

Comparison of the short-term effect of intra-articular hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis: a randomized clinical trial

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Keywords

Intra-Articular • Hyaluronic Acid • Platelet-Rich Plasma • Knee Osteoarthritis

Summary

Introduction. Osteoarthritis (OA) is one of the most common degenerative joint diseases which involved all joints. It is very important to choose a treatment method with high efficiency to reduce the pain and disability of patients and also to improve their quality of life. The current study aimed to investigate the therapeutic effects of intra-articular injection of PRP and hyaluronic acid (HA) in the knee of people with knee osteoarthritis (KOA).

Methods. In this randomized clinical trial study, 90 patients with KOA were randomly divided into two groups of intra-articular HA and PRP. The patients of the two groups were followed up for five months and different outcomes were recorded. The McMaster index (WOMAC) evaluated all patients at rest and during move-

ments. Measurements were taken at the beginning and after the third month of follow-up.

Results. Three month after the last injection (5th month) and after adjusting of baseline value using analysis of covariance, the mean of knee pain, stiffness, physical function and finally total score in the PRP group, was significantly lower than the HA group. Regarding the Osteoarthritis grade, the mean of knee pain, Stiffness, Physical function and finally total score in the PRP group was significantly lower than the HA group in all Osteoarthritis grades. Also, there were no complications in the studied groups.

Conclusions. The results of the current study showed that pain and stiffness reduction as well as physical function of the knee joint in the PRP group was better than in the HA group.

Introduction

Osteoarthritis (OA) is one of the most common degenerative joint diseases, involving all joints [1]. The nature of this disease is the progressive destruction of the joint, characterized by the progressive degeneration of articular cartilage and subchondral bone involvement [2]. While knee osteoarthritis (KOA) is one of the main causes of disability in the knee joint, this manifests itself with symptoms such as knee pain and stiffness, joint inflammation and degeneration, also has a major impact on disability and reduces quality of life [3]. The risk factors of this disease, include increasing age, obesity, female sex, and inflammation of the knee joint [4,5]. The knee is the most common joint affected by arthritis among the Iranian population. The prevalence of this disorder in Iran is estimated at 15.5% [6]. According to a study, knee osteoarthritis in Iran ranks ninth in terms of disease burden after accidents, natural disasters, cardiovascular diseases, etc. [7].

So far, many studies have been presented on the treatment methods of osteoarthritis such drug treatments, interventional methods, and auxiliary treatment regimens [8, 9]. Non-surgical measures are the first step to control patients' knee pain, which includes weight loss, specific exercise regimens, lifestyle changes, physical therapy, use of non-steroidal

anti-inflammatory drugs, painkillers, and intra-articular injections of corticosteroids, gels, etc. [10, 11]. Meanwhile, acetaminophen, non-steroidal anti-inflammatory drugs, and corticosteroids have analgesic and sometimes anti-inflammatory effects. However, the occurrence of common side effects in the use of such drugs limits their use in many patients. Gastrointestinal complications, aggravation of heart failure, increased blood pressure [12], liver disorders [13], kidney problems [14], exacerbation of asthma [15], and the risk of osteoporosis [16] in long-term use are common side effects of anti-inflammatory drugs.

The ability of cartilage to regenerate itself is unfortunately limited due to the lack of blood vessels and innervation, as well as its isolation from the body's systemic circulation, so the intra-articular injection of a drug or drug combination with the property of regeneration and repair of cartilage tissue has always been of interest to researchers [17]. In recent years, intra-articular injection of platelet-rich plasma (PRP) in knee osteoarthritis has attracted the attention of researchers [18, 19]. This injection contains PRP, which has a higher concentration of platelets than normal blood. PRP is an environment rich in high concentrations of cytokines and various growth factors that are obtained through blood centrifugation and can be considered a new solution to stimulate mesenchymal

cells to replicate and regenerate damaged tissues [20]. Samples from patients with knee osteoarthritis show that the number of mesenchymal cells in the synovial fluid of these people has significantly decreased compared to healthy individuals, as a result of PRP injection as a stimulating factor for the regeneration and replication of this cell can be effective in the treatment of arthritis [21]. Increasing the presence of mesenchymal cells in the synovial fluid of sick people can play a modulating role in the responses of the immune system, which accelerates the healing process [22]. The current study aimed to investigate the therapeutic effects of intra-articular injections of PRP and hyaluronic acid (HA) in patients with knee osteoarthritis.

