Treatment of knee osteoarthritis with platelet-rich plasma in comparison with platelet-rich plasma plus hyaluronic acid: a short-term double-blind randomized clinical study

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Background
Platelet-rich plasma (PRP) and hyaluronic acid (HA) intra-articular knee injections are widely accepted as modalities to treat pain and functional limitation associated with knee osteoarthritis. So it can be assumed that a combination of both HA and PRP in one injection could supply many advantages for cartilage repair. It adds the benefit of HA viscosupplementation with PRP regenerative properties. This study aims at finding out whether blending HA with PRP gives better clinical and functional results when compared with PRP intra-articular injection alone.
Patients and methods
A prospective, double-blind, randomized, multicenter clinical trial was conducted. It included 58 patients with average age of 35 years (range: 29–49 years), started on January 2016 and ended on June 2017. Each patient had initial assessment, and then were followed up after 6 months and then at 12 months. They were randomized into two groups: group 1 (PRP) (24 cases) was injected with PRP only and group 2 (PRP +HA) (34 cases) was injected with PRP plus highly cross-linked sodium hyaluronate.
Results
Initially, both groups were matched in age and BMI, with *P* value more than 0.05. Both groups were also matched on their initial assessment by the three clinical assessment methods, namely, knee society score, global impression of changes, and the Western Ontario and McMaster Universities Arthritis Index, with *P* value more than 0.05.
Comparing groups 1 and 2 regarding the follow-up results showed, globally, no significant superiority of group 2 (PRP+HA) over group 1 (PRP). It was quite apparent in global impression of changes at 6 and 12 months, and in Western Ontario and McMaster Universities Arthritis Index at 6 and 12 months, with *P* value more than 0.05. Knee society score gives results with group 1 (PRP group) at 6 month and after 1 year follow-up, which were better than the results of group 2 (PRP+HA), with *P* value less than 0.05.
Follow-up of each group of patient separately at 6 months and 1 year showed that each of them has highly significant improvement regarding pain and functional outcome, with *P* value less than 0.001.
Conclusion
PRP intra-articular injection appears to improve pain and function in middle-aged women with mild to moderate knee osteoarthritis, with no added benefit of blending HA with PRP during injection.

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

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Introduction

Multiple treatment modalities are used to treat knee pain and improve quality of life of patients with knee osteoarthritis (OA), including analgesics, physical therapy, exercise, and intra-articular injections of glucocorticoids, hyaluronic acid (HA), ozone gas, and autologous cells, for example, platelet-rich plasma (PRP) and stem cells [1].

OA is initiated by loss of proteoglycans from the extracellular matrix and failure of chondrocytes to synthesize new matrix which ends in weakening and degeneration of cartilage [2].

Hyaluronic acid intra-articular injection characteristic

(1) HA is a key regulator for maintaining chondrocyte functions and enhances its regenerative potential, reducing pain and improving viscoelasticity of synovial fluid [3].
(2) It enhances angiogenesis by creating a balanced environment for synoviocytes [4–6].

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Platelet-rich plasma intra-articular injection characteristic

It has different modes of action to improve the physiological balance of joints.

(1) It enhances cartilage healing and remodeling through delivering high concentration of growth factors, thus improving clinical and structural outcomes [7].
(2) It decreases catabolism of cartilage, increases anabolism, and promotes chondrocyte proliferation and production of matrix molecules [8]. Higher amounts of collagen II synthesis have been documented by Akeda *et al*. [9] and Pereira *et al*. [10].

So it can be assumed that a combination of both HA and PRP could supply many advantages for cartilage repair. It adds the benefit of HA viscosupplementation with PRP regenerative properties [11]

Aim

The aim of this study was to prospectively compare the clinical efficacy regarding pain and functional outcome of treating two groups of patients diagnosed to have symptomatic moderate knee OA (grade II and III knee OA) and to find out if blending HA with PRP adds an extra benefit. The first group was treated with intra-articular PRP injection and the second was treated with intra-articular PRP plus HA injection.

Patients and methods

Study design and patients

This study is a prospective, double blind, randomized, multicenter clinical trial. Enrolment started on January 2016 and ended by May 2016. Patients were recruited and followed up in Helwan University Hospital in Cairo Governorate, Egypt. Overall, 64 patients were first enrolled. They were all scheduled for knee injections. Study details were explained to them, and then they all signed an informed consent form agreeing to participate as volunteers. Six cases were excluded later on because they were noncompliant and used NSAID during the follow-up period, which has an antiplatelet effect and can alter the results. The remaining 58 cases were randomized by simple randomization method. The average age of the patients was 35 years (range: 29–49 years). All patients were nonathletic, housewives, and Egyptian women having within-normal healthy weight.

