


ORIGINAL ARTICLE

Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis

Hamada S. AHMAD,¹ Sherief E. FARRAG,¹ Amr E. OKASHA,¹ Aisha O. KADRY,² Tamer B. ATA,³ Amir A. MONIR⁴ and Ibrahim SHADY⁵ 

¹Rheumatology and Rehabilitation Department, Mansoura Faculty of Medicine, Mansoura University, Mansoura, ²Physical Medicine, Rheumatology, and Rehabilitation, Al Azhar Faculty of Medicine, Al Azhar University, Cairo, ³Medical Microbiology and Immunology, ⁴Diagnostic Radiology, and ⁵Community Medicine Department, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt

Abstract

Background: Hyaluronic acid (HA) and platelet-rich plasma (PRP) are two treatment options used for knee osteoarthritis (KOA) but studies comparing the efficacy of the two yield conflicting results. In addition, the association of clinical outcomes of PRP intra-articular injections with changes in the ultrasonography structural appearance of the knee has not been investigated.

Aim: To compare the efficacy of PRP and HA intra-articular injections as mono-therapeutic options for primary KOA, and to determine whether the clinical outcomes are associated with changes in the ultrasonography structural appearance.

Subjects and methods: A randomized clinical trial was conducted on 89 patients with KOA. The patients were given either PRP ($n = 45$) or HA ($n = 44$) intra-articular injections. The patients received three injections in the knee, which was more symptomatic at baseline evaluation, with a 2-week interval between injections. The outcome measures included visual analog score – pain, International Knee Documentation Committee Score, and assessment of synovial hypertrophy, synovial vascularity and knee effusion using ultrasonography. Outcome measures were assessed at baseline and at 3 and 6 months post-injection.

Results: While both PRP and HA injections resulted in the improvement of all outcome measures at 3 and 6 months follow up, they were significantly better in the PRP group than in the HA group.

Conclusion: Intra-articular injection of PRP is an effective treatment that reduced pain and improved functional status in patients with KOA. The clinical outcomes of the intra-articular injections of PRP are associated with improved synovial hypertrophy and vascularity scores, and less effusion.

Key words: clinical aspects osteoarthritis, clinical trials, drug treatment osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, especially among the elderly, and is a leading cause

of chronic disability worldwide, mostly as a consequence of knee OA (KOA).¹ Millions of people affected by KOA suffer from chronic pain which affects their quality of life.² Among those older than 45 years, 16.7% have symptomatic KOA, 27.8% show radiographic evidence for KOA, and the remaining 87% have bilateral KOA.³ Moreover, an increase in the prevalence of symptomatic KOA by 4.1% and 6% has been

Correspondence: Dr Ibrahim Shady, Community Medicine Department, Mansoura Faculty of Medicine, Mansoura University, El Gomhouria St, Mansoura, Dakahlia Governorate 35516, Egypt. Email: ebrshady@outlook.com

reported over the past 20 years among women and men, respectively.⁴ The prevalence of KOA is expected to increase further due to an aging population and increasing obesity prevalence.

Evidence from recent studies indicates that synovitis plays a critical role in the symptomatic and structural progression of OA.^{5,6} It has been reported that synovitis strongly correlates with the severity of symptoms, cartilage degeneration rate, and osteophyte formation, and determines, at least in part, the pattern of disease evolution and progression.⁷

An intra-articular injection of hyaluronic acid (HA) is currently used for the treatment of KOA. When compared to non-steroidal anti-inflammatory drugs (NSAIDs), HA has been found to be more effective and safer.^{8,9} There has been an increasing interest in recent years to use platelet-rich plasma (PRP) intra-articular injections for KOA treatment.¹⁰ PRP offers a low-cost and minimally invasive method of delivering highly concentrated autologous growth factors and bioactive molecules to the arthritic knees. Platelets are in fact used in the treatment of various diseases as they are a reservoir of growth factors which regulate the process of tissue healing and regeneration.^{11–13}

Several uncontrolled trials on patients with KOA indicate that intra-articular PRP injections result in better clinical outcomes at the end of the treatment in terms of pain reduction, tenderness, and functional capacity compared to the baseline values.^{14–20} However, studies comparing the efficacy of HA and PRP on KOA have yielded conflicting results. Studies show PRP to be either more effective than^{21,22} or equal to HA^{23,24} in the treatment of KOA. In addition, to our knowledge, no study so far has investigated the clinical outcomes of PRP intra-articular injections with changes in the ultrasonography structural appearance of the knee.

