Intra-articular platelet-rich plasma versus hyaluronic acid injections in patients with advanced knee osteoarthritis

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Background
Osteoarthritis (OA) is a chronic disease that can be treated by several modality, one of which intra-articular injection.
Hyaluronic acid (HA) and platelet-rich plasma (PRP) were approved in the management of OA grade 2 and grade 3 with good response.
The aim of this study was to compare the effect of intra-articular injection of PRP versus HA in patients with knee OA grade 4.
Patients and methods
The study was carried out on 67 patients having knee OA grade 4, who were divided into two groups: group 1 included 33 patients who were treated with intra-articular injection of leukocyte-low PRP, and group 2 included 34 patients who were treated with intra-articular injection of high-molecular-weight hyaluronic acid. Both groups were evaluated according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and MRI before and 6 months after injection.
Results
In group 1, there were no statistically significant improvements in total WOMAC score and WOMAC score of pain, stiffness, and function in both knees and no statistically significant difference in cartilage thickness of the knee measured by MRI.
In group 2, there were statistically significant improvement in total WOMAC score and WOMAC score of pain and function in both knees, no statistically significant improvement in WOMAC score of stiffness, and no statistically significant differences in cartilage thickness of the knee measured by MRI.
Comparing the two groups, intra-articular injection of HA showed significant improvement than that of PRP in the management of grade 4 knees OA.
Conclusions
The effect of intra-articular injection of HA is better than that of PRP in the management of grade 4 knees OA.

Keyword:
hyaluronic acid, intra-articular injection, osteoarthritis, platelet-rich plasma

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Background

Osteoarthritis (OA) is a chronic disease of the joints that occurs most frequently in older people and causes pain and disabilities [1].

Treatment of OA ranges from drug therapy to surgery. Drug and rehabilitation therapy are the first line of management, then intra-articular injection of steroid or hyaluronic acid (HA), and finally, total joint replacement in advanced OA [2].

The aims of treatment of OA are pain reduction, improvement of function and mobility, prevention or correction of the deformity, and decrease in the progression of the disease [3].

Viscosupplementation is a conservative management of OA. It was approved by the Food and Drug Administration for knee therapy in 1997 and was suggested by the American College of Rheumatology guideline as a therapeutic line for pain reduction in knee OA in 2000 [4].

HA is a high-molecular-weight glycosaminoglycan composed of repeating units of acetyl glucosamine and glucuronic acid synthesized by synoviocytes, fibroblasts, and chondrocytes and is responsible for lubricant features and viscoelasticity of synovial fluid [5].

New therapeutic options effective for tissue healing that try to prevent the progression of OA have been taken into consideration in the last years. One of these options is growth factors, which show the effectiveness

of these factors in the healing process of cartilage in patients with OA [6].

These growth factors have important roles in healing and remodeling of cartilage tissue through chemotaxis, differentiation of mesenchymal stem cells, chondrocyte proliferation, and synthetic activities of osseous and cartilaginous cells. Platelet-rich plasma (PRP) is considered a biologic treatment, which includes patients' own plasma; it contains growth factors that are released from platelets and endogenous fibrin scaffold, which stimulate the natural healing cascade and tissue regeneration [7].

There are recent studies showing the effects of PRP injection on the level of pain and function of the knee joint in patients with OA [8].

New studies show that PRP can be used as a complex of growth factors that stimulate cartilage healing process and improve the damage [9].

Many studies have compared the effect of PRP and HA in OA, but all of these studies have assessed their effect on grade 2 and grade 3 OA. However, in our study, we assessed their effect on grade 4 OA, which was indicated for total knee replacement but the operation was contraindicated owing to other reasons. In this study, there is an introduction of another plan of management that reduces pain, improves knee function, and improves the activity of daily living of those patients.

The aim of our study was to compare the effect of intra-articular injection of PRP versus HA in patients having advanced knee OA.

Patients and methods

This study was carried out in Jameel polyclinics in Jeddah in KSA from July 2018 until March 2021.

