Intra-articular injection of platelet-rich plasma and therapeutic exercise in knee osteoarthritis

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Context
There is no definite treatment strategy capable of decreasing destruction of cartilage and enhancing its healing. Intra-articular injection of platelet-rich plasma (PRP) provides a lot of growth factors that are capable of stimulating regeneration of cartilage and is supposed to be a future solution to patients with osteoarthritis (OA).
Aim
To detect the efficacy of intra-articular injection of PRP or therapeutic exercise (Ex) alone as well as a combination of both in the treatment of idiopathic knee OA.
Settings and design
A prospective randomized controlled clinical study was conducted.
Patients and methods
A total of 60 patients, 44 to 65 years of age, having idiopathic unilateral knee OA were included in the study and were divided into three groups: PRP group included 20 patients and were treated with intra-articular PRP injection, Ex group included 20 patients and were treated with only therapeutic Ex, and PRP and Ex group included 20 patients who were treated with both PRP intra-articular injection and therapeutic Ex. Evaluation of all patients was done by visual analogue scale, tenderness, range of motion, thigh circumference, and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at baseline and 1 and 6 months later. Objective evaluation was done through MRI of osteoarthritic knee at baseline and 6 months later.
Statistical analysis
Statistical analyses were performed using SPSS for windows, version 20.0.
Results
Baseline WOMAC score differences among the three groups were not statistically significant but were significant 6 months after treatment. In PRP and Ex groups, there was a significant improvement after treatment, whereas a highly significant improvement in PRP+Ex group. MRI grading differences among the three groups were not significant before or after treatment, with no improvement in all three groups after treatment.
Conclusion
A combination of intra-articular injection of PRP and therapeutic Ex resulted in significantly lesser visual analogue scale, WOMAC score, and joint tenderness compared with PRP or Ex alone.

Keywords:
knee osteoarthritis, platelet-rich plasma, therapeutic exercise, Western Ontario and McMaster Universities Arthritis Index

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Introduction

Knee osteoarthritis (OA) is the most common OA condition and is the most common cause of impaired mobility and disability in the elderly [1]. OA is associated with destruction of articular cartilage, which is progressive, and is partly owing to increased destruction and decreased production of proteoglycans, the main component of articular cartilage [2]. Besides, OA affects the subchondral bone, capsule, ligaments, synovial membrane, tendons, and even peri-articular muscles because of limitation of mobility, leading to their weakness, which act as an aggravating factor for the disease [3]. Various treatments, such as NSAIDs, hyaluronic acid (HA), chondroitin sulfate, glucocorticoids, and glucosamine, have been used as ways for treatment of pain and disability, with varying rates of success [4]. These agents have not been shown to be effective clearly, and owing to the defect in the common accepted evidence, they are not ideal solutions for the treatment of OA [5]. The American College of Rheumatology (ACR) subcommittee on OA

recommends corticosteroid injections collectively as effective ways for decreasing joint pain. However, American Society of Orthopaedic Surgeons have been incapable of suggesting for or against the intra-articular injection of corticosteroids in their recommendations [6]. Corticosteroid injections are often thought of as an associate adjunct to main treatment for management of cases with moderate to severe OA owing to its role in short-term pain relief [7].

In OA, inflammation results in a high permeable synovial membrane for HA. The increased levels of cytokines, proteolytic enzymes, and free radicals in the synovial membrane impair HA function and decrease its concentration, eventually leading to deterioration of OA. So, the intra-articular injection of HA restores normal visco-elastic properties of synovial fluid (SF). HA has beneficial effects such as protecting cartilage against erosion and promoting the intra-articular HA secretion. To sum up, the application of HA injections is safe and may be effective for reduction of pain in mild knee OA up to 24 weeks. However, cost should be taken in consideration before injection of HA in osteoarthritic knee [8]. The ACR does not recommend for the use of injection of HA in knee OA [6]. Moreover, American Society of Orthopedic Surgeons has no recommendations for the utilization of intra-articular HA. A study by Ayhan *et al.* [9] supports strong evidence of recommendation against the utilization of intra-articular HA in their guideline.

