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Effectiveness of ultrasound-guided platelets rich plasma injection in knee osteoarthritic cases

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Abstract

Background

Knee osteoarthritis is the most common articular disease. Different methods are used to alleviate the symptoms of patients with knee osteoarthritis, including analgesics, physical therapy, exercise prescription, and intra-articular injections (glucocorticoids, hyaluronic acid). New studies have focused on modern therapeutic methods that stimulate the cartilage healing process and improve the damage, including the use of platelet-rich plasma as a complex growth factor.

Aim of the work

To evaluate the effectiveness of intra articular PRP in mild to moderate degree knee osteoarthritis.

Objectives

To slow the rate of progression of knee Osteoarthritis by injection of PRP intraarticular. Decrease pain and disability of patients with knee osteoarthritis and postpone knee arthroplasty as possible.

Patients and methods

Ninety patients in the age range of 40–75 years who visited the Physical Medicine, Rheumatology, and Rehabilitation outpatient clinic with knee pain for a minimum of 6 months' duration were studied. In these patients, OA was diagnosed according to the visual analog scale (VAS) score, the American College of Rheumatology criteria, radiographic criteria proposed by the Kellgren and Lawrence score 1957 classification, and MSKUS. The patients were classified into three groups according to the number of ultrasonic-guided PRP injections. group I (GI) included 30 patients who received a single PRP injection. Group II (GII) included 30 patients who received two PRP injections 2 weeks apart. Group III (GIII) included 30 patients who received triple PRP injections with a 2-week gap between every injection. The patients were evaluated before treatment, and at the first, third, and 6 months after the PRP injection with the VAS for pain, the Western Ontario and Mc Master Universities Arthritis Index (WOMAC) for physical activity of the knee and MSKUS for the diagnosis and improvement of radiological signs of knee arthritis (grades, synovial hypertrophy, Doppler vascular activity, decreased usage of NSAIDs).

Results

After the first and second intra-articular PRP injections [i.e., GI (Table 1) and GII (Table 2)], the following results were obtained: According to demographic data (Table 3), the VAS score and the WOMAC score improved, and synovial hypertrophy and usage of NSAIDs decreased after the first and second injections (in mild and moderate cases); there was no significant difference as 50% of mild patients showed improvement, while 18.2% of moderate patients improved). Decreased numbers of improved patients at the sixth month after PRP injection.

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Conclusion

In conclusion, from our results, it was found that intra-articular injection of PRP in patients with mild and moderate knee OA is an effective and safe method. The maximum improvement was observed in mild cases with triple PRP injections.

Keywords: Intra-articular injection, musculoskeletal ultrasound, osteoarthritis, platelet-rich plasma

BACKGROUND

Osteoarthritis (OA) is a severe degenerative joint disease resulting from degenerative joint disease; it causes degradation of articular cartilage, degradation, and proliferative reformation of subchondral bone and a low degree of synovitis that leads to a reduced quality of life. It is a major cause of pain and disability in the elderly population [1]. OA alters the normal joint metabolism, favoring increased catabolism and decreased anabolism [2]. Inflammation and vascular pathology, in combination with cell death, meniscal changes, bone remodeling and subchondral sclerosis, produces a vicious cycle of progressive joint degeneration. This can be exacerbated by excessive mechanical stress and oxidative damage [3]. Moreover, under conditions of metabolic or cytotoxic stress, such as in aging, autophagy can be upregulated, further demonstrating homeostatic mechanisms [4].

Knee OA management strategies include improvement in function, reduction in disability, pain relief and hence, improved quality of life [5]. Platelet-rich plasma (PRP) is an autologous mixture of highly concentrated platelets and associated growth factors and other bioactive components produced by centrifugal separation of whole blood that is used in orthopedic and sports medicine practices to treat bone, tendons and ligaments injuries [6]. The growth factors released by PRP have been shown to promote cell recruitment, proliferation and angiogenesis, resulting in a reduction in the critical regulators of the inflammatory process and a decrease in the expression of inflammatory enzymes [7]. PRP may include a regenerative response by improving the metabolic function of damaged

structures[8] and has been shown to have a positive effect on chondrogenesis and mesenchymal stem cell proliferation [9].