The aim of this study was to compare the efficacy of PRP and HA intra-articular injection monotherapies in primary KOA treatment and to determine whether the clinical outcomes are associated with changes in the ultrasonography structural appearance.

SUBJECTS AND METHODS

Study design

A single-blinded randomized controlled trial was conducted on parallel treatment groups.

Study population

One hundred consecutive patients with primary KOA were enrolled for the study from March 2016 to

February 2017. To be eligible for inclusion, the patients had to meet the European League Against Rheumatism 2010 criteria for the diagnosis of primary KOA²⁵ and had to have radiographic evidence of mild to moderate OA as per the Kellgren–Lawrence classification.²⁶ The exclusion criteria included age < 40 years, coagulopathies, diabetes mellitus, intake of antithrombotic and antiplatelet drugs and NSAIDs, thrombocytopenia, and history of previous knee surgery or knee disorder other than the current primary OA. Before inclusion in the study, the procedure of the study was explained to the patients and all patients provided a written consent.

Baseline evaluation and outcome measures

The demographic characteristics of the patients and the baseline clinical and ultrasonography measurements were assessed. The clinical outcomes included visual analog scale – pain (VAS-pain), International Knee Documentation Committee (IKDC) subjective and objective scores,²⁷ synovial hypertrophy and presence of effusion assessed using grayscale ultrasound (US), and degree of synovial vascularity measured using power Doppler US. Synovial hypertrophy was scored using a semi-quantitative system grade ranging from 0 (absent) to 3 (severe),²⁸ while the extent of synovial vascularity was graded from 1 (minimal perfusion) to 4 (marked perfusion).²⁹ Patients were submitted at 3 and 6 months post-intervention for evaluation of the outcome measures.

Randomization

Out of the 100 patients invited to participate in the current study, four patients did not provide a written consent and six patients were excluded according to the exclusion criteria, leaving only 90 eligible participants. After the baseline evaluation, the patients were randomized 1 : 1 by means of block randomization and allocated into one of the two treatment groups. One patient in the HA intra-articular injection (HA-IAI) group died during follow up; therefore, data of only 89 patients (45 in the PRP intra-articular injection (PRP-IAI) group and 44 in HA-IAI group) were analyzed at the end of the study.

Intervention

The patients were instructed to discontinue any NSAIDs from 2 weeks prior to starting treatment until the end of the study. US-guided injections were given three times in the more symptomatic knee (as determined at baseline evaluation) to each patient, with an interval of 2 weeks between the injections.

For PRP-IAI preparation, 8 mL of peripheral blood was extracted and centrifuged for 9 min at 3500 rpm. The protocol that was used in this study did not include a second centrifugation step. Subsequently, 4 mL of PRP were obtained from each patient and were used for the intra-articular injection. PRP used in this study was not leucocytes-free.³⁰

For the HA-IAI injection, 2.0 mL (20 mg of HA) of high molecular weight HA were given to patients in the HA group. Post-injection, patients were instructed to an apply icepack on the injected area for 30 min three times a day during the first 2 days, and switch to hot packs on the third and fourth days post-injection.

Statistical analysis

All statistical analyses were performed using SPSS for windows version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as means \pm standard deviation (SD), while categorical data were expressed in numbers and percentages. The differences between two groups or more were determined using independent samples Student's *t*-test for variables with continuous data or Chi-square test for variables containing categorical data. Statistical significance was set at $P < 0.05$.

RESULTS

According to the inclusion and exclusion criteria, only 90 patients with KOA were eligible for inclusion in the study. The patients were randomized 1 : 1 into two treatment groups. One patient in the HA-IAI group died during follow up and therefore data of only 89 patients were analyzed (45 in the PRP-IAI group and 44 in HA-IAI group). Table 1 shows that the baseline characteristics, namely the age, sex, body mass index, duration of KOA and the radiological grade, did not differ significantly between the two groups. In addition, the clinical, as well as the ultrasonography outcome measures, were statistically not different between the two groups at baseline evaluation (Table 2).

