Comparative study between platelet-rich plasma intraarticular injection versus hyaluronic acid in knee osteoarthritis

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Background
Osteoarthritis (OA) is a major public health problem that causes pain and disability in one-third of all affected patients. It primarily affects the elderly populations. This study aimed to evaluate the efficacy of intraarticular injections of platelet-rich plasma (PRP) versus hyaluronic acid (HA) in knee OA.
Patients and methods
This was a prospective study that included 40 adult patients with knee OA grades II and III, where 20 patients were treated with PRP intraarticular injection two injections 1 month apart (group A), and 20 patients were treated with HA injections generally administered as a weekly injection for 3 weeks (group B). Data were collected from January 2017 till February 2018.
In group A, the age of patients ranged from 45.0 to 67.0 years; five (25%) patients were males and 15 (75%) patients were females; unilateral side was affected in four (20%) patients, and bilateral side was affected in 16 (80%) patients; and grade II OA cases were 12 patients, and grade III OA cases were seven (40%) patients. In group B, the age of patients ranged from 49 to 75 years; five (25%) patients were males and 15 (75%) patients were females; unilateral side was affected in eight (40%) patients, and bilateral side was affected in 12 (60%) patients; and grade II OA cases were 11 (55%) patients, and grade III OA patients were nine (45%) patients. The procedure was done on an outpatient basis and under complete aseptic technique. PRP or HA was injected intraarticularly through an anterolateral or anteromedial portal. Follow-up with the patients was for at least 6 months, and the results of treatment were assessed by the knee injury and osteoarthritis outcome score (KOOS).
Results
At the end of the follow-up period, which was 6 months, the KOOS in group A had improved to a mean score of 64.89 ± 17.97 points, as compared with the pre-injection score, which was 49.95 ± 14.21 points. In group B, at end of follow-up, the period score was 58.60 ± 19.10 points and the pre-injection score was 49.39 ± 19.97 points.
Conclusion
Both PRP and HA injections show significant improvement in grades II and III OA. The KOOS symptom subscale showed that PRP injections were more effective than HA injections in patients with grade II arthritis.

Keywords:
hyaluronic acid, knee osteoarthritis, platelet-rich plasma

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Introduction

Osteoarthritis (OA) is a degenerative process of the joints characterized by progressive destruction and erosion of cartilage associated with an osteophyte response [1].

OA represents a huge burden to the society in terms of personal suffering and health resource utilization [2]. It remains by far the most common disease of joints with 65% of individuals older than 65 years having radiographic evidence of the disease in at least one joint [3,4].

It has been shown that the water content of an osteoarthritic joint is increased due to the marked decrease in type IX collagen content which normally prevents the highly hydrophilic proteoglycans from absorbing too much water [5–7].

The metabolic changes affecting the joint in OA include an increased levels of interleukin-l leading to increase in synthesis and secretion by chondrocytes of active matrix-degrading enzymes such as stromelysin and collagenase, which can break down all of the

components of the extracellular matrix and rapidly degrade the articular cartilage [8].

A marked reduction in concentration and molecular weight of endogenous hyaluronic acid (HA) ultimately reduced viscosity (viscoelastic properties) of synovial fluid, leading to induction of pre-inflammatory pathways. The overall result is gradual but irreversible degradation of the articular cartilage, formation of osteophytes, and the development of subchondral bone cysts leading to subsequent pain and deformity [7–9].

Treatment of OA includes nonpharmacologic management such as weight loss, physical therapy, and pharmacologic therapy, for example, oral chondroprotective drugs, acetaminophen, NSAIDs, COX-2-selective inhibitors, intraarticular either steroid injection, HA injection, or platelet-rich plasma (PRP), and surgical options, such as debridement, osteotomy, partial replacement, and total knee replacement [10].

HA is a highly viscous polysaccharide produced by synoviocytes, fibroblasts, and chondrocytes. It is a major integral chemical component of synovial fluid acting as a joint lubricant [11]. The native HA has a molecular weight of 4–10 million Daltons [12]. It is essential for the viscoelastic properties of the fluid because of its high viscosity and has a protective effect on articular cartilage and soft tissue surfaces of joints [13,14].

In OA, the concentration and molecular weight of HA are reduced, resulting in synovial fluid of lower elasticity and viscosity [11,15].

HA treatment aims to replace OA-induced deficiency, stimulate the production of endogenous HA, reduce pain, and improve physical function by supplementing the viscosity and elasticity of synovial fluid, which are reduced in OA [16].