Ultrasound (US) has become popular among rheumatologists as the first choice imaging investigation for the evaluation and monitoring of OA. Because of the recent improvement in technology, US has the ability to demonstrate and assess the minimal structural abnormalities, which involve the pathophysiology and progression of OA, such as articular cartilage, synovial tissue, bony cortex, and soft tissue. Nowadays, the US is a promising technique for assessing soft tissue abnormalities such as joint effusion, synovial hypertrophy, Baker cyst, and structural changes, including the disease in cartilage thickness, meniscus bulging, and formation of osteophytes [10].

Ultrasonography has also been proven to be a useful tool in guiding therapeutic interventions and monitoring treatment effectiveness. US guidance notably improves injection accuracy in the target intra-articular joint space of large joints, including the knee. The enhanced injection accuracy achieved with US needle guidance directly improves patient-reported clinical outcomes and cost-effectiveness [11].

PATIENTS AND METHODS

Ninety patients in the age range of 40–75 years who visited the Physical Medicine, Rheumatology and Rehabilitation outpatient clinic with knee pain for a minimum of 6 months’ duration were studied. In these patients, OA was diagnosed according to the visual analog scale (VAS) score, the American College of Rheumatology criteria, radiographic

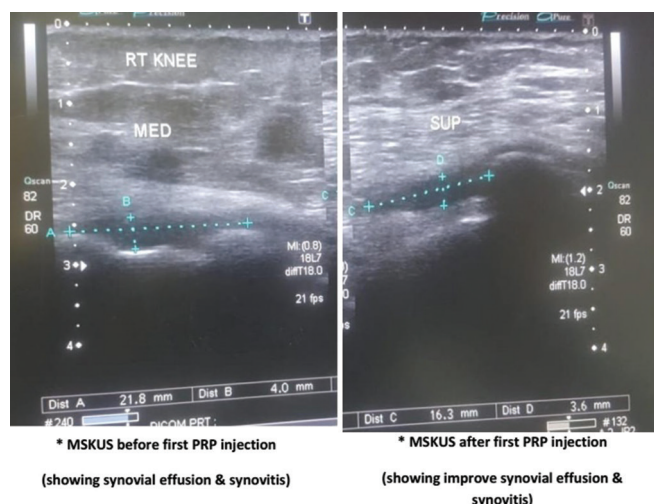


Figure 1: MSKUS before and after first PRP injection (showing decrease synovial effusion and synovitis after first PRP injection).

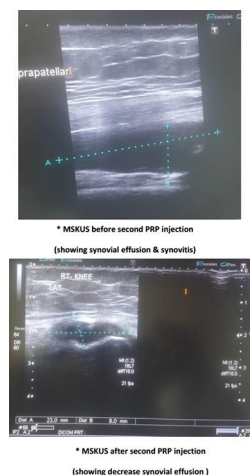


Figure 2: MSKUS before and after second PRP injection (showing decrease synovial effusion after second PRP injection).

Table 1: Group I (after a single injection)

Criteria	1 month after injection [N/n (%)]	3 months after injection [N/n (%)]	6 months after injection [N/n (%)]	P
VAS				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	
WOMAC				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	
MSKUS				
Mild	0/8 (0)	0/8 (0)	0/8 (0)	1.000
Moderate	0/22 (0.0)	0/22 (0.0)	0/22 (0.0)	1.000
P	1.000	1.000	1.000	
Doppler decreased				
Mild	2/4 (50.0)	2/4 (50.0)	2/4 (50.0)	1.000
Moderate	2/10 (20.0)	2/10 (20.0)	2/10 (20.0)	1.000
P	0.262	0.262	0.260	
Synovial hypertrophy				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	
Decreased use of NIAIDs				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	

VAS, visual analog scale; WOMAC, Western Ontario & Mc Master Universities Arthritis Index. * χ^2 test. $P>0.05$, nonsignificant. $P<0.05$, significant. $P<0.01$, highly significant.

criteria proposed by the Kellgren and Lawrence score 1957 classification and MSKUS(Figs 1–5). The ethics committee approval was taken.

The patients were classified into three groups according to the number of ultrasonic-guided PRP injections. group I (GI) included 30 patients who received a single PRP injection. Group II (GII) included 30 patients who received two PRP injections 2 weeks apart. Group III (GIII) included 30 patients who received triple PRP injections with a 2-week gap between every injection.

The patients were evaluated before treatment, and at the first, third, and 6 month after the PRP injection with the VAS for pain, the Western Ontario and Mc Master Universities Arthritis Index (WOMAC) for physical activity of the knee and MSKUS for the diagnosis and improvement of radiological signs of knee arthritis (grades, synovial hypertrophy, Doppler vascular activity, decreased usage of NSAIDs).