The role of exercise (Ex) in the treatment of knee OA has been acknowledged. According to recommendations by ACR regarding knee OA [6] and OA Research Society International [10], Ex therapy is one of the effective methods for knee OA management. Ex reduces pain and improves the joint range of motion and muscle strength [11].

Another line of treatment of knee OA is platelet-rich plasma (PRP). It is a biological autologous management option obtained from patients' own plasma, which contains a high concentration of growth factors (GFs) that are platelet-derived growth factor such as insulin-like growth factor-1, transforming growth factor-beta, epidermal growth factor (EGF), and vascular endothelial growth factor [12]. All the GFs may lead to healing of soft tissue and regeneration of bone by the increased physiologic secretion of platelet-derived factors at the management site directly [13,14].

PRP is one of the options in the management of knee OA [15]; however, its effectiveness and wide application is still controversial [16]. Although good results were reported about PRP in knee OA, most studies are based on subjective data and use only questionnaires for evaluation of patients [15]. Therefore, studies based on objective data as MRI evaluation of patients after PRP injections are needed in this regard.

So in this research work, we prepared PRP and used the preparation for intra-articular injection; moreover, an Ex program was also applied. We used both methods to find their efficacy in the improvement of knee OA. Besides, the results were evaluated objectively using MRI before and after treatment.

Aim

The aim was to detect the efficacy of intra-articular injection of PRP alone, therapeutic Ex alone, and combination of both in the treatment of idiopathic knee OA.

Patients and methods

This study was carried out in Rheumatology, Rehabilitation & Physical Medicine Department, Faculty of Medicine, Mansoura University, and Aga Central Hospital during the period from November 2015 to February 2017. It consisted of 60 patients, 44 to 65 years old, having idiopathic unilateral knee OA according to ACR criteria of OA [6].

The patients were randomly divided into three groups:

PRP group had 20 patients who received PRP intra-articular injection.

Ex group had 20 patients who were treated with therapeutic Ex.

PRP and Ex group had 20 patients who were treated with PRP intra-articular injection and therapeutic Ex. This study was ethically approved by IRB committee of Faculty of Medicine, Mansoura University under code number MS/15.07.06.

Exclusion criteria [17]

The following were the exclusion criteria:

(1) Patients with secondary OA or inflammatory arthritis.
(2) History of knee trauma, surgery or fractures.
(3) Patients with any hematological disorder like thrombocytopenia.
(4) Treatment with antiplatelet drugs.

(5) Treatment with therapeutic Ex or intra-articular injection of corticosteroids during the last 3 months.
(6) Severe knee OA according to Kellgren classification [18].
(7) BMI more than 30 kg/m^2.

Methods

All patients gave consent and were subjected to the following:

(1) Detailed history taking.
(2) Pain assessment by pain visual analogue scale (VAS):
VAS of pain is a one-dimensional tool to measure pain severity. It is 10-cm transverse line that is marked every 1 cm, and pain severity range from 0 to 10 (0 reflects no pain at the left end of horizontal line and 10 reflects worst pain at the right end of the line) [19]. Patients stated their severity of pain during the past 4 weeks.
(3) Knee examination included the following:
  (a) Inspection:
    (i) Gait abnormality especially limping.
    (ii) Alignment (normal, varus, valgus, and flexion),
    (iii) Swelling (localized or diffuse).
    (iv) Muscle wasting.
    (v) Scars (previous operation or trauma).
    (vi) Color.
    (vii) Posterior aspect.
  (b) Palpation:
    (i) Swelling (localized or diffuse, bony prominence, or synovial thickening).
    (ii) Tenderness was evaluated on a rating scale 0–3:[20]
    Grade 0: there is no tenderness.
    Grade 1: there is tenderness.
    Grade 2: there is tenderness and wince.
    Grade 3: there is tenderness, wince, and withdrawal in the joint.
    (iii) Crepitus feeling through the range of knee motion.
    (iv) Effusion was assessed on a rating scale 0–3 [21]:
    Grade 0: no effusion.
    Grade 1: mild effusion by fluid displacement test.
    Grade 2: moderate effusion by patellar tap test.
    Grade 3: tense effusion by cross fluctuation test.
    (v) Measurement of the range of motion of knee joint [22].
    (vi) Assessment of quadriceps wasting by measurement the circumference of the thigh at 10 cm above the upper pole of the patella [23].
  (c) Special testes:
    (i) For menisci: MacMoury's test.
    (ii) For ligaments of the knee:
    Valgus stress test for medial collateral ligament.
    Varus stress test for lateral collateral ligament.
    Anterior drawer test for anterior cruciate ligament.
    Posterior drawer test for posterior cruciate ligament.
(4) Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire for functional evaluation of patients with OA [24].
(5) Laboratory investigation: complete blood count, serum uric acid, rheumatoid factor, and erythrocyte sedimentation rate.
(6) Radiological evaluation:
  (a) Plain radiograph of knee joint with grading of OA by Kellgren and Lawrence radiological scale:[18]
    (i) Grade 0: no evidence of OA.
    (ii) Grade 1: probable joint space narrowing (JSN) and possible occurrence of osteophytes.
    (iii) Grade 2: definite osteophytic lipping and possible JSN on anteroposterior weight-bearing radiograph.
    (iv) Grade 3: multiple osteophytic lipping, definite JSN, possible bony deformity and sclerosis.
    (v) Grade 4: large osteophytic lipping, marked JSN, definite bony deformity, and severe sclerosis.
  (b) MRI was performed with assessment of knee OA severity according to the following:[25]
    (i) Grade 0: no evidence of cartilage injury with no or minimal osteophyte (<5 mm).
    (ii) Grade 1: cartilage injury grade I with at least one of the following:
      (a) Osteophyte more than 5 mm.
      (b) Bone marrow edema more than 10 mm.
      (c) Subchondral cyst more than 10 mm.
    (iii) Grade 2: cartilage injury grade II with at least one of the following:
      (a) Osteophyte more than 5 mm.
      (b) Bone marrow edema more than 10 mm.

(c) Subchondral cyst more than 10 mm.

(iv) Grade 3: cartilage injury grade III with at least one of the following:
(a) Osteophyte more than 5 mm.
(b) Bone marrow edema more than 10 mm.
(c) Subchondral cyst more than 10 mm.

(v) Grade 4: cartilage injury grade III with meniscal injury grade III.

Joint effusion grading: [26]

Grade 0: normal.
Grade 1: mild.
Grade 2: moderate or large.

(7) PRP injection:
Two PRP injections with 4-week interval were done [15].
Pre-injection precautions published by American Academy of Orthopaedic Surgeons are as follows:[27]
(a) No corticosteroid medications for 2–3 weeks before the injection.
(b) Stop taking NSAID 1 week before the injection.
(c) No anticoagulation medication 5 days before the injection.