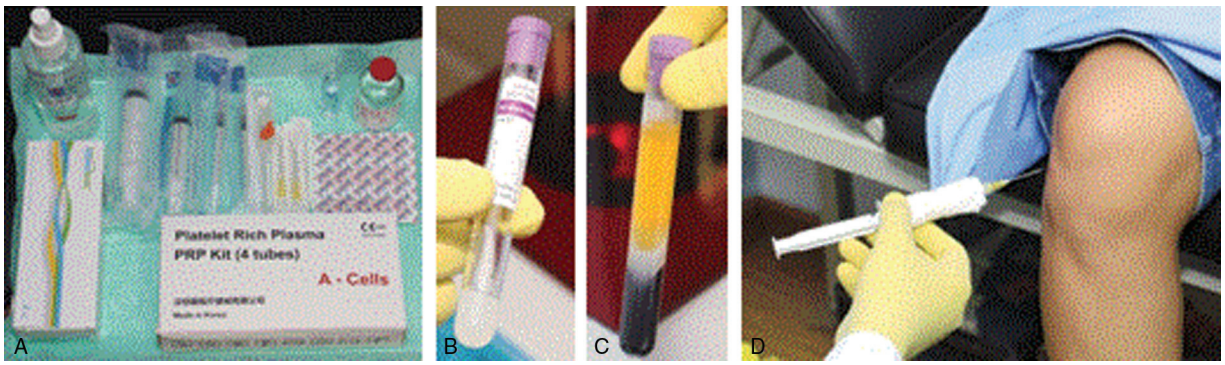
Two groups were identified: the first group (PRP) consisted of 24 cases, and their affected knees were injected with 5 ml of PRP only. The second group (PRP+HA) included 34 cases, and their affected knees were injected with 3 ml of PRP plus 2 ml of HA.

Platelet-rich plasma preparation

PRP was prepared by taking 12 ml of autologous blood in "A-cells" Korean made kit (Fig. 1a and b), then centrifuged once for 10 minutes at speed of 3500 rotation per minute (Fig. 1c). Then supernatant platelet rich plasma was aspirated then injected into the patient's diseased knee.

Second group (PRP+HA) consisting of 34 cases, and their affected knees were injected with 3 ml PRP, prepared by the same technique as of group 1, plus 2 ml (44 mg) of (MONOVISC, ANIKA THERAPUTICS, INC., Bedford, MA, USA) (Fig. 1a). It is a single injection viscosupplement comprising highly purified, partially cross-linked sodium hyaluronate in a PBS. MONOVISC is a non-animal sourced HA, used as a single-injection treatment approved for use in the USA and cheapest in the Egyptian market (Fig. 1a) [12,13].

Figure 1



(a) Materials used for injection including A-cell platelet-rich plasma (PRP) kit and MONOVISC. (b) A-cell PRP 12 ml test tube for blood sampling and separation. (c) Blood components after centrifugation: PRP (upper, yellow part), puffy coat (middle part) and red cells (lower red part). (d) Blinded knee injection through anterolateral parapatellar portal.

Anterolateral parapatellar portal was used for injection after using 1 ml of local anesthetic in skin and subcutaneous tissues. The two groups received one injection weekly for 5 consecutive weeks (Fig. 1d). At the time of injection, patients were avoided from knowing the substance they were receiving by covering the syringe (Fig. 1d).

No analgesics or anti-inflammatory agent was given. They were advised to utilize between 2 and 3 liters of water daily. Each patient had initial assessment (day 0), and then were followed up after 6 months (day 180), and then at 12 months (day 360). Clinical assessments were performed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), patients' global impression of change scale, and functional knee society score (KSS). Both assessor and patients were blinded to the study protocol.

Inclusion criteria

Only patients who have been experiencing a painful knee for at least 3 months with clinical and radiological diagnoses of mild to moderate knee OA according to Kellgren–Lawrence classification (grade II and III) were included with the following characteristics [14]:

(1) Female.
(2) Age was between 25 and 50 years.
(3) Egyptian.
(4) Nonathletic.
(5) Housewife (nonworker).
(6) Normal healthy weight (BMI) [15].

