribed prior to referral to secondary care in an attempt to provide symptomatic management or postponed surgery. In general, there is a possibility of associated side effects that do not seem to provide symptomatic improvement for more than 6 weeks [9]. One of these therapeutic methods that has a growing trend is intra-articular platelet-rich plasma (IA PRP) injection, which has been shown in systematic reviews and meta-analyses to reduce pain and improve function in OA patients [10]. PRP is not associated with the harmful effects of IA CS on cartilage, making it a safer option, especially when repeated injections may be required [11]. Platelets are cellular elements without a cell nucleus that exist in large numbers in human blood and have hemostatic, immune, and inflammatory and anti-inflammatory properties [12]. Platelets contain a number of different granules including alpha, dense and lysosomal types. Alpha-granules are the most abundant in platelets, and also store high levels of a wide variety of bio specific molecules, including fibrinogen, von Willebrand factor (vWf), factor V, and factor XIII, factor IX, protein S, antithrombin and plasminogen. In addition, platelets contain chemokines and a large number of growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), Fibroblastic growth factor (FGF) and transforming growth factor (TGF) [13-15]

Platelets not only contribute to homeostasis, but also influence immune responses against potential infectious agents through their interactions with endothelial cells and white blood cells [12]. In general, PRP is divided into two types: leukocyte-poor platelet-rich plasma (LP-PRP) and leukocyte-rich platelet-rich plasma (LR-PRP). Some researchers have suggested that LR-PRP may have more catabolic effects in intra-articular injections because its catabolic activity is greater, compared to LP-PRP whose anabolic effects are greater in the formation of scar tissue [16]. In another study, it was shown that LR-PRP increased pro-inflammatory factors such as IL-1b, IL-8 and fibroblast growth factor-2, as well as decreased anti-catabolic mediators such as hepatocyte growth factors and metalloproteinase tissue inhibitors [17]. Although the use of PRP technique is still not the standard method in the treatment of knee osteoarthritis. The method of administration and preparation and the number of injections and their intervals are still discussed. However, IA PRP injection has been shown to reduce inflammatory markers and enhance anti-inflammatory mediators [18]. There is also some debate about how many times to inject IA PRP, with some authors suggesting the use of 3 injections [19]. On the other hand, some researchers consider only one injection to be enough [20]. However, many questions remain unanswered, including the optimal number of PRP injections and its composition, for example, the type with low leukocyte compared to the high leukocyte, or its short and long-term effect compared to corticosteroids [21]. Considering the priority of PRP injection with low leukocyte inside the joint and the need to compare this method in the short and long term with the common method such as intra-articular corticosteroid injection, we conducted this research.

Methods

This research was conducted as a randomized, single-blind, parallel-group clinical trial on patients with knee osteoarthritis who referred to the pain clinic of Imam Khomeini Hospital (RA) in Tehran, Iran, July 2021 to March 2023. All patients signed written informed consent prior to injections. The research was approved by the ethics committee number IR.TUMS.NI.REC.1401.081 of Tehran University of Medical Sciences and IRCT20211017052785N5. This study follows most of CONSORT guidelines.

131 patients who visited the pain clinic from July 2021 to March 2023 with knee pain were examined. 91 patients were excluded from the study for various reasons and finally 40 patients were divided into two equal groups by equal randomization method. These 40 patients had a radiographic grade 2 Kellgren and Lawrence classification and mild to moderate knee pain during walking and normal movement, but had no pain at rest. Inclusion criteria were chronic joint pain for more than 3 months and clinical and radiographic confirmation of knee osteoarthritis (Kellgren-Lawrence grade 2) and age between 35 and 75 years. Exclusion criteria include post-traumatic knee osteoarthritis, cancer diseases, autoimmune diseases (rheumatoid arthritis), acute and chronic infectious disorders, blood coagulation disorders (coagulopathy, thrombocytopenia), endocrine diseases (gout, diabetes), previous interventions on knee joint (i.e., knee block, arthroscopy), and non-steroidal anti-inflammatory drugs (NSAIDs) (within 10 days) or

hormonal treatment before the intervention. After obtaining the conditions to enter the study, the patients are randomly divided into two groups using the website https://www.sealedenvelope.com/simple-randomiser/v1/lists. Based on this, 40 patients were placed in two PRP groups with low leukocyte and corticosteroid group (Figure 1).