The mechanical effect of HA in the treatment of OA is due to the viscosity of the HA, which restores the viscoelastic properties of the synovial fluid (cushioning, lubrication, and elasticity) [17–19]. Moreover, HA is thought to provide a range of biological actions including anti-inflammatory by inhibiting proinflammatory cytokines and prostaglandins, also another analgesic effect through creating a barrier around nociceptors – pain receptors, and anabolic effect by stimulating chondrocyte growth, synthesizing extracellular matrix protein, and inhibiting metalloprotease activity [17–20]. It has also been suggested that exogenous HA induces endogenous HA synthesis, possibly by stimulating the regenerative process within the joint [19,20].

At present, preparations with different molecular weights are available (low and high molecular weight), which display distinct pharmaceutical effects [20–22]. The enhanced penetration of low-molecular-weight preparations (0.5–1.5 million Dalton) through the extracellular matrix of the synovium is thought to maximize the concentration and to facilitate the interaction with target synovial cells, so reducing the synovial inflammation [22].

Recently, an HA cross-linked preparation (Hylan G – F 20), with high molecular weight (6–7 million Dalton), has been developed with the advantage of the reduced number of injections needed to obtain the therapeutic effect [22–24].

PRP has been used since the 1950s to manage maxillofacial and dermatological conditions [25,26]. The use of biological agents including PRP and mesenchymal stem cells in orthopedics has increased exponentially over the last few years owing to its autologous nature, supposed effectiveness, and lack of adverse effects [27,28]. PRP is an autologous blood product with platelet concentrations above baseline values [29]. The preparation process involves the extraction of blood from the patient, which is then centrifuged to obtain a concentrated suspension of platelets by plasmapheresis. It then undergoes a two-stage centrifugation process to separate the solid and liquid components of the anticoagulated blood [30]. The initial phase separates the plasma and platelets from the erythrocytes and leukocytes. The second stage uses a hard spin to concentrate the platelets further into platelet-rich and platelet-poor plasma components. The final PRP product is then injected into the knee joint space. There is also debate on the potential benefits of platelet-poor plasma on healing, and some formulations do not incorporate this step [31]. Many of the cytokines and growth factors believed to be responsible for the effects of PRP are contained within the α-granules of platelets. Basic cytokines contained within platelets include insulin-like growth factor, transforming growth factor-β, platelet-derived growth factor, fibroblast growth factor, epidermal growth factor, and vascular endothelial growth factor [32]. Platelet activation triggers degranulation and release of these growth factors. The application of this growth factor treatment is safe and minimally invasive. PRP provides an opportunity to improve patient outcomes using an autologous biological alternative to HA while also addressing the underlying inflammation through the stimulation of growth factors and the suppression of inflammatory cytokines [33].

Aim

This study aimed to evaluate the efficacy of intraarticular injection of PRP versus HA in knee OA.

Patients and methods

This is a prospective study that included 40 adult patients with unilateral or bilateral knee OA, where 20 patients were treated with PRP intraarticular injection two injections 1 month apart (group A) and 20 patients were treated with HA injections generally administered as a weekly injection for 3 weeks (group B).

The randomization was done by the presentation to our outpatient clinic with alternating injection between PRP and HA. Data were collected from January 2017 till February 2018.

All patients completed at least 6 months of follow-up.

The inclusion criteria included OA of the knee grades II and III according to the Kellgren–Lawrence grading system [34].

The exclusion criteria included rheumatoid arthritis, previous knee surgery, a previous local steroid injection into knee joint within 1 month, blood diseases, thrombocytopenia (<100 000 platelets/μl), and anemia (>10 g/dl).