Injection procedure [28] :Vein puncture and subsequent collection of 10 cm^3 of venous blood into a tube containing an anticoagulant (sterile sodium citrated tubes) were done by 10 ml syringe with needle bore of 21 G.
The tube with citrated blood was exposed to double spin technique. First centrifugation (the used device was manufactured by dragon labs company and the model was DMO 412) was at 1600 rpm for 15 min, resulting into three layers: the lower layer is made of red blood cells, intermediate layer is formed of white blood cells, and the upper one is formed of plasma. The upper two layers were then collected in plain tube, and second centrifuged at 3500 rpm was done for another 10 min to yield two layers: the superficial layer is platelet-poor layer, which was withdrawn, leaving the concentrate of platelets at the bottom (second layer), for obtaining more concentrated platelet layer (PRP) [15].
The patient was asked to relax in the supine position during the injection for facilitation and for making it less painful.
Skin of injection site was disinfected by betadine. Then a 3 cm^3 of PRP by 5 ml syringe with 21 G needl was injected in a sterile place at the anteromedial part of the knee joint in flexed knee position.
The patient was then asked after 15 min to move his/her knee actively in flexion and extension, so that PRP unfolds across the joint area [15]. The patient was then discharged.
Postinjection precautions were as follows [15]:
(a) No anti-inflammatory medication.
(b) Relative rest for 24 h once injection was administered.
(c) Reduction of weight bearing over injected joint.
(d) Cold compress three times every day for about 10 min each time to decrease postinjection swelling and pain, because the injection site may be painful and swollen for about 3 days.

(8) Home-based strengthening and stretching Exs for 3 months in only two groups: Ex group and the combined (Ex and PRP) group.
The following muscle groups will be gradually trained: quadriceps, hamstrings, and calf muscles [29].
The following six Exs (three strengthening and three stretching) were recommended [29,30]:
(a) Quadriceps and hamstring strengthening (leg presses).
(b) Calf stretching strengthening (calf raises).
(c) Hamstring stretching (supine hamstring stretching).
(d) Quadriceps stretching (prone quadriceps stretching).
(e) Quadriceps strengthening (leg extension).
(f) Hamstring strengthening (prone hamstring strengthening).

(9) Follow-up for all patients was done by VAS, tenderness, WOMAC, range of motion, circumference of the thigh, and MRI. Patients were evaluated at 1 and 6 months after the end of treatment.

Statistical analysis

The collected data were summarized, tabulated, and analyzed using the SPSS (version 20.0; SPSS, Chicago, Illinois, USA) program for statistical analysis. The appropriate statistical test was used to analyze the data. The level of significance was considered at P value less than or equal to 0.05 and high significance at P value less than or equal to 0.001.

Results

This study included 60 patients having unilateral OA of the knee joint.The mean age of PRP group was 53.7±6.9 years, of Ex group was 55.7±5.7 years, and of PRP+Ex group was 55.2±6.2 years. Male to female distribution in PRP, Ex, and PRP+Ex groups were 20 : 80%, 25 : 75%, and 30 : 70%, respectively. The mean disease duration of

PRP, Ex, and PRP+Ex groups was 8.6±4.4, 9.9±3.7, and 9.4±4.3 years, respectively.

The mean baseline VAS of pain in Ex, PRP, and Ex+PRP groups was 5.45±1.67, 5.30±1.49, and 5.15±2.03 cm, respectively, with insignificant difference among the three groups. One and 6 months after treatment, the group treated with combination of Ex and PRP showed more significant improvement of pain VAS than the other two groups. Compared with the Ex group, the PRP group had a greater improvement of pain VAS, as shown in Table 1.

The mean baseline tenderness scores in Ex, PRP, and Ex+PRP groups were 2.23±0.68, 2.17±0.61, and 2.11±0.83, respectively, with insignificant difference among the three groups. One and 6 months after treatment, the group treated with combination of Ex and PRP showed more significant improvement of tenderness score than the other two groups. Compared with the Ex group, the PRP group had a greater improvement of tenderness score, as shown in Table 2.

The mean baseline WOMAC scores in Ex, PRP, and Ex+PRP groups were 55.4±3.6, 54.1±3.6, and 55.4 ±3.8, respectively, with insignificant difference among the three groups. One and 6 months after treatment, the group treated with combination of Ex and PRP showed more significant improvement of WOMAC score than the other two groups. Compared with the Ex group, the PRP group had a greater improvement of WOMAC score, as shown in Table 3.