Each patient identification number was placed in a package. After introducing the patient to the operating room, a coordinator who was unaware of the purpose of the study, opened the package and guided the patient to perform the procedure. The main coordinator records the overall results. In order to facilitate the implementation of the research, a pain fellowship assistant was present to prepare PRP product. The preparation method of LP-PRP compounds has been implemented in two steps according to the research of reference 22 [22]. To prepare the product with LP-PRP, 40 cc of blood from the basilic vein of the upper limb is used. Centrifugation is done first with 1800 rounds for 12 minutes, then a 10-minute break then the second step with 3300 rounds for 5 minutes. The centrifuge used is Richplat Ortho (Fidia, Abano Terme, Italy). The final samples were prepared by using a sterile pipette from each one milliliter container, which was a total of 4 milliliters product from four containers. Patients assigned to group one (autologous platelet-rich plasma (PRP)) received an intra-articular injection of 4 mL of the PRP formulation. Patients assigned to group two (corticosteroid (CS)) received an intra-articular injection of triamcinolone acetate (Kenalog) 40 mg/ml along with 4 ml of lidocaine 0.02% (Abureyhan Co.) for a total of 5 ml. Arthrocentesis was not performed for any of the patients. Intra-articular injection was performed using a sterile technique without the use of local anesthesia or anesthesia. The needle used is a 22-gauge pencil-point Quincke needle (Dr. Japan Co, Ltd), which is performed with the Sonosite Edge II ultrasound guide and in an anterior-lateral manner in the knee joint. The supremacy hypothesis has been used to calculate the sample size. Pain was assessed on a visual analog scale (VAS range 0-10 points) before, one week, one month, two month and 3 months after the operation, the average score was 7.3 in the control group with a standard deviation of 1.6. This meant that detecting a 1.5-point reduction in the treatment group versus the control group with a power of 80% and a 2-sided significance level of 0.05 required the inclusion of a total of 36 patients [23].

VAS index and WOMAC questionnaire were utilized to evaluate patients pre- and post-injection. VAS was evaluated before injection, one week, one month and three months after injection. In VAS evaluation, a 10 cm line is used, the two starting and ending points of which represent 0 ("no pain") and 10 ("worst pain in question"). The patient was asked to indicate his current pain level by placing his or her finger on the line. The WOMAC questionnaire was also filled before injection and three months following injection. The WOMAC questionnaire takes approximately 10 minutes to complete and can be taken on paper. Test questions are scored on a scale of 0-4, which corresponds to: none (0), mild (1), moderate (2), severe (3), and very severe (4). The total score can be calculated after adding up all the scores. Higher scores on the WOMAC indicate worse pain.

The statistical analysis of the research was done using chi-square tests and independent student t-test and using SPSS version 23 software. Chi-square and Fisher's exact tests were used for qualitative variables, and t-test was used to compare quantitative variables of two groups. Using chi-square tests, $p<0.05$ was considered statistically significant for all tests.