At the 3-month evaluation, both groups showed improvement in all the clinical and ultrasonography outcome measures compared to the baseline. However, VAS-pain, synovial vascularity and synovial hypertrophy were significantly lower while the IKDC score was significantly higher in the PRP-IAI group compared to the HA-IAI group. Furthermore, patients in the PRP-IAI group had less frequent effusions than patients in the HA-IAI group (Table 3). At the 6-month evaluation, both groups showed further improvements in all the clinical and ultrasonography outcome measures when

Table 1 Comparison of the sociodemographic data, BMI, duration of KOA and Kellgren–Lawrence grade between the PRP-IAI group and HA-IAI group at baseline

	PRP-IAI group	HA-IAI group	<i>P</i>
Age (years)	56.2 \pm 6.8	56.8 \pm 7.4	0.691
Females (<i>n</i> , %)	31, 68.9%	30, 68.2%	0.336
BMI (kg/m ²)	26.7 \pm 3.6	26.5 \pm 3.5	0.791
Duration of KOA (years)	9.7 \pm 3.9	10.1 \pm 4.2	0.643
Kellgren–Lawrence grade:			
Grade I	8, 17.8%	7, 15.9%	
Grade II	17, 37.8%	19, 43.2%	
Grade III	20, 44.4%	18, 40.9%	0.873

BMI, body mass index; HA-IAI, hyaluronic acid intraarticular injection; KOA, knee osteoarthritis; PRP-IAI, platelet-rich plasma intraarticular injection.

Table 2 Comparison of the outcome measures between the PRP-IAI group and HA-IAI group at baseline

	PRP-IAI group	HA-IAI group	<i>P</i>
Clinical parameters			
VAS-pain	5.8 \pm 1.9	6.1 \pm 1.7	0.435
IKDC score	49.2 \pm 14.9	47.2 \pm 16.2	0.546
US findings			
Synovial vascularity	1.99 \pm 0.95	2.05 \pm 0.85	0.755
Synovial hypertrophy	2.13 \pm 0.89	2.16 \pm 0.94	0.876
Effusion (<i>n</i> , %)	23 (51.1%)	21 (47.7%)	0.749

HA-IAI, hyaluronic acid intraarticular injection; IKDC, International Knee Documentation Committee; PRP-IAI, platelet-rich plasma intraarticular injection; US, ultrasound; VAS, visual analog scale.

compared to values at both baseline and 3 months post-injection. However, the outcome measures at the 6-month follow up were significantly better in the PRP-IAI group than in the HA-IAI group (Table 4).

DISCUSSION

The main findings of the current study were: (i) PRP-IAI and HA-IAI both resulted in improvement of all the clinical and ultrasonography outcome measures at 3 and 6 months post-injection; and (ii) the outcome measures were significantly better in the PRP-IAI group compared to the HA-IAI group. In agreement with our findings, several other clinical trials have also shown that injections of PRP were better than HA injections in managing KOA.

Table 3 Comparison of the outcome measures between the PRP-IAI group and HA-IAI group after 3 months

	PRP-IAI group	HA-IAI group	P
Clinical parameters			
VAS-pain	4.6 ± 1.6	5.3 ± 1.6	0.042
IKDC score	67.9 ± 13.7	59.6 ± 15.4	0.009
US findings			
Synovial vascularity	1.59 ± 0.86	1.98 ± 0.81	0.031
Synovial hypertrophy	1.60 ± 0.81	1.95 ± 0.83	0.047
Effusion (n, %)	9 (20%)	18 (40.9%)	0.032

HA-IAI, hyaluronic acid intraarticular injection; IKDC, International Knee Documentation Committee; PRP-IAI, platelet-rich plasma intraarticular injection; US, ultrasound; VAS, visual analog scale.

Table 4 Comparison of the outcome measures between the PRP-IAI group and HA-IAI group after 6 months

	PRP-IAI group	HA-IAI group	P
Clinical parameters			
VAS-pain	4.14 ± 1.44	5.95 ± 1.52	0.012
IKDC score	75.7 ± 15.1	65.6 ± 16.9	0.004
US findings			
Synovial vascularity	1.46 ± 0.79	1.86 ± 0.76	0.017
Synovial hypertrophy	1.49 ± 0.75	1.84 ± 0.79	0.035
Effusion (n, %)	6 (13.3%)	15 (34.1%)	0.021

HA-IAI, hyaluronic acid intraarticular injection; IKDC, International Knee Documentation Committee; PRP-IAI, platelet-rich plasma intraarticular injection; US, ultrasound; VAS, visual analog scale.

Sanchez *et al.*³¹ compared the efficacy of intra-articular injections of an autologous preparation of PRP with hyaluronan injections for KOA treatment. They found that PRP injections resulted in a significantly lower pain severity and better physical function subscale than in the hyaluronan group. Furthermore, Kon *et al.*³² compared the efficacy of autologous PRP intra-articular injections with high molecular and low molecular weight HA injections in a randomized trial. The group receiving three autologous PRP injections fared better in terms of pain and symptom reduction compared to the HA injection groups. In addition, the PRP injections were also more effective in restoring joint function compared to HA injections.