A total of 67 patients with advanced OA grade 4 according to Kellgren–Lawrence grade in radiograph studies of both knees were recruited for this study. Both knees were included in this study. These patients were indicated for total knee replacement but refused operation or were unfit for surgery. Their age ranged from 60 to 80 years, with symptom duration of more than 3 months [10].

This study was approved by the local ethical committee.

All of the patients who were included in the study signed a written consent form in the clinic before taking the injection.

Patients were divided into two groups randomly, matching in age and sex.

Group 1 included 33 patients who were treated with intra-articular injection of PRP.

The preparation of leukocyte-poor PRP was as follows: 20-ml blood sample was drawn under sterile conditions and placed in a specialized centrifuge. Then, the blood was centrifuged for 6 min at a rotation speed of 3200 rpm. This sample was then centrifuged into two layers: an inferior layer containing erythrocytes and a superior layer consisting of plasma, in which the platelet layer was isolated and injected into the patient's knee under a sterile environment. Then, 6 ml of the separated plasma was prepared for intra-articular injection. A single intra-articular injection of PRP was injected in each knee guided by ultrasound [11,12].

Group 2 included 34 patients who were treated with intra-articular injection of high-molecular-weight (>1500 kDa) hyaluronic acid (HWHA) sodium salt, obtained by bacterial fermentation of a fraction of the HA. A single injection of 60-mg HA was injected in each knee guided by ultrasound.

Exclusion criteria included a history of autoimmune disease, history or presence of malignant disorders, infection in the knee area, recent history of severe trauma to the knee, platelet disorders, history of knee intra-articular injections of corticosteroids during the past 3 weeks or HA injection during the last year, and genu valgus or varum greater than 20°.

The patients stopped anticoagulant and antiplatelet medication 10 days before the injection, and nonsteroidal anti-inflammatory medication was stopped 1 week before the injection; as these medication affect platelet stability and function, they will affect PRP efficacy and must be discontinued at an appropriate time frame before injection therapy [13].

All patients were subjected to full history taking; physical examination; laboratory testing, including complete blood count with, erythrocyte sedimentation rate, and C-reactive protein; knee radiography (standing anterior–posterior and lateral views); and survey of used medications and supplements.

All patients were evaluated according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC measures five items for pain (score range, 0–20), two items for stiffness (score range, 0–8), and 17 items for functional

limitations (score range, 0–68). So, the WOMAC scores are between 0 and 96.

WOMAC scores were assessed for all patients before treatment, 1 month after injection, 3 months after injection, and 6 months after injection.

MRI was used to evaluate intra-articular injections, including viscosupplements, growth factors, stem cells, and PRP, which show a positive effect on cartilage structure at 8 weeks of injection up to 12 months of injection [14,15].

MRI of both knees was performed before the start of treatment and 6 months after injection using a 3.0 T magnetic resonance unit (MAGNETOM Verio, A Tim System; Siemens, Erlangen, Germany). The patients were positioned in the supine position with a fully extended knee and the foot perpendicular to the MRI table, and then scans were performed. The imaging protocol for sagittal spin-echo proton density-weighted and T2-weighted images [repetition time (TR), 2200 ms; time to echo (TE) 20/80 ms] included a slice thickness of 3 mm, a 1-mm inter-slice gap, 1 excitation, a field of view of 12 cm, and a matrix of 256 × 192 pixels, and for coronal and axial spin-echo fat-suppressed proton density-weighted and T2-weighted images (TR 2200 ms; TE 20/80) included a slice thickness of 3 mm and a 1-mm interslice gap. Mean cartilage thickness normalized to the total area of subchondral bone was obtained for a total of 16 locations in the femur and 24 in the tibia, distributed in five tibial subregions (central, external, internal, anterior, and posterior) and three femoral subregions (central, external, and internal).

Statistical analysis

For statistical analysis, we utilized SPSS 11.0 (IBM Company, Chicago, Illinois, USA). The mean and SD of the mean were used to present the data. χ^2 test was used to look at the statistical differences and correlations between the two groups. If the difference was smaller than 0.05, it was considered significant. If the *P* value was less than 0.01, then the differences were judged very significant.