Methods

In the current randomized clinical trial study, 90 patients with painful knee arthritis with radiological grades one to three of the Kellgren and Lawrence radiological criteria were included. More details were shown in figure 1.

INCLUSION CRITERIA

Patients aged 40 to 65 years, history of knee pain for at least three months, knee osteoarthritis grade 1 to 3 based on the Kellgren and Lawrence criteria (based on knee osteoarthritis criteria of the American College of Rheumatology) were included.

EXCLUSION CRITERIA

Patients suffering from diseases such as diabetes, rheumatoid arthritis, hemophilia, dysfunction of blood platelets, any infection or active wound at the injection site, taking antiplatelet or anticoagulant drugs in the last ten days before injection, taking non-steroidal anti-inflammatory drugs, having history of intra-articular corticosteroid injection in the previous three weeks or systemic corticosteroid use in the last two weeks, peripheral blood platelet count less than 150,000 per microliter, patients with drug or alcohol addiction and abnormal ESR or CRP levels were excluded.

After selection of the cases, their basic information including age, sex, height, weight, and body mass index was recorded and patients were divided into the PRP and HA groups using simple random allocation methods.

INTERVENTIONS

PRP GROUP

After taking the patients' history, examining them, and performing routine monitoring such as blood pressure, heart rate, and electrocardiogram (if necessary), 30-35 ml of the patient's venous blood was taken from the upper limb with an 18G needle under sterile conditions and placed in special centrifuge kits (produced by Royagen, Iran) containing 5 ml of acid citrate dextrose solution-A to prepare platelet-rich plasma. This solution was placed

in a centrifuge for 15 minutes with a rotation speed of 1600 rpm. The Buffy coat and plasma layer of the solution inside the test tube was separated and centrifuged again for 7 minutes with a rotation speed of 2800 rpm. Finally, 5 ml PRP was prepared for intra-articular injection. Anesthetic injections may also affect platelet activation by changing the PH of the environment, so no local anesthetic was injected. Instead, patients were given a single dose of acetaminophen and codeine two hours before injection. Under sterile conditions, a 22-gauge, 50 mm needle was inserted from the upper external area of the knee patella (suprapatellar) and the outside to the inside of the knee joint and the prepared plasma was injected inside the knee joint. In our study, the frequency of intra-articular injection of PRP was three times at one-month intervals.

HYALURONIC ACID GROUP

In this group, HA (Hyalgan®) was injected. Hyalgan produced by Fidia Farmaceutici S.p.A., Abano Terme, Italy, is a viscous solution consisting of a high molecular weight (500,000-730,000 Da) fraction of purified natural sodium hyaluronate in buffered physiological sodium chloride, having a PH of 6.8-7.5. The sodium hyaluronate is extracted from rooster combs. Hyalgan was supplied as a sterile, non-pyogenic solution in 2 mL pre-filled syringes containing 20 mg of sodium hyaluronate, 17 mg of sodium chloride, 0.1 mg of monobasic sodium phosphate, 1.2 mg of dibasic sodium phosphate, and up to 2 cc water for injection. After resting for 15-20 minutes, the patients were asked to flex and extend their knees to ensure even distribution of the HA in the joint space. The patients were monitored in the clinic for one hour after the injection and were discharged with written instructions regarding the following issues if no side effects occurred. Hyaluronic acid injections were administered three times at one-week intervals.

STUDY OUTCOMES

The intensity of pain, dryness, and knee function of the patients before the first injection and three months after the last injection were evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores. The WOMAC criterion consists of three parts: pain level, joint stiffness level, and knee function level. Scoring in each case is from 0 to 4 and the total score of this scale is from 0 to 96.

STATISTICAL ANALYSIS

Descriptive statistics including mean \pm standard and frequency (percentage) was used to present quantitative and qualitative findings. Data were analyzed using the independent sample t-test, paired sample t-test, Chi-square, or Fisher exact test and Analysis of covariance (ANCOVA) test. The statistical significance level was considered at: 0.05. All data were analyzed using SPSS, version 22.0, Armonk, NY, USA: IBM Corp. Released 2015.

Tab. I. Descriptive characteristics of understudied cases.