RESULTS

After the first and second intra-articular PRP injections [i.e., GI (Table 1) and GII (Table 2)], the following results were obtained:

According to demographic data (Table 3), the VAS score and the WOMAC score improved, and synovial hypertrophy and usage of NSAIDs decreased after the first and second injections (in

mild and moderate cases); there was no significant difference as 50% of mild patients showed improvement, while 18.2% of moderate patients improved). But with follow up at sixth month the number of patients who still improved after first and second PRP injection decreased.

According to MSKUS findings, there were no improvements at all, in patients with mild and moderate knee OA.

A total of 50% of patients with mild knee OA showed a decrease in Doppler vascularity in comparison with only 20% of patients with moderate knee OA, but this was not significant and there was no difference in the number of patients at the first, third, and sixth month after the PRP injection.

The previous results showed a symptomatic improvement (due to resolution of the inflammatory process), with no morphological changes after the first and second PRP injections, and there was also a decline in the number of patients to half, that is, 50%, for the duration after PRP, that is, at 6 months after the injection.

After the third PRP injections (GIII – Table 4), the following results were obtained:

According to VAS, there was 100% decreased Doppler activity and decreased usage of NSAIDs, that is, all patients showed improvement in symptoms and signs of activity in mild cases, although there was a difference in the number of patients who improved between mild and moderate cases of OA, as according

Table 2: Group II (after the second injection)

Criteria	1 month after injection	3 months after injection	6 months after injection	P
VAS				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	
WOMAC				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	
MSKUS				
Mild	0/8 (0)	0/8 (0)	0/8 (0)	1.000
Moderate	0/22 (0.0)	0/22 (0.0)	0/22 (0.0)	1.000
P	1.000	1.000	1.000	
Doppler decreased				
Mild	2/4 (50.0)	2/4 (50.0)	2/4 (50.0)	1.000
Moderate	2/10 (20.0)	2/10 (20.0)	2/10 (20.0)	1.000
P	0.262	0.262	0.260	
Synovial hypertrophy				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	
Decreased use of NIAIDs				
Mild	4/8 (50)	4/8 (50)	2/8 (25.0)	0.504
Moderate	4/22 (18.2)	4/22 (18.2)	2/22 (9.1)	0.624
P	0.081	0.081	0.257	

VAS, visual analog scale; WOMAC, Western Ontario & Mc Master Universities Arthritis Index. * χ^2 test. $P>0.05$, nonsignificant. $P<0.05$, significant. $P<0.01$, highly significant.

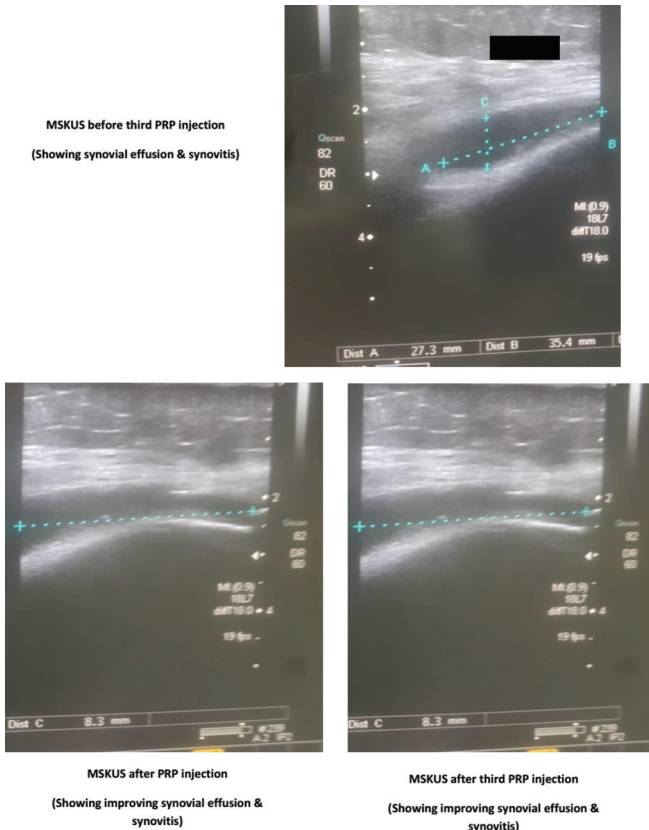


Figure 3: MSKUS before and after third PRP showing improved synovial effusion and synovitis.