Exclusion criteria

The following were the exclusion criteria:

(1) Coagulopathies or those on anticoagulant therapy.
(2) Diabetes mellitus.
(3) Rheumatoid disease.
(4) Lower limb axis deviation of more than ±5°.
(5) Severe cardiovascular diseases.
(6) Local or systemic infection.
(7) Immunosuppressive diseases.
(8) Those who received anti-inflammatory drugs until 7 days before blood sampling.
(9) Abnormal complete blood count.
(10) Previous knee surgeries.

Data analysis

Final data before and after the treatment were uploaded and statistically analyzed and represented using statistical package for the social sciences (SPSS 15.0.1 for Windows; SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were represented as mean±SD, and minimum and maximum values (range). For analytical statistics, quantitative data were tested for normality to select either a parametric (pooled *t*-test) or a nonparametric (Mann–Whitney/Wilcoxon) test of significance. Paired *t*-test was used for parametric data follow-up. *P* value was considered significant if less than 0.05.

Results

This study included 58 patient recruited and followed up in Helwan University Hospital during the period from January 2016 till May 2017. On initial visit, patients were randomly divided into two groups based on the management done. The first group included 24 cases who are subjected to intra-articular injection of PRP group (group 1). The second group included 34 cases subjected to PRP-HA group (group 2). Follow-up longitudinal assessment was done for all cases after 6 months and then after 12 months from their initial visit/intervention (Table 1).

Regarding demographic data

From the previous table, there was no significant difference between group 1 and group 2 regarding age and BMI (i.e. both groups were marched in age and BMI).

Regarding functional knee society score

Both groups were matched in KSS at initial assessment ($P>0.05$); after 6 months, there was a significant difference between group 1 and group 2, being higher in group 1, and after 12 months, there was a significant difference between group 1 and group 2, being higher in group 1.

On analyzing the changes from initial assessment till 6 months, there was a significant difference between both groups, as the changes in group 1 overrode group 2. On analyzing the changes from initial assessment till 12 months, there was a borderline significant difference ($P=0.06$) between both groups, as the changes in group 1 overrode group 2, and on analyzing the changes from 6 months assessment till 12 months), there was no significant difference ($P>0.05$) between both groups.

Patients' global impression of change scale

There was no significant difference between both groups regarding patient's global impression score after 6 months, as well as after 12 months.

Regarding Western Ontario and McMaster Universities Arthritis Index

Both groups were matched in WOMAC at initial assessment ($P>0.05$). After 6 months, there was no significant difference between group 1 and group 2, whereas after 12 months, there was a borderline

Table 1 Descriptive and analytical statistics between group 1 and group 2

	Group 1 [mean±SD (range)]	Group 2 [mean±SD (range)]	*t*/*z*	*P* (significant)
Demographic data				
Age (years)	34.08±5.01 (29–45)	36.71±6.37 (29–49)	1.68	>0.05 (NS)
BMI (kg/m^2)	21.65±2.12 (18.5–25.0)	21.55±1.97 (19–25)	0.16	>0.05 (NS)
KSS				
Initial assessment	40.83±4.58 (35–50)	41.18±4.93 (35–50)	0.26	>0.05 (NS)
After 6 months	93.75±4.95 (90–100)	89.71±7.58 (80–100)	2.29	<0.05 (S)
After 1 year	95.42±6.58 (80–100)	90.88±8.30 (80–100)	2.23	<0.05 (S)
Change (6 months to 0)	52.92±6.90 (40–65)	48.53±8.12 (30–65)	2.15	<0.05 (S)
Change (12 months to 0)	54.58±7.50 (40–65)	49.71±10.51 (30–65)	1.94	0.06
Change (12 months to 6)	1.67±8.16 (–20 to 10)	1.18±10.08 (–10 to 20)	*Z*=0.19	>0.05 (NS)
Global impression of changes				
After 6 months	5.67±0.64 (5–7)	5.74±0.66 (5–7)	0.39	>0.05 (NS)
After 1 year	6.00±0.66 (5–7)	6.09±0.75 (5–7)	0.46	>0.05 (NS)
WOMAC				
Initial assessment	46.25±12.09 (32.6–61.4)	48.14±12.88 (32.6–62.9)	0.56	>0.05 (NS)
After 6 months	72.26±3.46 (68.2–77.3)	71.65±3.71 (68.2–78.0)	0.64	>0.05 (NS)
After 1 year	77.17±1.54 (74.2–78.9)	75.91±2.90 (68.2–78.9)	1.93	0.06
Change (6 months to 0)	26.00±12.96 (6.8–44.7)	23.50±13.84 (5.3–45.4)	0.69	>0.05 (NS)
Change (12 months to 0)	30.91±12.22 (13.6–46.3)	27.77±13.73 (5.3–46.3)	0.89	>0.05 (NS)
Change (12 months to 6)	4.90±3.26 (0.7–10.7)	4.27±3.93 (–3.8 to 9.8)	*Z*=0.65	>0.05 (NS)