The mean baseline knee flexion limitation in Ex, PRP, and Ex+PRP groups was 32.62±10.02, 31.80±8.94, and 30.91±12.18°, respectively, with insignificant difference among the three groups. One and 6 months after treatment, the Ex group and the group treated with combination of Ex and PRP showed more significant improvement of knee flexion limitation than the PRP group, as shown in Table 4.

The mean baseline thigh circumference in Ex, PRP, and Ex+PRP groups was 48.9±3.5, 48.1± 3.6, and 48.4±3.2 cm, respectively, with

Table 1 Comparison of visual analogue scale pain score at baseline and 1 and 6 months after treatment in the exercise, platelet-rich plasma, and platelet-rich plasma+exercise groups

				Dependent sample Student's *t* test	
VAS	At baseline (mean±SD)	1 month after treatment (mean±SD)	6 months after treatment (mean±SD)	P_1	P_2
Ex	5.45±1.67	4.35±0.92	4.57±0.94	0.024*	0.047*
PRP	5.30±1.49	3.68±1.08	3.87±1.05	0.003*	0.012*
Ex+PRP	5.15±2.03	2.03±1.10	3.08±1.12	<0.001**	0.003*
Independent Student's *t* test					
P_3	0.766	0.041*	0.032*		
P_4	0.613	<0.001**	<0.001**		
P_5	0.719	0.036*	0.027*		

Ex, exercise; PRP, platelet-rich plasma; VAS, visual analogue scale. P_1, comparison between baseline value and 1 month after treatment for each group. P_2, comparison between baseline value and 6 months after treatment for each group. P_3, comparison between Ex group and PRP group. P_4, comparison between Ex group and Ex+PRP group. P_5, comparison between PRP group and Ex+PRP group. **P* value less than 0.05, significant. ***P* value less than 0.001, highly significant.

Table 2 Comparison of tenderness score at baseline and 1 and 6 months after treatment in the exercise, platelet-rich plasma, and platelet-rich plasma+exercise groups

				Dependent sample Student's *t* test	
Tenderness	At baseline (mean±SD)	1 month after treatment (mean±SD)	6 months after treatment (mean±SD)	P_1	P_2
Ex	2.23±0.68	1.78±0.38	1.87±0.39	0.014*	0.047*
PRP	2.17±0.61	1.51±0.44	1.59±0.43	0.004*	0.013*
Ex+PRP	2.11±0.83	0.93±0.45	1.26±0.46	<0.001**	0.003*
Independent Student's *t* test					
P_3	0.771	0.045*	0.037*		
P_4	0.620	<0.001**	<0.001**		
P_5	0.760	0.002*	0.037*		

Ex, exercise; PRP, platelet-rich plasma. **P* value less than 0.05, significant. ***P* value less than 0.001, highly significant.

insignificant difference among the three groups. One and 6 months after treatment, the group treated with combination of Ex and PRP showed more significant improvement of thigh circumference than the other two groups. Compared with the PRP group, the Ex group had a greater improvement of thigh circumference, as shown in Table 5.

There was an insignificant difference between baseline and 6-month post-treatment MRI grading in Ex, PRP, and Ex+PRP groups, as shown in Table 6.

There was an insignificant improvement of effusion in Ex and PRP groups but significant in Ex+PRP group as shown in Table 7.

Discussion

OA of the knee is a chronic disease associated with pain and morbidity. The increasing number of patients with

Table 3 Comparison of Western Ontario and McMaster Universities Arthritis Index score at baseline and 1 and 6 months after treatment in exercise, platelet-rich plasma, and platelet-rich plasma+exercise groups

				Dependent sample Student's *t* test	
WOMAC score	At baseline (mean±SD)	1 month after treatment (mean±SD)	6 months after treatment (mean±SD)	P_1	P_2
Ex	55.4±3.6	51.3±3.7	51.7±3.5	0.008*	0.040*
PRP	54.1±3.6	50.5±3.8	50.9±3.5	0.041*	0.044*
Ex+PRP	55.4±3.8	49.8±3.4	49.9±2.9	<0.001**	<0.001**
Independent Student's *t* test					
P_3	0.505	0.049*	0.043*		
P_4	0.671	0.010*	<0.001**		
P_5	0.821	<0.001**	0.004*		

Ex, exercise; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Arthritis Index. **P* value less than 0.05, significant. ***P* value less than 0.001, highly significant.