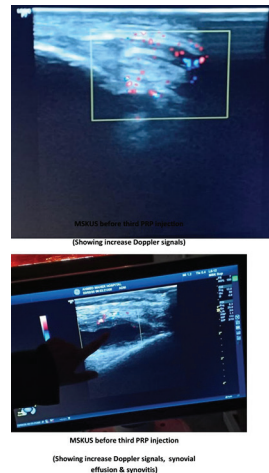


Figure 4: MSKUS before third PRP showing increased dopplar signals, synovial effusion and synovitis.

to VAS, only 45% of patients showed decreased use of NSAIDs and decreased Doppler activity was shown in 83% of patients. There was a highly significant difference between the number of improved patients between mild and moderate cases of knee OA at each time of follow-up according to VAS. Other than VAS, no significant difference was found between mild cases and time point of follow-up; this also found in moderate cases.

For WOMAC, 75% of patients with mild OA improved in comparison to 36% of moderate cases at the first and third

months after injections. However, at 6 months, there was a significant difference between mild and moderate cases as (75% of mild cases in comparison with 27% in moderate cases); 50% of patients with mild OA and 45% of patients with moderate knee OA showed improvement in synovial hypertrophy. These differences did not reach to significance; MSKUS findings remained unchanged.

There was minimal decrease in the number of patients who showed improvement during follow-up of patients at 6 months after injection, about 10–20%.

Table 3: Demographic data

	n=90
Sex	
Male	8 (8.9)
Female	84 (91.1)
Age (years)	
Mean±SD	56.7±10.3
Range	45-70
Side	
Right	90 (100.0)
Left	90 (100.0)
Duration of pain (months)	
Mean±SD	15.3±7.8
Range	6-24

DISCUSSION

OA is a major public health problem that causes pain disability in one-third of all affected patients.

It is one of the crucial MSK disorders characterized by imbalanced homeostasis and destruction of articular cartilage in proinflammatory cytokines, which are important catabolic regulators during the OA cascade [12]. PRP is a natural

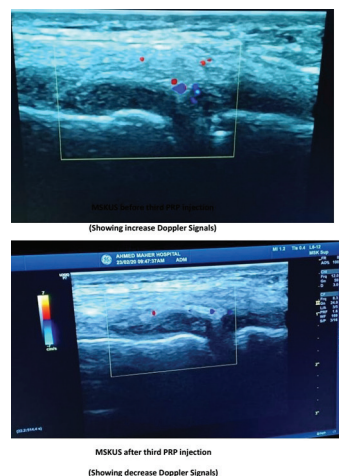


Figure 5: MSKUS after third PRP Injection (showing decreased dopplar signals).

Table 4: Group III (after the third injection)

Criteria	1 month after injection	3 months after injection	6 months after injection	P
VAS				
Mild	8/8 (100)	8/8 (100)	8/8 (100)	1.000
Moderate	10/22 (45.5)	10/22 (45.5)	8/22 (36.4)	0.780
P	0.007	0.007	0.002	
WOMAC				
Mild	6/8 (75.0)	6/8 (75.0)	6/8 (75.0)	1.000
Moderate	8/22 (36.4)	8/22 (36.4)	6/22 (27.3)	0.761
P	0.061	0.061	0.018	
MSKUS				
Mild	0/8 (0)	0/8 (0)	0/8 (0)	1.000
Moderate	0/22 (0.0)	0/22 (0.0)	0/22 (0.0)	1.000
P	1.000	1.000	1.000	
Doppler decreased				
Mild	4/4 (100.0)	4/4 (100.0)	4/4 (100.0)	1.000
Moderate	10/12 (83.3)	10/12 (83.3)	8/12 (66.7)	0.526
P	0.383	0.383	0.182	
Synovial hypertrophy				
Mild	4/8 (50)	4/8 (50)	4/8 (50)	1.000
Moderate	10/22 (45.5)	10/22 (45.5)	8/22 (36.4)	0.780
P	0.825	0.825	0.450	
Decreased use of NIAIDs				
Mild	8/8 (100)	8/8 (100)	8/8 (100)	1.000
Moderate	10/22 (45.5)	10/22 (45.5)	8/22 (36.4)	0.780
P	0.007	0.007	0.002	

VAS, visual analog scale; WOMAC, Western Ontario & Mc Master Universities Arthritis Index. * χ^2 test. $P>0.05$, nonsignificant. $P<0.05$, significant. $P<0.01$, highly significant.

concentrate of autologous growth factors from the blood. It is a simple, low-cost and minimally invasive way to obtain the concentration of many growth factors [13]. PRP application to treat OA of the knee can be considered a relatively new therapeutic indication [14].