KSS, functional knee society score; S, significance; WOMAC, The Western Ontario and McMaster Universities Arthritis Index.

Table 2 Follow-up studies in group I

	Group 1 (mean±SD)	Paired *t*-test	*P* (significant)
KSS			
Initial assessment	40.83±4.58	37.55	<0.001 (HS)
After 6 months	93.75±4.95		
Initial assessment	40.83±4.58	35.62	<0.001 (HS)
After 1 year	95.42±6.58		
After 6 months	93.75±4.95	1.00	>0.05 (NS)
After 1 year	95.42±6.58		
WOMAC			
Initial assessment	46.25±12.09	9.82	<0.001 (HS)
After 6 months	72.26±3.46		
Initial assessment	46.25±12.09	12.39	<0.001 (HS)
After 1 year	77.17±1.54		
After 6 months	72.26±3.46	7.37	<0.001 (HS)
After 1 year	77.17±1.54		

HS, highly significant; KSS, functional knee society score; WOMAC, The Western Ontario and McMaster Universities Arthritis Index.

significant difference between group 1 and group 2, being higher in group-1. On analyzing the changes from initial assessment till 6 months, there was no significant difference between both groups, and on analyzing the changes from initial assessment till 12 months, there was no significant difference between both groups.

Analyzing the changes from 6 months assessment till 12 months), there was no significant difference (P>0.05) between both the groups (Table 2).

Regarding knee society score of group 1

The mean of KSS at initial assessment was 40.83±4.58, whereas after 6 months was 93.75±4.95. There was highly significant improvement from initial till 6 months, with P value of less than 0.001. The mean of KSS at initial assessment was 40.83±4.58, whereas after 12 months was 95.42±6.58. There was highly significant improvement from initial till 12 months, with P value of less than 0.001. The mean of KSS at 6 months was 93.75±4.95, whereas after 12 months was 95.42±6.58. There was no significant improvement from 6 months till 12 months, with P value of more than 0.05.

Regarding Western Ontario and McMaster Universities Arthritis Index for group 1

The mean of WOMAC at initial assessment was 46.25 ±12.09, whereas after 6 months was 72.26±3.46. There

Table 3 Follow-up studies in group 2

	Group 2 (mean±SD)	Paired *t*-test	*P* (significant)
KSS			
Initial assessment	41.18±4.93	34.84	<0.001 (HS)
After 6 months	89.71±7.58		
Initial assessment	41.18±4.93	27.57	<0.001 (HS)
After 1 year	90.88±8.30		
After 6 months	89.71±7.58	0.68	>0.05 (NS)
After 1 year	90.88±8.30		
WOMAC			
Initial assessment	48.14±12.88	9.90	<0.001 (HS)
After 6 months	71.65±3.71		
Initial assessment	48.14±12.88	11.79	<0.001 (HS)
After 1 year	75.91±2.90		
After 6 months	71.65±3.71	6.34	<0.001 (HS)
After 1 year	75.91±2.90		

HS, highly significant; KSS, Functional knee society score; WOMAC, The Western Ontario and McMaster Universities Arthritis Index.

was a highly significant improvement from initial till 6 months, with *P* value of less than 0.001. The mean of KSS at initial assessment was 46.25±12.09, whereas after 12 months was 77.17±1.54. There was a highly significant improvement from initial till 12 months, with *P* value of less than 0.001. The mean of KSS at 6 months was 72.26±3.46, whereas after 12 months was 77.17±1.54. There was a highly significant improvement from initial till 12 months, with *P* value of less than 0.001 (Table 3).