The age in group A ranged from 45 to 67 years, with a mean value of 54.90 ± 6.85 years, and in group B, it ranged from 49 to 75, with a mean value of 58.80 ± 6.65 years. Males in group A were five (25%) patients and females were 15 (75%) patients. Similarly, in group B, males were five (25%) patients and females were 15 (75%) patients. There was no significant statistical difference regarding age and sex in the two studied groups (P>0.05). The unilateral side in group A was four (20%) patients and the bilateral side was 16 (80%) patients, and in group B, the unilateral side was eight (40%) patients and the bilateral side was 12 (60%) patients. There was no significant statistical difference regarding the side affected in the two studied groups (P>0.05). Nonoffice workers in group A were 13 (65%) patients, whereas in group B were 15 (75%) patients. Office workers in group A were seven (35%) patients whereas in group B were five patients [25]. There was no significant statistical difference between the two studied groups regarding the occupation (P>0.05). Grade II OA cases in group A were 12 (60%) patients, whereas in group B were 11 (55%) patients. Grade III OA cases in group A were seven (40%) patients, whereas in group B were nine (45%) patients. There was no significant statistical difference between the two studied groups regarding the grade of OA (P>0.05). In group A, the duration of symptoms ranged from 2 to 30 months, with a mean value of 8.15 ± 7.34 months and in group B ranged from 2 to 18 months with a mean value of 8.0 ± 4.87 months. There was no significant statistical difference regarding the duration of symptoms before surgery in the two studied groups (P>0.05). In group A the BMI ranged from 21.60 to 45.50, with a mean value of 21.60–45.50, and in group B, it ranged from 22.50 to 38.10, with a mean value of 27.27 ± 3.78. There was no significant statistical difference regarding BMI in the two studied groups (P>0.05). Patients with no associated deformity were 16 (80%) patients in each group. Patients with associated deformity in group A were four (20%) patients, having varus deformity, whereas in group B were four (20%) patients, where three had varus deformity and one had valgus deformity. There was no significant statistical difference between the two studied groups regarding the associated deformity (P>0.05).

Informed consent was taken from every patient in the study.

Each patient was assessed clinically and with a radiological examination including plain radiograph films for both knees in standing anteroposterior view, lateral view, and Stitch view (to detect deformity). Laboratory investigations included total and differential blood count as well as serum uric acid (to detect gouty arthritis).

Preparation of platelet-rich plasma

Overall, 20 ml of whole blood is obtained for each knee by venipuncture in acid citrate dextrose tubes (two tubes for each knee). The blood was centrifuged using a 'soft' spin for 10 min at a speed of 1400 r/min. The lower 1/3rd is PRP and the upper 2/3rd is platelet-poor plasma. The supernatant plasma containing platelets is transferred into another sterile tube (without anticoagulant). The tube is centrifuged at a higher speed for 10 min in speed of 2000 r/min to obtain a platelet concentrate. At the bottom of the tube, platelet pellets are formed. Platelet-poor plasma is removed and the platelet pellets are suspended in a minimum quantity of plasma (2 ml) by vortex. PRP is activated by calcium salts and auto thrombin just before injection.

Injection technique

The procedure was done on an outpatient basis and under complete aseptic technique. Low-molecular-weight HA was administered intraarticularly one injection per week for three weeks and PRP was injected intraarticularly twice with 1 month apart. Sterile dressing was applied for the site of injection.

Methods of assessment of results

Follow-up for the patients was done for at least 6 months, and the results of treatment were assessed regarding knee injury and osteoarthritis outcome

score (KOOS) [35]. All patients were assessed using the score before the injection and at the end of the follow-up period. KOOS consists of five subscales: pain, other symptoms, activities of daily living, sport and recreation function (Sport/Rec), and knee-related quality of life. KOOS is patient administered, the format is user friendly, and it takes about 10 min to complete.

Interpretation of scores

Scores are transformed to a 0–100 scale, with 0 representing extreme knee problems and 100 representing no knee problems as common in orthopedic scales and generic measures. Scores between 0 and 100 represent the percentage of the total possible score achieved.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. Qualitative data were described using numbers and percentages. Quantitative data were described using range (minimum and maximum), mean, SD, and median. The significance of the obtained results was judged at the 5% level. The used tests were the χ^2 test, Fisher's exact correction for χ^2, Spearman coefficient *t*, and Mann–Whitney test.

Results

At the end of the follow-up period, which was 6 months, the KOOS in group A was improved to a mean score of 64.89 ± 17.97 points as compared with the pre-injection score, which was 49.95 ± 14.21 points, whereas in group B, at the end of follow-up period, the score was 58.60 ± 19.10 points and the pre-injection score was 49.39 ± 19.97 points. The results showing improvement following intraarticular PRP and HA injections of the knee were statistically significant (Table 1).

The percentage of improvement in group A was 31.18 ± 16.26 and in the group B was 27.74 ± 32.6.

There was no significant statistical difference regarding the percentage of improvement in KOOS and age in the two studied groups (P>0.05).

There was no significant statistical difference regarding the percentage of improvement in KOOS and sex in the two studied groups (P>0.05).

There was a significant statistical difference regarding the percentage of improvement in KOOS and occupation in group A, but with no significant statistical difference in group B (Table 2).