Table 4 Comparison of knee flexion limitation at baseline and 1 and 6 months after treatment in the exercise, platelet-rich plasma, and platelet-rich plasma+exercise groups

				Dependent sample Student's *t* test	
Knee flexion limitation	At baseline (mean±SD)	1 month after treatment (mean±SD)	6 months after treatment (mean±SD)	P_1	P_2
Ex	32.62±10.02	22.08±6.48	22.22±6.30	<0.001**	<0.001**
PRP	31.80±8.94	26.1±5.52	27.10±5.24	0.020*	0.049*
Ex+PRP	30.91±12.18	12.20±6.59	15.48±6.72	<0.001**	<0.001**
Independent Student's *t* test					
P_3	0.786	0.041*	0.039*		
P_4	0.631	<0.001**	<0.001**		
P_5	0.794	<0.001**	<0.001**		

Ex, exercise; PRP, platelet-rich plasma. **P* value less than 0.05, significant. ***P* value less than 0.001, highly significant.

Table 5 Comparison of thigh circumference at baseline and 1 and 6 months after treatment in the exercise, platelet-rich plasma, and platelet-rich plasma+exercise groups

				Dependent sample Student's *t* test	
Thigh circumference	At baseline (mean±SD)	1 month post-treatment (mean±SD)	6 months post-treatment (mean±SD)	P_1	P_2
Ex	48.9±3.5	52.8±3.4	51.6±3.3	0.006*	0.039*
PRP	48.1±3.6	50.6±3.4	50.4±3.3	0.039*	0.042*
Ex+PRP	48.4±3.2	53.7±3.6	53.9±2.7	<0.001**	<0.001**
Independent Student's *t* test					
P_3	0.481	0.047*	0.041*		
P_4	0.639	0.008*	<0.001**		
P_5	0.782	<0.001**	0.002*		

Ex, exercise; PRP, platelet-rich plasma. **P* value less than 0.05, significant. ***P* value less than 0.001, highly significant.

Table 6 Comparison of the magnetic resonance imaging grading among the exercise, platelet-rich plasma, and platelet-rich plasma+exercise groups at baseline and after treatment

MRI grading	MRI grading at baseline [*n* (%)]			MRI grading after treatment [*n* (%)]			χ^2 (*P*)
	G1	G2	G3	G1	G2	G3	
Ex	8 (40)	10 (50)	2 (10)	7 (35)	9 (45)	4 (20)	0.786 (0.765)
PRP	9 (45)	10 (50)	1 (5)	9 (45)	9 (45)	2 (10)	χ^2=0.386 0.824
	(%)	(50%)	(5%)	(45%)	(45%)	(10%)	
PRP+exercise	8 (40)	11 (55)	1 (5)	8 (40)	10 (50)	2 (10)	χ^2=0.381 *P*=0.827
	(40%)	(55%)	(5%)	(40%)	(50%)	(10%)	
χ^2		0.645			1.321		
Test		*P*=0.958			*P*=0.858		

Ex, exercise; PRP, platelet-rich plasma. **P* value less than 0.05, significant. ***P* value less than 0.001, highly significant.

Table 7 Comparison of presence of effusion by magnetic resonance imaging at baseline and after treatment among the exercise, platelet-rich plasma, and platelet-rich plasma+exercise groups

Effusion	Effusion at baseline [*n* (%)]	Effusion after treatment [*n* (%)]	χ^2	*P*
Ex	14 (70)	13 (65)	0.114	0.736
PRP	11 (55)	6 (30)	2.558	0.110
PRP+Ex	12 (60)	5 (25)	5.013	0.025*
χ^2	0.987	7.917		
	P=0.610	*P*=0.019*		

Ex, exercise; PRP, platelet-rich plasma. **P* value less than 0.05, significant. ***P* value less than 0.001, highly significant.

symptomatic OA will continue to place an increasingly large economic burden on global health care systems [31].