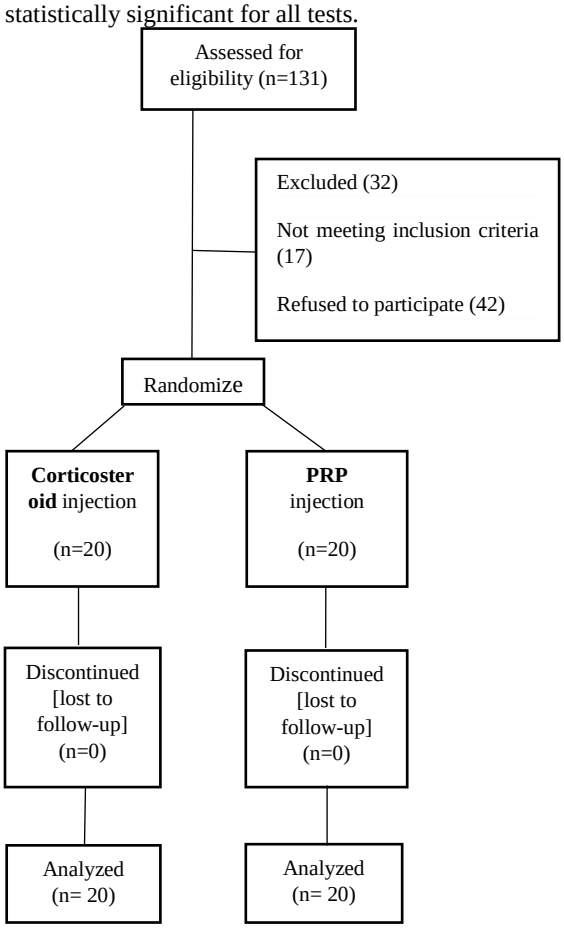

Figure 1- Flowchart

Results

A total of 131 patients were examined for PRP and corticosteroid injections. Finally, 40 patients were included in the study. 20 patients were in the PRP group and 20 patients were in the corticosteroid group. Fortunately, all 40 patients were present until the end of the follow-up period and none of them were excluded from our final analysis.

The level of pain was evaluated according to VAS scores in four time periods which is before, one week, one month, two months and three months after the injection. WOMAC questionnaire scores were evaluated before the study and at the end of 3 months.

The group receiving LP-PRP injection consisted of 6 males (30%) and 14 females (70%), and the group receiving corticosteroid injection consisted of 8 males (40%) and 12 females (60%). There were no significant differences between the groups across all the baseline parameters including age, sex and body mass index (Table 1). There was no significant difference between the two groups before the study in terms of comorbidities including high blood pressure, diabetes and smoking. Details of this analysis are shown in (Table 2).

Both injection groups were effective in reducing patients' pain from one week to three months after injection (Table 3). The level of pain in the first week after injection was significantly lower in the corticosteroid group than in the PRP group (P: 0.020). In the first month and the third month after the injection, the pain reduction according to mean scores of VAS was the same in both groups (P: 0.261 and P: 0.470 respectively) (Table 3). There were no major complications including infection and hematoma in any of the two injection groups.

According to the WOMAC questionnaire that was filled before the injection and three months after the injection, there is a significant improvement in both groups compared to before the injection (p: 0.155 for PRP group and p: 0.163 for corticosteroid group). There was no significant difference between the two groups three months after the injection in terms of the superiority of the two injections (P: 0.112 for PRP group and P: 0.115 for corticosteroid group) (Table 4).

Table 1- Demographical details

Variables	PRP group	Corticosteroid group	P value
Age	64.5	62.4	0.56
Sex	14 Female	12 Female	0.65
	6 Male	8 Male	
BMI	25.05	25.80	0.935

Table 2- Comorbidity status

Groups	PRP group	Corticosteroid group	P value
High blood pressure	16 (80%)	11 (55%)	0.088
Diabetes	16 (80%)	16 (80%)	1
Smoking Habit	7 (35%)	7 (35%)	1

Table 3- Pain reduction through time

Pain intensity (VAS)	Before injection	1st week	1st month	3rd month
PRP group	7.1	5.3	4.9	5.05
Corticosteroid group	7.7	3.75	4.65	5.42
P VALUE	0.691	0.020	0.261	0.470

Table 4- Womac scores through time

Groups	PRP group	Corticosteroid group	P value
WOMAC scores before	56.2	59	0.155
WOMAC scores after	38	41.2	0.112

Discussion

According to the results of this study, during the first week of treatment, the level of pain reduction in the corticosteroid group is higher than in the PRP group. But from one week to 3 months, there is no difference between the two groups in reducing pain.