Table 1 Comparison between the two studied groups according to knee injury and osteoarthritis outcome score (*N*=40)

KOOS	PRP	HA	*t*	*P*
Pre-injection	*N*=20	*N*=20		
Minimum–maximum	20.70–66.10	7.70–82.70		
Mean±SD	49.95 ± 14.21	49.39 ± 19.97	0.103	0.918
Median	54.25	48.50		
6-month f/u score				
Minimum–maximum	31.0–87.0	19.0–84.80		
Mean±SD	64.89 ± 17.97	58.60 ± 19.10	1.073	0.290
Median	70.30	59.70		
% of improvement	↑31.18 ± 16.26	↑27.74 ± 32.6		
P_1	<0.001*	<0.001*		

HA, hyaluronic acid; KOOS, knee injury and osteoarthritis outcome score; PRP, platelet-rich plasma; *t*, *P*, *t* and *P* values for Student *t* test for comparing between the two groups. P_1: *P* value for paired *t* test for comparing between pre and 6 months follow up. *Statistically significant at *P* value less than or equal to 0.05.

Table 2 Relation between % of improvement of knee injury and osteoarthritis outcome score and occupation in each group

% of improvement of KOOS	Occupation		*U*	*P*
	Nonoffice work	Office work		
PRP (*N*=20)	*N*=13	*N*=7		
Minimum–maximum	15.17–62.09	5.9–45.04		
Mean±SD	36.57 ± 15.23	21.16 ± 13.89	4.410*	0.036*
Median	33.33	16.50		
HA (*N*=20)	*N*=15	*N*=5		
Minimum–maximum	2.54–146.7	4.88–24.18		
Mean±SD	32.46 ± 36.38	13.60 ± 9.13	22.0	0.176
Median	23.02	9.84		

HA, hyaluronic acid; KOOS, knee injury and osteoarthritis outcome score; PRP, platelet-rich plasma; *U*, *P*, *U* and *P* values for Mann–Whitney test for comparing between the two categories. *Statistically significant at *P* value less than or equal to 0.05.

Table 3 Relation between % of improvement of knee injury and osteoarthritis outcome score and duration of complaint in months in each group

% of improvement of KOOS	Duration of complaint in months			*H*	*P*
	<5	5–10	>10		
PRP (*N*=20)	*N*=9	*N*=7	*N*=4		
Minimum–maximum	16.50–62.09	5.90–57.36	10.12–49.76		
Mean±SD	35.26±13.96	30.94±18.18	22.40±18.45	2.172	0.338
Median	32.89	25.31	14.85		
HA (*N*=20)	*N*=5	*N*=9	*N*=6		
Minimum–maximum	2.54–23.02	6.75–48.64	4.88–146.75		
Mean±SD	8.99±8.09	21.59±12.14	52.60±50.88	6.996*	0.030*
Median	6.52	19.47	32.84		

HA, hyaluronic acid; *H*, *P*, *H* and *P* values for Kruskal–Wallis test; KOOS, knee injury and osteoarthritis outcome score; PRP, platelet-rich plasma. *Statistically significant at *P* value less than or equal to 0.05.

Table 4 Relation between % of improvement of knee injury and osteoarthritis outcome score and grade of osteoarthritis in each group

% of improvement of KOOS	Grade of OA Kellgren and Lawrence		*U*	*P*
	II	III		
PRP (*N*=20)	*N*=12	*N*=8		
Minimum–maximum	16.50–62.09	5.90–49.76		
Mean±SD	38.55±13.72	20.11±13.72	14.00*	0.009*
Median	33.59	15.99		
HA (*N*=20)	*N*=11	*N*=9		
Minimum–maximum	2.54–28.01	4.88–146.75		
Mean±SD	13.52±8.74	45.13±42.55	16.00*	0.011*
Median	9.84	29.22		

HA, hyaluronic acid; KOOS, knee injury and osteoarthritis outcome score; OA, osteoarthritis; PRP, platelet-rich plasma; *U*, *P*, *U* and *P* values for Mann–Whitney test for comparing between the two categories. *Statistically significant at *P* value less than or equal to 0.05.

There was no significant statistical difference in the percentage of improvement in KOOS and duration of complaint in group A but with a significant statistical difference in group B (Table 3).

There was no significant statistical difference in the percentage of improvement in KOOS and BMI in group A but with a significant statistical difference in group B.

There was a significant statistical difference in the percentage of improvement in KOOS and Kellgren–Lawrence grading of OA in each of the studied groups (Table 4).

Discussion

OA is a major public health problem that causes pain and disability in most of the affected patients. It is one of the crucial musculoskeletal disorders characterized by the imbalanced homeostasis and destruction of the articular cartilage, in which proinflammatory cytokines are important catabolic regulators during the OA cascade [36].