The various agents for treatment of OA have not been showed to be effective clearly, and owing to the defect in commonly accepted evidence, there may not be ideal solutions for the treatment of OA [5]. This has led to the emergence of other options for functional improvement and symptom relief in these patients [32].

Although there are a good amount of studies documenting the use of HA in the management of knee OA, there are limited studies documenting the use of PRP. More importantly, there are no studies comparing the utilization of PRP with Ex in the management of knee OA [33].

However, strong proof from elegant clinical trials to support PRP utilization for OA of the knee joint continues to be little [34]. Therefore, PRP requires more investigation to assess its effectiveness in the intra-articular injection [35].

According to the recommendations by ACR about knee OA [6] and OA Research Society International [10], Ex therapy is one of the effective methods for knee OA management. Light to moderate intensity Ex has been shown to positively influence knee OA [36]. In a study done in 2015, Nejati *et al.* [37] demonstrated that Ex for muscles around knee can promote the efficacy of different therapeutic interventions for knee OA.

PRP decreases pain and has anti-inflammatory effect and Ex has anti-inflammatory effect. Thus, an additional result, in treating knee OA, could be obtained from this combination [37].

To our information, this is the first study that evaluates the combination of PRP intra-articular injection treatment and therapeutic Ex in treatment of idiopathic knee OA.

The aim of this study was to compare the efficacy of intra-articular injection of PRP alone, therapeutic Ex alone, and combination of both in the treatment of idiopathic knee OA.

In our study, there was a significant improvement in all evaluation scores (VAS, tenderness, and WOMAC) after treatment at 1or 6 months. Moreover, there was a significant difference between these scores among the three groups after management either after 1or 6 months, with improvement in PRP group more than Ex group and in PRP+Ex group more than the other two groups.

The result of PRP group was in agreement with many studies that used PRP for the treatment of OA [14,34,38–41]. It was demonstrated that there was an improvement in VAS and all WOMAC parameters, pain scores, and clinical and functional scores after PRP and supported that intra-articular PRP injections had a better response in younger patients, more active patients, and those with

low-grade OA [14,38]. In a study done in 2013, 78 patients (156 knees) had bilateral knee OA, and patients were administered two PRP injections 3 weeks apart. PRP was effective in alleviating symptoms and lowering scores of WOMAC and VAS. The results, however, deteriorated after 6 months [34]. The result of Ex group was in agreement with many studies [37,42,43]. The mechanisms underlying beneficial effects of Ex are largely unknown [44].

Ex for persons with knee OA results in small-to-moderate improvements in function and pain. In spite of the variability in results and inherent biases in trials, Ex seems to decrease pain and enhance function for the persons with knee OA [42].

There is overwhelming proof that light to moderate physical activity does not lead to knee OA or even accelerate the condition. In fact, Ex could stop its onset and is clearly effective in the management of the pain and functional decline associated with OA. Health care providers should not hesitate to include recommendations for Ex as part of the clinical management of knee OA [43].