Results

This study was carried out on 67 patients divide into two groups:

Group 1 included 33 patients, comprising 17 (51.52%) males and 16 (48.84%) females. Their ages varied between 60 and 80 years, with a mean of 70.90 ± 4.03 years (Table 1).

Group 2 included 34 patients, comprising 18 (52.94%) males and 16 (47.06%) females. Their ages varied between 60 and 80 years, with a mean of 71.06 ± 4.13 years (Table 1).

There was no statistically significant difference between both groups regarding age and sex.

Regarding the WOMAC scores for pain in group 1 patients, there was no statistically significant improvement along the whole 6 months (Table 2).

Regarding the WOMAC scores for pain in group 2 patients, there was a statistically significant improvement in the first month and after 3 months, but it became worse 6 months after injection but better than before injection (Table 2).

There was a statistically significant improvement in WOMAC scores for pain in group 2 compared with group 1 (Table 2).

The WOMAC scores for stiffness in group 1 showed that there were no statistically significant improvement along the whole 6 months (Table 3).

Table 1 Ages and sexes of patients of both groups

Variables	Group 1	Group 2	*P* value
Age (years)	70.90 ± 4.03	71.06 ± 4.13	>0.05
Male [*n* (%)]	17 (51.52)	18 (52.94)	>0.05
Female [*n* (%)]	16 (48.84)	16 (47.06)	>0.05

Table 2 Western Ontario and McMaster Universities Osteoarthritis Index scores for pain before and after injection of both groups

Variables	Group 1	Group 2	*P* value
Before injection	17.23 ± 1.33	17.35 ± 1.39	>0.05
1 month after injection	17.18 ± 1.28	11.29 ± 2.56	<0.05
3 months after injection	17.10 ± 1.29	10.67 ± 1.95	<0.05
6 months after injection	17.14 ± 1.31	13.86 ± 2.14	<0.05
P value in same group	>0.05	<0.05	

The WOMAC scores for stiffness in group 2 showed that there was improvement but not statistically significant in the first month and after 3 months, but it became worse 6 months after injection but better than before injection (Table 3).

There was no statistically significant difference in WOMAC scores for stiffness in both groups (Table 3).

The WOMAC scores for function in group 1 showed that there was no statistically significant improvement along the whole 6 months (Table 4).

The WOMAC scores for function in group 2 showed that there was a statistically significant improvement along the whole 6 months (Table 4).

There was a statistically significant improvement in WOMAC scores for function in group 2 compared with group 1 (Table 4).

The WOMAC total scores in group 1 patients showed that there was no statistically significant improvement along the whole 6 months but better than before injection (Table 5).

The WOMAC total scores in group 2 showed that there was a statistically significant improvement in the first month and after 3 months but it became worse 6 months after injection (Table 5).

There was a statistically significant improvement in WOMAC total scores in group 2 compared with group 1 (Table 5).

When we compared both groups, we found that there was a statistically significant improvement in pain and function of both knees of patients who were injected with HA than those who were injected with PRP, but no statistically significant improvement in the stiffness of both knees of patients who were injected with HA than those who injected with PRP. The maximum improvement occurred 3 months after injection, and then the condition regressed until the end of 6 months after injection.

Regarding the assessment of thickness difference of the cartilage by MRI of each knee before injection and after injection, there was reduction in thickening of cartilage at all tibial and femoral subregions in both groups, before injection and 6 months after injection, but it was not statistically significant. Comparing the two groups, no statistically significant difference was found in reference to the cartilage thickness reduction (Tables 6 and 7 and Fig. 1).

Table 3 Western Ontario and McMaster Universities Osteoarthritis Index scores for stiffness before and after injection of both groups

Variables	Group 1	Group 2	*P* value
Before injection	6.78±0.94	6.79±0.93	>0.05
1 month after injection	6.75±0.92	6.68±0.89	>0.05
3 months after injection	6.73±0.91	6.66±0.91	>0.05
6 months after injection	6.72±0.96	6.67±0.92	>0.05
P value in same group	>0.05	>0.05	

Table 4 Western Ontario and McMaster Universities Osteoarthritis Index scores for function before and after injection of both groups