Recently, various studies, including systematic reviews, have reported the effects of PRP on knee OA. Kon *et al.* [37] first reported on intraarticular PRP injections at 21-day intervals to 115 osteoarthritic knees, for a total of three sets of injections. International Knee Documentation Committee scores demonstrated statistically significant improvement at 6- and 12-month follow-up as compared with baseline. The authors studied PRP versus HA injections in 150 patients, with PRP treatment giving better results than HA in reducing pain and symptoms and recovering articular function [38].

Patel *et al.* [39] compared the effects of single injection or double injections of PRP and injection of normal saline (as a control group) in patients with knee arthritis, which showed that single injection was as effective as two times injections and both had better effects than normal saline injection. In their study, PRP obtained was lacking leukocytes with a concentration of 2.5 million/μl with a single centrifuge turn.

The results of the present study are similar to those of Wang-Saegusa *et al.* [40] who evaluated the effects of PRGF (platelet rich in growth factors) on functional capacity and quality of life of patients with knee OA. In their study, the improvements of the mean WOMAC and its components, as well as mean changes of physical parameters of the SF36 questionnaire, were significant.

The study by Filardo *et al*. [41] showed that in patients with higher BMI and higher grades of OA, the amounts of improvement were lower.

Several randomized control trials (RCT) and several systematic reviews of RCTs on PRP for knee OA have been published [42–44]. For example, a 2014 systematic review was conducted by Chang *et al*. [42] comprising five RCTs, three quasi-RCTs, and eight single-arm prospective series (total *N*=1543 patients) comparing PRP with HA (four RCTs, two quasi-randomized) or saline placebo (one RCT). The meta-analysis of functional outcomes found that the effectiveness of PRP was greater than that of HA and improved over 12 months.

Xie *et al*. [45] revealed the anti-inflammatory potential of PRP, its anabolic effect on chondrocytes mesenchymal stem cells and synoviocytes, and even its possible role in cartilage regeneration acting as a bioactive cell scaffold.

Platelet concentration is one of the most topical factors in PRP treatment. Some authors suggest that the PRP platelet concentration should be at least two times the whole blood platelet concentration; however, concentrations up to eight times that of blood levels have been reported with good results [46,47]. In practice, there is evidence that positive clinical outcomes in knee OA can be obtained with relatively low platelet concentrations [48].

Chang *et al*. [42] reviewed the effects of intraarticular PRP injection in knee OA compared with HA in a systematic review performed in 2014. The study demonstrated that PRP led to significant functional improvement in patients with knee cartilage pathology, whose effects last at least 12 months. Compared with patients receiving HA, patients in the PRP group had more and longer improvement. There were also better results among those patients with milder forms of OA than advanced ones. Similar results were obtained in another meta-analysis by Khoshbin *et al*. [49] who found the PRP injection was more efficient than HA and normal saline in mild to moderate OA in 2013. This prospective study included 40 adult patients with knee OA, who were divided into two groups: group A comprised 20 patients managed by intraarticular PRP injection and group B comprised the other 20 patients managed by intraarticular low-molecular weight-HA injections.

There was no significant statistical difference regarding age, side affected, and sex in the two studied groups (P>0.05).

The improvement of the KOOS at the end of the follow-up period, which was a minimum of 6 months, following intraarticular PRP and HA injections of the knee was statistically significant. The percentage of improvement in group A was 31.18 ± 16.26 and in group B was 27.74 ± 32.6.

There was a statistically significant difference in the percentage of improvement in KOOS and the duration of complaint in group B unlike group A. This could be explained by that the effect of HA injection is better with a more advanced grade of OA compared with PRP.

There was a statistically significant difference in the percentage of improvement in KOOS and the occupation of the patients in group A unlike group B, with significant improvement in the case of nonoffice workers with PRP injection. This needs further studies to prove that PRP is a better option than HA in more demanding patients.

There was a significant statistical difference in the percentage of improvement in KOOS and Kellgren–Lawrence grading of OA in each of the studied groups.

The KOOS symptom subscale showed that PRP injections were more effective than HA injections in patients with grade II arthritis but not as effective in patients with grade III arthritis. In agreement with the present work, recent studies have shown that PRP is as effective as HA in the treatment of knee arthritis, showing more effective for patients with lower grades of arthritis [42,50].

Conclusion

Both PRP and HA injections show significant improvement in grades II and III OA. The KOOS symptom subscale showed that PRP injections were more effective than HA injections in patients with grade II arthritis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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