Several subsequent studies confirmed the significantly better clinical outcomes of intra-articular injections of PRP compared to that of HA in terms of reducing

pain,^{33–36} tenderness³⁷ and stiffness,³⁶ and improving functional capacity^{33–37} of the arthritic knee. Moreover, in elderly (> 80 years) KOA patients, who are not eligible for autologous PRP treatment, homologous PRP has produced a significant short-term improvement in pain and IKDC score with an excellent safety profile.³⁸

Duymus *et al.*³⁹ compared the efficacy of three treatment lines, the intra-articular injection of PRP, HA and ozone gas, in patients with KOA, and found that PRP was more effective than either HA or ozone injections in providing at least 12 pain-free months. On the other hand, Montañez-Heredia *et al.*⁴⁰ found that both PRP and HA treatments improved pain in KOA patients and that there were no significant differences between the groups in their immediate post-injection outcomes. However, PRP was more effective in reducing pain 3 months after the final injection compared to HA.

Two meta-analyses have investigated the long-term efficacy of the PRP versus HA intra-articular injections and concluded that PRP was associated with significantly better pain relief and functional outcome compared to HA 1 year²¹ and 2 years post-injection.²²

In our study, the degree of synovial vascularity, synovial hypertrophy, and the presence of effusion were evaluated for all patients at baseline and after 3 and 6 months post-injection by US examination score. Intra-articular injections of PRP resulted in significantly lower synovial hypertrophy and synovial vascularity scores, along-with less frequency of effusion compared to that of HA at 3 and 6 months post-injection. To our knowledge, this is the first study to investigate the effect of intra-articular injections of PRP on ultrasonography parameters in patients with KOA.

Halpern *et al.*⁴¹ investigated whether PRP therapy for early KOA was associated with good clinical outcomes and a change in magnetic resonance imaging structural appearances, and observed that pain scores significantly decreased during the follow-up period, whereas radiological scores increased at 6 and 12 months from baseline. In our study, pain severity was decreased at the end of the study while the radiological scores were increased in all participants. However, at the end of the study, the US scores were significantly better in the PRP group than in the HA group, indicating that PRP injections slowed down the progression of the radiologic changes. Unfortunately, the study by Halpern *et al.*⁴¹ did not include a control group to verify the effect of PRP injections on radiological progression of the lesions.

Conversely, two recent studies found that intra-articular injection of PRP did not have a better effect than HA

in the management of knee degenerative disease and KOA. The patient cohort in the study by Feller *et al.*²³ was heterogeneous and included, in addition to KOA patients, those with other degenerative conditions including meniscal tears. In the study by Wang *et al.*²⁴ the protocol of injection was not explained by the authors. However, in both studies the intra-articular injections PRP and HA produced significant improvements in the pain and functional status scores compared to the baseline, but no significant differences were seen between the two treatment groups.

All these trials were very heterogeneous in terms of the administration interval for PRP intra-injections as well as the number of injections. Nevertheless, most studies reported better outcomes with PRP compared to other approaches such as HA injections.

CONCLUSION

Intra-articular injection of PRP is an effective treatment of KOA that reduced pain and improved the functional status of the patients. The clinical outcomes of the intra-articular injections of PRP included improved synovial hypertrophy and vascularity scores, and less frequency of effusion as per the ultrasonography examination.

AUTHOR CONTRIBUTIONS

Dr. Hamada Ahmed: study hypothesis starter, clinical management of patients, follow up of patients, analysis of clinical results, interpreting the clinical result, writing and reviewing the article. Dr. Shereif Farrag: shared in study hypothesis starter, clinical management of patients, follow up of patients, analysis of clinical results, interpreting the clinical result, writing and reviewing the article. Dr. Amro Okasha: shared in study hypothesis starter, clinical management of patients, follow up of patients, analysis of clinical results, interpreting the clinical result, writing and reviewing the article. Dr. Aisha Kadry: shared in study hypothesis starter, clinical management of patients, follow up of patients, analysis of clinical results, interpreting the clinical result, writing and reviewing the review article. Dr. Tamer Ata: responsible for the microbiological aspects of the research, and help in analyzing, interpreting of clinical results in addition to writing and reviewing the article. Dr. Amir Monir: responsible for the radiological aspects of the research, and help in analyzing, interpreting of clinical results in addition to writing and reviewing the

article. Dr. Ibrahim Shady: help in the design of the research methodology, collecting and statistically analyzing data as well as writing and reviewing.

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CONFLICT OF INTEREST

The researchers acknowledge that there are no conflicts of interests.

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