Variables	Group 1	Group 2	*P* value
Before injection	60.53±5.74	60.64±5.86	>0.05
1 month after injection	59.85±5.69	52.31±6.46	<0.05
3 months after injection	59.42±5.53	50.83±6.71	<0.05
6 months after injection	59.94±5.61	51.21±6.82	<0.05
P value in same group	>0.05	<0.05	

Table 5 Western Ontario and McMaster Universities Osteoarthritis Index total scores before and after injection of both groups

Variables	Group 1	Group 2	*P* value
Before injection	84.54±8.01	84.78±8.18	>0.05
1 month after injection	83.79±7.89	70.28±9.91	<0.05
3 months after injection	83.25±7.73	68.16±9.57	<0.05
6 months after injection	83.8±7.88	71.74±9.88	<0.05
P value in same group	>0.05	<0.05	

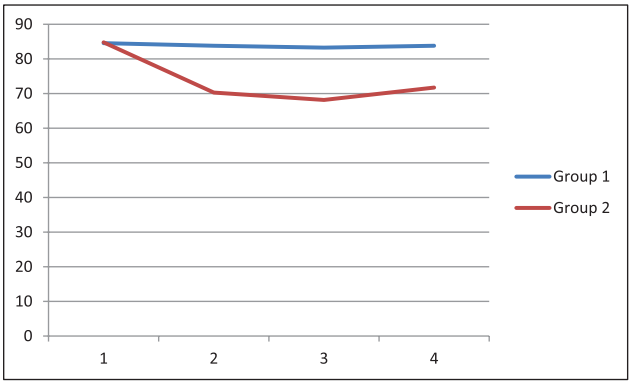
Table 6 Cartilage thickness (mm) by MRI before and 6 months after injection in group 1

Variables	Before injection	After injection	*P* value
Femoral subregions			
Central	0.45±0.05	0.44±0.02	>0.05
External	0.41±0.06	0.39±0.08	>0.05
Internal	0.54±0.09	0.53±0.08	>0.05
Tibial subregions			
Anterior	0.41±0.07	0.41±0.03	>0.05
Posterior	0.43±0.03	0.42±0.07	>0.05
Central	0.46±0.04	0.45±0.08	>0.05
External	0.45±0.03	0.44±0.04	>0.05
Internal	0.47±0.04	0.46±0.08	>0.05

Table 7 Cartilage thickness (mm) by MRI before and 6 months after injection in group 2

Variables	Before injection	After injection	*P* value
Femoral subregions			
Central	0.44±0.09	0.44±0.01	>0.05
External	0.42±0.03	0.41±0.09	>0.05
Internal	0.54±0.07	0.54±0.01	>0.05
Tibial subregions			
Anterior	0.41±0.08	0.41±0.02	>0.05
Posterior	0.42±0.06	0.42±0.09	>0.05
Central	0.45±0.09	0.45±0.02	>0.05
External	0.45±0.04	0.44±0.09	>0.05
Internal	0.46±0.02	0.45±0.09	>0.05

Figure 1



WOMAC total scores of both groups. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Discussion

Intra-articular injection of PRP is one of the latest modalities used in the treatment of OA.

In our study, we found that the effect of intra-articular injection of HA had significant improvement of pain and function of the knees in patients who have advanced OA than the effect of intra-articular of PRP.

According to our knowledge, this is the first study that manages advanced OA with PRP. Previous studies were carried out over second and third degree of OA.

The studies of local intra-articular injection of knees in patients who had OA knees are summarized in Table 8.

Li *et al.* [16], reported that intra-articular knee injection of PRP to treat patients who had knee articular cartilage degeneration is safe, but there was no significant difference in the International Knee Documentation Committee score, the WOMAC score, and the Lequesne index among patients who received PRP and those who received HA. This study differs from our study in that it was carried over patients who had early OA, and there was no significant difference between PRP and HA in the management of OA, whereas in our study, it was carried over advanced OA and there was significant improvement in HA than PRP [16].

Duymus *et al.* [17], found that PRP was more successful than HA in the treatment of mild to moderate knee OA, and application of PRP alone was enough to provide at least 12 months free of pain and to improve daily living activities of patients with knees OA.