Variables	PRP (n: 41)	Hyaluronic Acid (n: 44)	p
Gender			
Females	26(63.4%)	26(59.1%)	0.682
Osteoarthritis grade			
1	14(34.1%)	15(34.1%)	
2	14(34.1%)	14(31.8%)	
3	13(31.7%)	15(34.1%)	0.961
Age	Mean \pm SD	Mean \pm SD	
	60.24 \pm 1.97	61.90 \pm 2.06	0.014
BMI			
	29.47 \pm 1.52	28.78 \pm 1.39	0.032

Results

BASELINE CHARACTERISTICS

Regarding the gender, 26(63.4%) and 26(59.1%) of cases in the PRP and Hyaluronic Acid groups were females respectively (P: 0.682). Mean of age in the PRP and Hyaluronic Acid groups were 60.24 \pm 1.97 and 61.90 \pm 2.06 and the difference between two groups was statistically significant (P: 0.001). The mean of BMI in the PRP and Hyaluronic Acid groups were 29.47 \pm 1.52 and 28.78 \pm 1.39 and the difference between two groups was statistically significant (P: 0.032) (Tab. I).

MAIN OUTCOMES

WITHIN GROUPS COMPARISON

PRP GROUP

In this group, the knee pain score three months after

Tab. II. Comparison of different outcome scores within groups over the time.

Group	N	Outcome	Baseline	Three months after the intervention	
			Mean \pm SD	Mean \pm SD	p
PRP	41.00	Pain	13.66 \pm 3.60	6.44 \pm 1.42	0.001
	41.00	Stiffness	3.10 \pm 0.80	1.80 \pm 0.93	0.001
	41.00	Physical function	36.07 \pm 6.71	18.85 \pm 6.70	0.001
	41.00	Total	52.37 \pm 9.19	27.10 \pm 8.46	0.001
Hyaluronic acid	44.00	Pain	11.93 \pm 1.59	10.61 \pm 1.17	0.001
	44.00	Stiffness	2.91 \pm 0.86	2.52 \pm 0.73	0.001
	44.00	Physical function	35.36 \pm 6.42	33.05 \pm 6.41	0.001
	44.00	Total	50.20 \pm 8.41	46.18 \pm 7.90	0.001

intervention decreased significantly from 13.66 \pm 3.60 to 6.44 \pm 1.42 (P: 0.001), also the knee stiffness score decreased from 3.10 \pm 0.80 to 1.80 \pm 0.93 (P: 0.001). Regarding the knee physical function score, this score decreased significantly from 36.07 \pm 6.71 to 18.85 \pm 6.70 (P: 0.001), and finally the total score decreased significantly from 52.37 \pm 9.19 to 27.10 \pm 8.46 (P: 0.001) (Tab. II, Fig. 1).

HYALURONIC ACID

In this group, the knee pain score decreased significantly from 11.93 \pm 1.59 to 10.61 \pm 1.17 (P: 0.001) in three months after the intervention compared to baseline.