This study has been carried out on 90 patients suffering from mild to moderate OA. They received three PRP injections into their knees at 2-week intervals.

In our patients, an improvement was observed in most of the clinical aspects, such as tenderness in the joint line, crepitus, and range of motion. There was also an improvement in the number of patients with hotness, effusion, and backer cyst, but these improvements were not statistically significant after the first and second intra-articular PRP injections. However, a highly significant difference was found after the third PRP injection in the number of patients with mild and moderate degrees of knee OA. Better results were achieved in those with short disease duration and those who had received three PRP injections. This can be explained by the high percentage of living and vital cells, and thus the high response to growth factors.

Sampson and colleagues evaluated the effect of 3 monthly doses of PRP in 14 patients with OA of the knee refractory to conservative treatment. They observed a linear improvement in VAS and knee injury OA outcome in 60% of patients at follow-up. The same results were reported by Wang and colleagues. More recently, improvements in all WOMAC parameters, pain scores, clinical and functional scores were reported after three PRP injections [15]. Intra-articular PRP injections led to better responses in younger patients, those who were more active and those with low-grade OA [16].

According to MSK Doppler US, there was about 100% improvement in patients with mild degree of OA and about 83% improvement in patients with moderate degree of knee OA after triple PRP injections; in comparison, 50% of patients with mild OA showed improvement and 20% of patients with moderate OA showed improvement after the first and second PRP injections. Also, in terms of synovial hypertrophy, there was an improvement in 50% of patients with mild OA after all injections, improvement in 45% of patients with moderate OA after the third injection and improvement in 20% of patients after the first and second PRP injections. However, there were no changes in the ultrasonographic grading of cartilage degeneration after PRP injections.

Actually, the role of PRP in cartilage repair is a matter of debate. A recent study reported that qualitative MRIs demonstrated no change per compartment in at least 73% of patients after PRP injections [15]. However, several in-vitro studies evaluated the effect of PRP on chondrocytes; Gaissmair *et al.*[17] reported that the addition of human platelet supernatant might accelerate chondrocyte expansion, even though it can lead to differentiation. Wu and colleagues investigated the feasibility of PRP to support chondrogenesis;

they found that gelled PRP provided a three-dimensional environment for seeded chondrocytes and successfully used it to deliver chondrocytes in cartilage defects in the rabbit model. Mitsuyama and colleagues reported that PRP promotes human chondrocyte proliferation, cells expanded with 30% PRP can express the chondrocyte phenotype and it can serve as a scaffold for autologous chondrocyte implantation that has potential availability for the repair of OA with chondral defects. Recently, it has been stated that PRP has an anabolic effect on chondrocytes and bone marrow-derived stem cells with a resulting increase in cell proliferation and matrix production, as well as an inflammatory effect through downregulation of known catabolic signaling pathways [18].

The usage of PRP in the treatment of degenerative knee OA has increased in recent years, given its high margin of safety and ease of production and administration [19]. Contrasting scientific evidence exists on PRP injections for knee OA, with the efficacy of PRP injections widely reported [20]. A meta-analysis was carried out to compare the efficacy of PRP injections against placebo or other therapeutic means for the treatment of knee OA; Bennell *et al.*[21] reported greater pain reduction[22] and functional improvement have been reported with the use of PRP. This could be due to the immediate and sustained release of growth factors over a prolonged period, which enhances healing, resulting in sustained clinical effects [2]. Symptomatic relief for up to 12 months with increased benefits to patients with early knee degenerative changes has been found [23]. In addition, better WOMAC scores were achieved at 24 weeks using PRP by Sanchez *et al.* [24], who examined 126 patients in RCT with different grades of OA and compared three PRP injections at 1-week intervals with hyaluronic acid.

Our study showed that this treatment method is very safe, with no complications such as infection or fever occurred, except for only mild pain at the injected area and skin bruises. Patel and colleagues reported mild complications such as nausea and dizziness, which were of short duration, but these were not reported in our patients.

In conclusion, from our results, it was found that an intra-articular injection of PRP in patients with mild and moderate knee OA is an effective and safe method. The maximum improvement was observed in mild cases with triple PRP injections.

Conflicts of interest

None.

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