Regarding knee society score of group 2

The mean of KSS at initial assessment was 41.18±4.93, whereas after 6 months was 89.71±7.58. There was a highly significant improvement from initial till 6 months with *P* value of less than 0.001. The mean of KSS at initial assessment was 41.18±4.93, whereas after 12 months was 90.88±8.30. There was highly significant improvement from initial till 12 months, with *P* value of less than 0.001. The mean of KSS at 6 months was 89.71±7.58, whereas after 12 months was 90.88±8.30. There was no significant improvement from 6 months till 12 months, with *P* value of more than 0.05.

Western Ontario and McMaster Universities Arthritis Index in group 2

The mean of WOMAC at initial assessment was 48.14 ±12.88, whereas after 6 months was 71.65±3.71. There was a highly significant improvement from initial till 6 months, with *P* value of less than 0.001. The mean of KSS at initial assessment was 48.14±12.88, whereas after 12 months was 75.91±2.90. There was a highly significant improvement from initial till 12 months, with *P* value of less than 0.001. The mean of KSS at 6 months was 71.65±3.71, whereas after 12 months was 75.91±2.90. There was a highly significant improvement from initial till 12 months, with *P* value of less than 0.001.

Discussion

Knee pain affecting quality of life and rendering activities of daily living difficult in young females with early stages of knee OA is seen in good numbers in our daily practice. In such cases, intra-articular injection is an option which is agreed upon by evidence-based scientific studies. We have chosen this group of patients to study and compare the effect of PRP versus PRP combination with HA injection. We only included patients with no other risk factors that might bias our results, for example, overweight and excessive daily activities. Some of them have moderate physical activities. This study is mainly targeted to groups of patients with grade II and III knee OA in our center who were seeking type of treatment that will help their pain and function with limited adverse effects to continue with their normal activities of daily living.

An in-vitro study done by Russo *et al.* [11] had an opposite opinion than our results and concluded that the combination of HA and PRP could supply many advantages for tissue repair and they both have a synergistic anabolic actions. The contradiction between this study and ours can be explained by using different methodology in addition to that it is an in-vitro study with no functional or clinical outcome assessment.

Chen *et al.* [3] studied three case reports and suggested that PRP and HA blend may be useful to treat advanced knee OA. However, this case series was on a different patient age group with different degree of

OA from our study. Moreover, PRP injection only was not compared with HA plus PRP in this series.

In January 2016, Guo *et al.* [16] conducted a cohort study comparing results of injecting PRP only with PRP plus HA to treat patients with pain owing to mild to moderate knee OA and found out that blending PRP and HA is effective and safe. It was also concluded in this study that combination of both PRP and HA has no differences in functional outcomes when compared with PRP only group [16]. Their conclusion is similar to ours stating that there is no added benefit in blending HA to PRP when injected to symptomatic arthritic knees. However, there was a trend in the study results of Guo *et al.* [16] that PRP plus HA could obtain relatively better functional scores. These contradicting results when compared with our study might be owing to difference in demographic data of patients between the two studies. Guo *et al.* [16] enrolled older age group and males together with females with higher BMI. On the contrary, we enrolled only middle-aged females with normal BMI. Regarding methodology, they only used three injections to treat their patients, whereas we gave five injections. Moreover, they instructed their patients to do exercise after injection, which is not the case in our study. Regarding methods of assessment, they used Visual Analog Scale and WOMAC, whereas we used WOMAC, patients' global impression of change, and functional KSS. These differences in demographic data, number of injections, and different postinjection protocol, along with different scales for assessment might be responsible for the minute difference in results between our study and their study.

Three meta-analysis and systematic reviews were done in the past 3 years on PRP efficacy in treatment of knee OA that need to be mentioned. A meta-analysis done by Shen *et al.* [17] concluded efficacy of using PRP in treatment of knee OA. It concluded that intra-articular PRP injections probably are more effective in the treatment of knee OA in terms of pain relief and functional improvement at 3, 6, and 12-month follow-up, compared with HA injection alone.

Another meta-analysis published in 2017 by Dai *et al.* [18] showed that PRP may have more benefit in pain relief and functional improvement than HA injection in patients with symptomatic knee OA at 1 year after injection.

Moreover, a 2-year follow-up systematic review and meta-analysis following PRP injection done in 2016 by Sadabad *et al.* [19] showed the efficacy of PRP versus HA. However, they recommended further studies to determine the longer term effects.

Conclusion

PRP intra-articular injection appears to improve pain and function in middle-aged women with mild to moderate knee OA. However, there is no added benefit of blending HA with PRP during injection.

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Conflicts of interest

There are no conflicts of interest.

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