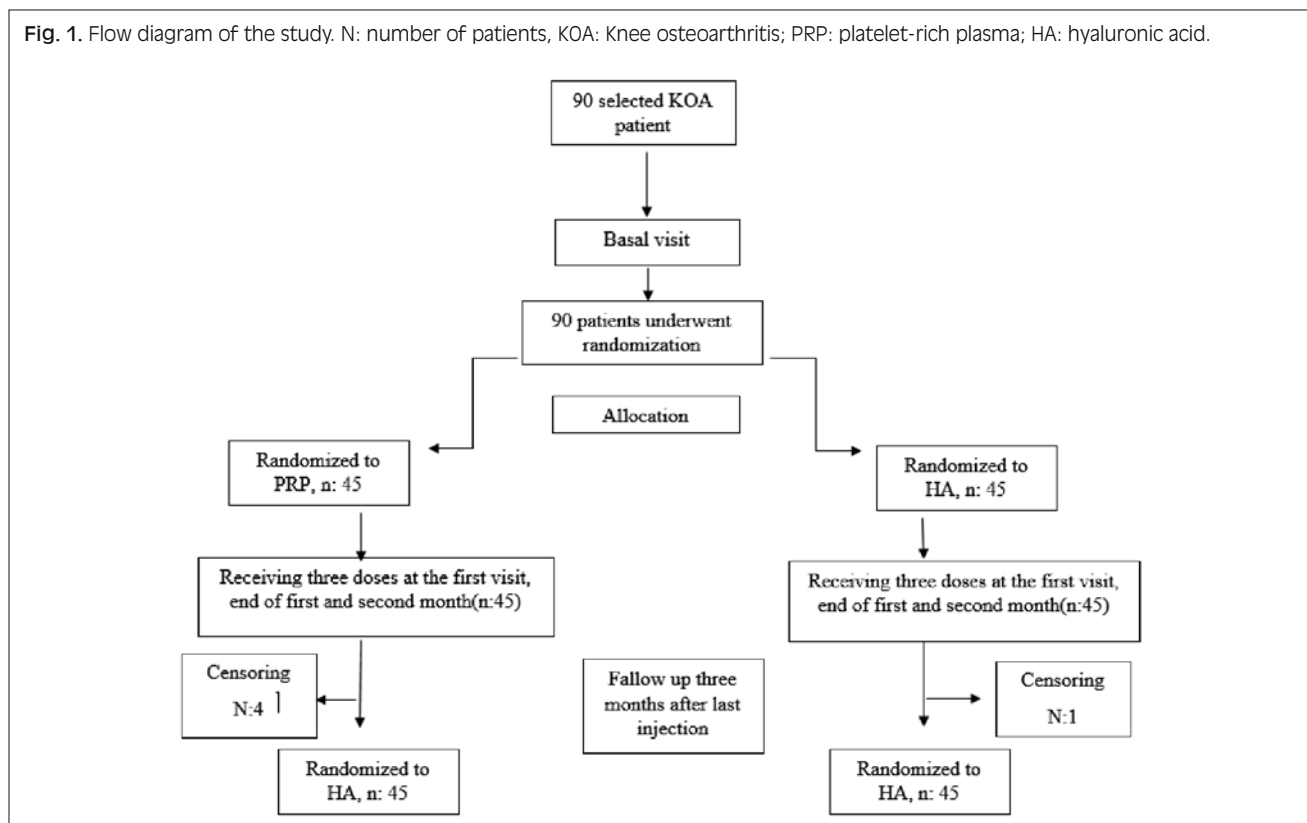
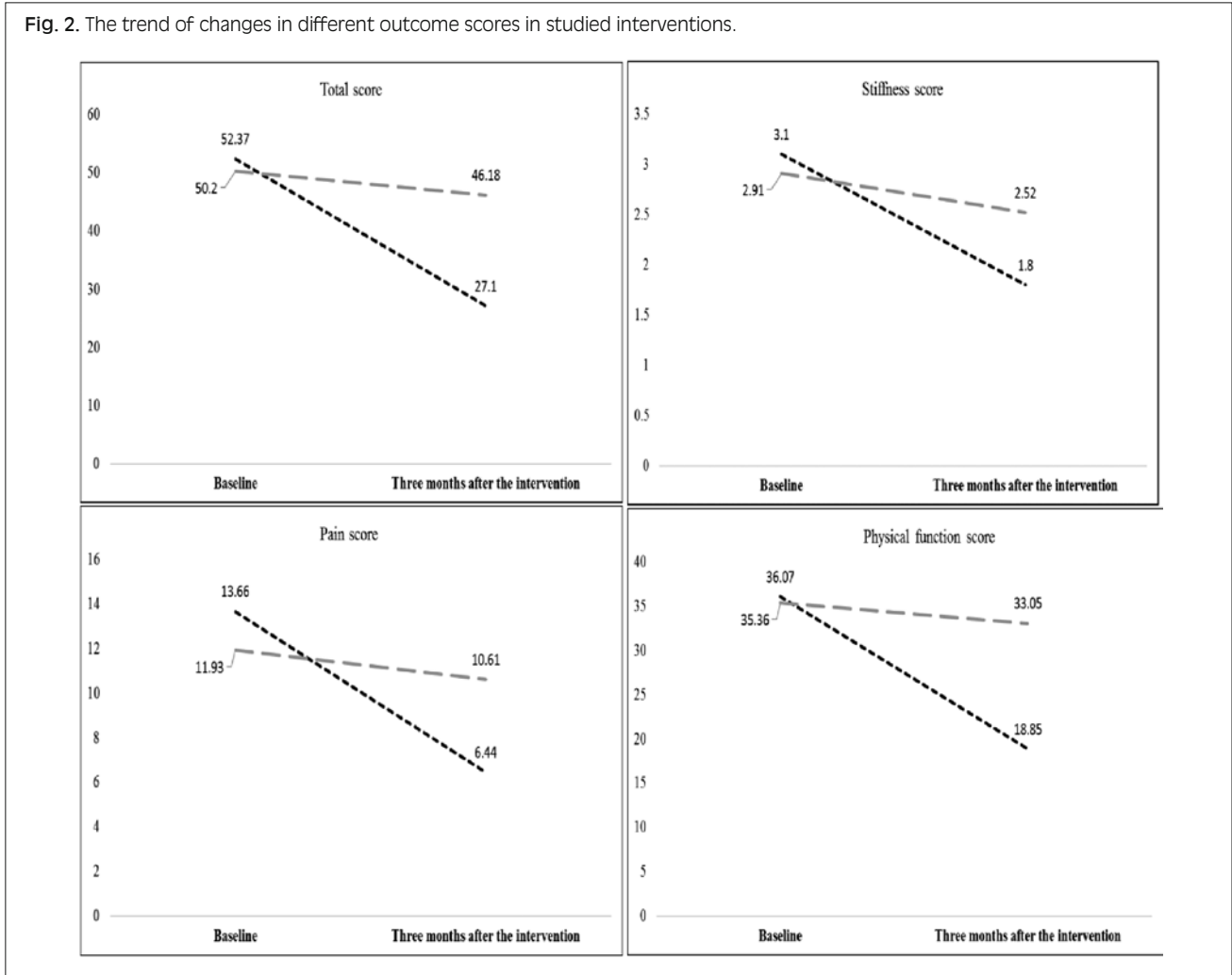
Fig. 1. Flow diagram of the study. N: number of patients, KOA: Knee osteoarthritis; PRP: platelet-rich plasma; HA: hyaluronic acid.