Rahimzadeh *et al.* [18], found that there were significant improvements in the overall WOMAC score of patients who had OA of both knees who underwent PRP therapy. There were improvements in the quality of life of patients with knee OA after the first injection of PRP.

Chang *et al.* [19], compared the effects of PRP and HA injection for management of knee OA and found that PRP injection is more effective than HA for patients with damaged articular cartilage and patients

Table 8 Several studies of intra-articular injection of knee osteoarthritis

References	Number of patients	Degree of OA	Injectable medication	Results
Li and colleagues	30	2nd and 3rd degree	PRP vs. saline	PRP is more effective
Duymus and colleagues	102	2nd and 3rd degree	PRP vs. hyaluronic acid vs. ozone	PRP is more effective
Rahimzadeh and colleagues	42	2nd and 3rd degree	PRP vs. 25% dextrose	PRP is more effective
Chang and colleagues	1543	2nd and 3rd degree	PRP vs. hyaluronic acid	PRP is more effective
Raeissadat and colleagues	160	2nd and 3rd degree	PRP vs. hyaluronic acid	PRP is more effective
Kon and colleagues	150	2nd and 3rd degree	PRP vs. hyaluronic acid	PRP has longer effect
Filardo and colleagues	109	2nd and 3rd degree	PRP vs. hyaluronic acid	PRP is more effective
KeSu and colleagues	86	2nd and 3rd degree	PRP vs. hyaluronic acid	PRP is more effective
Cole and colleagues	111	2nd and 3rd degree	PRP vs. hyaluronic acid	PRP has same effective as hyaluronic acid
López and colleagues	106	2nd and 3rd degree	PRP vs. hyaluronic acid vs. daily NSAIDs	PRP is more effective

PRP, platelet-rich plasma.

who received PRP injections had more and longer improvements. Moreover, patients with mild OA had better response to PRP injection than those had severe OA.

Raeissadat *et al*. [20], suggest that PRP injection is more effective than HA injection in reducing symptoms and improving quality of life of patients with knee OA and is the treatment of choice in managing knees OA.

Kon *et al*. [21], compared PRP injection with low-molecular-weight hyaluronic acid (LWHA) and with HWHA injection in patients who had knee OA. They found improvements in all patients, but patient satisfaction with treatment with PRP was more than that with HA. At the end of 2 months, the patients who received PRP and those who received LWHA showed similar improvements and more than the patients who received HWHA. However, after 6 months, patients who received PRP had better improvement than those who received HA injections. Moreover, patients, who received PRP, unlike the patients who receive LWHA, had an ascending course of improvement between 2 and 6 months. The degree of improvement was related to the degree of OA, as more improvement was achieved in patients with milder than those with advanced OA [21].

Filardo *et al*. [22], compared PRP and HA injection in the treatment of knee OA. They found that there were significant improvements in all patients with no significant differences between patients who receive PRP and those who receive HA and concluded that PRP does not have priority over HA in the management of patients with moderate OA.

Su *et al*. [23], stated that there was no significant difference between intra-articular injection of PRP and HA in patients who had OA in both knees evaluated by the visual analog scale, but PRP had superior effect than HA when patients were evaluated by WOMAC.

Cole *et al*. [24], concluded that that there was no significant difference between intra-articular injection of PRP and HA in patients who had OA of both knees evaluated by WOMAC, but patients treated with PRP injection had a significant decrease in proinflammatory cytokines, which suggest that the anti-inflammatory effect of PRP is better than that of HA.

In our study, we did not observe a significant change in cartilage thickening in any subregion, femoral or tibial, in both groups, which agreed with Buendía *et al*. [25], as they stated that there were no differences in cartilage thickness assessed by MRI in patients treated by hyaluronic injection, PRP injection, or nonsteroidal anti-inflammatory.

Conclusions

The effect of intra-articular injection of HA had significant improvement of pain and function of the knees in patients who had grade 4 OA of knees for up to 6 months than the effect of intra-articular injection of PRP, so it is better to inject such knees with HA every 6 months.

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Nil.

Conflicts of interest

We have no conflicts of interest to disclose.

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