Nejati *et al.* [37] observed that the patients with knee OA and treated with Ex only had significant improvement in pain, walking, disability, sit-up speed, and stair climbing after treatment when compared with non-Ex group, with significant difference in VAS between the groups. The result of PRP+Ex group reflected the importance of Ex combination with PRP, which significantly reduced the OA symptoms and improved quality of life in these patients. This combination effect could also be owing to the nature of the OA disease and its effect on tissues and structures within the whole joint. So, this combination of PRP therapy and Ex holds promise for pain and inflammation relief, resulting in a reduction in medications. Moreover, in our study, there was a significant difference of knee flexion limitation and thigh circumference after management among the three groups either after 1or 6 months, but improvement in Ex group was more than PRP group and in PRP+Ex group was more than the other two groups. In all groups, there was a significant improvement after treatment in all scores either after 1 or 6 months. The result of PRP group was in agreement with a study done in 2015 [40] which showed significant improvement 6 months after PRP injection. The result of Ex group was in agreement with another study done in 2012 [45]. The results of PRP+Ex group also reflect the importance of Ex combination with PRP, which significantly reduce the OA symptoms. Flexion limitation and thigh circumference were improved with Ex than PRP. This result may be owing to that therapeutic Ex would effectively target these specific deficits [45]. In this study, there was a statistically significant improvement in all previous parameters after 1 and 6 months, with nearly same result at the 6-month follow-up, which is in agreement with the study by Maheshwari and Harshwardhan. This may reflect sustained effect for 6 months [41]. A number of approaches to OA management have failed to restore normal knee function and anatomy, or to slow the progression of OA [46]. PRP has been proposed to improve clinical and structural outcomes by delivering a high concentration of GFs that mediate remodeling. MRI is suitable for searching about this point [47]. Some theories have been proposed to clarify the mechanism by which PRP improves cartilage healing, such as PRP augments the secretion of HA, which has been observed in the presence of PRP [48]. Besides, the exposed osteoarthritic chondrocytes to PRP demonstrated less interleukin-1β which resulted in inhibition of collagen 2 and aggrecan gene expression, and diminished nuclear factor-B activation. These factors are considered as pathways involved in OA pathogenesis [49]. In an ovine model, a proliferation of autologous chondrocytes and mesenchymal stem cells was demonstrated after PRP exposure [50]. In this study, the baseline MRI demonstrated that most patient in all groups had grade 1 or 2 (nearly equal), with only four from 60 patients had grade 3, without significant differences between the groups. The difference among groups after treatment was insignificant. There were also insignificant differences between baseline and post-treatment MRI grading in Ex, PRP, and PRP+Ex groups. This result goes with a study done in 2013 by Halpern and his colleagues, who evaluated 22 patients defined anatomically by degeneration of articular cartilage and subchondral bone. This degeneration involved the lateral, medial, or patellofemoral compartments of the knee with Kellgren and Lawrence grading 0–4 of radiograph, confirmed by a baseline MRI and treated with a single PRP injection. The patients underwent clinical assessments by WOMAC score. There was a significant improvement of WOMAC scores, with a decrease of 41.7% (P=0.003) after 6 months. However, there was no change in the appearance of OA in 83.3% of all cases by MRI after 1 year when compared with baseline [28].So, the role of PRP in the cartilage repair is a matter of debate. The small sample of this study and other few studies that use MRI push us for further researches to fully comprehend the long-term clinical significance of MRI changes seen after PRP therapy. Ex may be sufficient in reducing pain and functional limitation,

but they may not be adequate for the cartilage repair or even minimizing the rates of disease progression [51].

There was an improvement in effusion detected by MRI in PRP group and significant in PRP+Ex group after treatment. This reflected a combination effect of PRP and Ex. This result was in agreement with a study done in 2015 [40].

Conclusion

This study suggested that PRP and Ex may play a role in improving clinical outcomes in patients with knee OA in agreement with most of studies, but combination of PRP and Ex was better than PRP and Ex alone, which reflects the additive effects of both. However, it seemed to be noneffective in the repair process or disease progression.

Recommendation

From this study, we recommend the combination of PRP and Ex in the treatment of idiopathic knee OA. This combination therapy is considered safe and may result in improvement of resistant cases to traditional lines of treatment. The response can be sustained for a period up to 6 months.

Further studies may be required to optimize PRP or Ex prescription and to determine the best way to use them.

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Conflicts of interest

There are no conflicts of interest.

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