In Elksniņš-Finogejevs's study in 2020, the effects of PRP and corticosteroids in reducing pain in knee osteoarthritis patients were examined. According to the results of this study, there was no difference between the two groups in terms of pain reduction and function until 15 weeks, but after that the results were in favor of PRP [24]. In Naderi et al.'s study, a comparison was made between PRP and corticosteroids. In this study, no significant difference was observed among the two groups during the first month after knee injection. But in three months and six months, PRP was better than triamcinolone in reducing pain and improving function [25]. In our study, unlike Naderi's study, corticosteroids have effects similar to PRP except for the first week until three months, which is the end of follow-up. Our findings are more similar to Anderjs's study regarding the effectiveness of triamcinolone and PRP in the short term.

In the study of Forough et al., the amount of pain reduction and improvement of quality of life in patients with knee osteoarthritis in two groups of PRP and corticosteroids was investigated. Questionnaires were filled two months and six months after the injection. Pain reduction was observed in both groups, but the amount of pain reduction and improvement in quality of life was better in the PRP group than in the corticosteroid group [23].

In a new study conducted by Di Martino et al. in 2022 on 192 patients with osteoarthritis of the knee, the amount of pain and improvement in performance was scrutinized in two months, six months and twelve months following knee injection. In this clinical trial, two PRP groups including leukocyte poor and leukocyte rich were compared. Finally, there was no significant difference between the two groups in terms of the rate of improvement during one year. In terms of side effects, there was no difference between the two groups [26]. In Aazad meta-analysis, the difference in effectiveness of PRP leukocyte concentration has been investigated. In this meta-analysis, there is no difference between leukocyte concentrations in the final result of treatment [27]. In the meta-analysis of Riboh in 2016, similar results were reported about the effects of leukocyte concentration. In such a way that there is no difference between LP-PRP and LR-PRP in knee osteoarthritis [28]. Of course, in both of the mentioned meta-analyses, the results of SUCRA analysis showed the superiority of LP-PRP compared to LR-PRP. But at the moment it is not possible to make a definite conclusion in this field. The said superiority in SUCRA analysis was one of the reasons for choosing LP-PRP in our study. Maybe if there was another LR-PRP group, it would be better to comment on this issue. Although some researchers consider the role of monocyte/macrophage important in the healing process after PRP injection, and consider this role to be helpful along with platelets, but this theory has not been proven in many studies. In fact, LP-PRP can be as effective as LR-PRP [29].

It is unclear whether multiple injections of PRP are better than a single injection in osteoarthritis of the knee. In the 2019 meta-analysis conducted by Vilchez-Cavazos et al., the same issue was investigated. According to the results of this study, it is still not possible to make a definite conclusion about the superiority of multiple injections of PRP. It seemed that one session of PRP is as effective as several sessions in reducing the pain of patients with knee osteoarthritis. However, regarding the improvement of patients' function, the results are in favor of multiple injections of PRP [30]. The fact that a single PRP session can be as effective as a corticosteroid injection is fascinating. Especially, the cost of treatment is reduced compared to several sessions of PRP, and there are no special side effects related to corticosteroid injections. In Chouhan's experimental study on a pig animal model, it was shown that multiple PRP injections are more beneficial for achieving long-term effects. But in this study, it was also shown that even one PRP injection can induce anti-inflammatory effects on the synovium [31].

In most of the clinical trials, either PRP rich in leukocytes is injected, or the method of preparing PRP in terms of leukocytes is not mentioned in detail. However, in this study, LP-PRP is used for comparison with corticosteroids. The current study had some important limitations. The patients' follow-up period could be increased. Considering the better effects of PRP over time, this matter becomes more important. Using the group with LR-PRP to compare with LP-PRP could also be helpful. Using tools such as MRI after injection to check the inflammatory effects and cartilage healing could also be considered.

Conclusion

In short, one injection of PRP can reduce the pain of patients with osteoarthritis of the knee as much as corticosteroids during a three-month treatment process. Considering the possible side effects of corticosteroids, this alternative treatment can be considered with further investigation.

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