Fig. 2. The trend of changes in different outcome scores in studied interventions.



Also the knee stiffness score decreased significantly from 2.91 ± 0.86 to 2.52 ± 0.73 ($P: 0.001$). Regarding the knee physical function score, this score decreased from 35.36 ± 6.42 to 33.05 ± 6.41 ($P: 0.001$), and finally the total score decreased from 50.20 ± 8.41 to 46.18 ± 7.90 ($P: 0.001$) (Tab. II, Fig. 2).

BETWEEN GROUPS COMPARISON

Three months after the intervention, the mean of knee pain, stiffness, physical function and finally total score in the PRP group, was significantly lower than the Hyaluronic Acid group. More details were shown in the Table III. Regarding the Osteoarthritis grade, the mean of knee pain, Stiffness, Physical function and finally total score in the PRP group was significantly lower than the Hyaluronic Acid group in all Osteoarthritis grades (Tab. IV). Also, there were no complications in the studied groups.

Discussion

One of the effective factors in the development and progression of knee arthritis is inflammation, which

aggravates the symptoms. Therefore, the use of treatments that have an anti-inflammatory effect can have an effective role in reducing the symptoms of the disease as well as the side effects of osteoarthritis of the joints. One of these treatments is the use of blood derivatives such as PRP, which can play an important role in reducing symptoms. PRP as an anti-inflammatory factor can affect various cells, including mesenchymal stem cells, and as a result, it can modulate various cellular activities [23-25]. Another property of PRP is the absorption of other cells effective in treatment [23].

Tab. III. Comparison of different outcome scores between groups three month after the intervention.

Outcome	PRP (n: 41)	Hyaluronic acid (n: 44)	Partial eta squared	P
	Mean \pm SD	Mean \pm SD		
Pain	6.44 ± 1.42	10.61 ± 1.17	0.82	0.001
Stiffness	1.80 ± 0.93	2.52 ± 0.73	0.41	0.001
Physical function	18.85 ± 6.70	33.05 ± 6.41	0.95	0.001
Total	27.10 ± 8.46	46.18 ± 7.90	0.98	0.001

Tab. IV. Comparison of different outcome scores between groups three month after the intervention by Osteoarthritis grades.

Outcome	PRP (n: 41)	Hyaluronic acid (n: 44)	Partial eta squared	P
Pain				
Osteoarthritis grade	Mean \pm SD	Mean \pm SD		
1.00	4.93 \pm 0.73	9.73 \pm 0.80	0.96	0.001
2.00	6.86 \pm 1.10	10.71 \pm 0.73	0.81	0.001
3.00	7.62 \pm 0.65	11.40 \pm 1.24	0.96	0.001
Stiffness				
1.00	1.07 \pm 0.73	1.93 \pm 0.26	0.60	0.001
2.00	1.71 \pm 0.61	2.29 \pm 0.47	0.33	0.001
3.00	2.69 \pm 0.63	3.33 \pm 0.49	0.17	0.03
Physical function				
1.00	13.21 \pm 1.97	27.60 \pm 1.80	0.39	0.001
2.00	16.79 \pm 1.63	31.36 \pm 2.98	0.50	0.001
3.00	27.15 \pm 5.08	40.07 \pm 5.23	0.98	0.001
Total				
1.00	19.21 \pm 1.97	39.27 \pm 2.43	0.98	0.001
2.00	25.36 \pm 2.71	44.36 \pm 3.59	0.75	0.001
3.00	37.46 \pm 5.84	54.80 \pm 6.29	0.99	0.001

This multifaceted property of PRP has made this drug play an important role in reducing joint inflammation and play an important role in improving function and reducing pain in people with osteoarthritis [26, 27]. It is believed that intra-articular injection of PRP and HA can reduce pain and improve quality of life in patients with OA [28-30]. Due to the importance of the issue the current study aimed to assess the short-term effect of intra-articular hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis in a randomized clinical trial study.

Our results showed that the knee pain, knee stiffness, physical function and total WOMAC scores decreased significantly from baseline to three months after the intervention in both PRP and HA groups. Also, three months after the intervention the mean of knee pain, stiffness, physical function and finally total WOMAC scores in the PRP group, was significantly lower than the HA group. Regarding the osteoarthritis grade, the mean of knee pain, stiffness, physical function and finally total score in the PRP group, was significantly lower than the hyaluronic acid group in all osteoarthritis grades. This finding indicates that the PRP as well as HA improved OA indices, but the amount of changes in the PRP group was significantly more than HA group.

Several studies have been conducted comparing the effectiveness of PRP, and HA in the treatment of osteoarthritis [31-33]. In the study of Lana et al., they concluded that PRP has a greater effect on reducing patients' pain scores compared to HA at different times after treatment [34]. The results of Sampson et al.'s study indicated a significant reduction in pain within one

year after PRP injection in patients with OA [35]. The study by Sanchez et al showed a reduction in knee pain intensity for 5 weeks after PRP [36].

The findings of the meta-analyses conducted in this field also indicate the superiority of PRP over HA, and in reducing pain [27, 37, 38]. The results of the meta-analysis showed that the greatest effectiveness of PRP in reducing WOMAC pain and VAS pain outcomes was observed 6 months after treatment [32]. The results of other studies in this field indicate that the effectiveness of drug injection is not stable and usually decreases over times [37].

The results of our study indicated that PRP is more effective in reducing the stiffness and function of patients. Also, there were no significant complications among patients, and most of the patients only experienced brief pain at the injection site, which improved within a short time after the intervention. Other studies also support this finding. The meta-analysis results showed that pain, stiffness, and WOMAC performance in the PRP group improved the most in the 12 months after injection [32]. These results have been confirmed in other studies that have shown that after PRP injection, a drug effect lasts up to 12 and even 24 months [27, 39]. Another study showed improvement in patients' quality of life in 12 months after injection of PRP and HA [30]. Tucker et al.'s study results showed that the pain stiffness and functional scores, improved significantly in the PRP group compared to the control group [40]. Therefore, as mentioned, the findings of various studies indicate that PRP is more effective in reducing knee joint pain than HA. In justification of these findings, it can be said that PRP has anti-inflammatory properties. Indeed, PRP reduces inflammation by inducing a more targeted and controlled anti-inflammatory response, modulating the immune response, and increasing angiogenesis and re-epithelialization [41]. Also, PRP can potentially reduce the impact of other underlying knee joint diseases [42-44]. In fact, by promoting tissue repair and regeneration, PRP can reduce the impact of these diseases on the progression of osteoarthritis [32].

LIMITATIONS OF THE STUDY

The present study had limitations, including the small sample size and the short follow-up period of the patients.

Conclusions

The results of the study indicate a significant improvement in pain, stiffness, and physical function of the knee joint in patients with arthritis especially in the PRP group. Due to its positive effect, safety, and availability, PRP has attracted the interest of Physician in the treatment of knee arthritis and it can be concluded that PRP injection can be considered a more effective treatment than HA in patients with knee osteoarthritis.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This research approved by the ethical committee of Shahed University with approval id IR.SHAHED.REC.1399.028. The written informed consent was obtained from all participants.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the study conception and design. OG, DB: participated in the design of the study; OG, PYT: performed data collection, wrote the manuscript, and helped with statistical analysis; OG, DB: edited the manuscript. All authors read and approved the final manuscript.

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Received on May 1, 2024. Accepted on June 19, 2024.

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How to cite this article: Ghorbani O, Mahdibarzi D, Yousefi-Toodeshki P. Comparison of the short-term effect of intra-articular hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis: a randomized clinical trial. *J Prev Med Hyg* 2024;65:E214-E220. <https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3270>

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