Effectiveness of the intra-articular injection of platelet rich plasma in the treatment of patients with primary knee osteoarthritis

Ali Soliman Hassan a, Abeer Mohamed El-Shafey a,*, Hanan S. Ahmed b, Mohamed Soliman Hamed c

a Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University, Egypt
b Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt
c Rheumatology and Rehabilitation Department, Al-Ahraar Hospital, Ministry of Health, Egypt

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KEYWORDS
Platelet rich plasma; Intra-articular injection; Osteoarthritis; Knee; Ultrasonography; International knee document committee (IKDC) scale

Abstract  Osteoarthritis (OA) is the most prevalent form of arthritis in the world.  

Aim of the work: To evaluate the effect of 6-monthly intra-articular injection of platelet rich plasma (PRP) on the functional status of knee joint measured by the International Knee Document Committee scale (IKDC), the visual analogue scale for pain (VAS) on the ultrasonographic findings of OA knee. Assessment of its safety as a new line of treatment was taken into consideration.

Patients and methods: The study was carried out on 20 patients with mild to moderate primary knee OA. They were injected intra-articularly with 5 ml PRP for each affected joint, at 1 month intervals for 6 injections. Clinical examination, VAS, IKDC score and diagnostic Doppler ultrasonography were performed before and after PRP treatment.

Results: After 6 months of PRP, there was a significant improvement in the duration of inactivity stiffness (8.3 ± 2.4 min), VAS score (3.9 ± 1.1) and IKDC score (74.3 ± 10.2) compared to baseline values (18.7 ± 6.5 min, 5.9 ± 1.3 and 40.9 ± 10.4 respectively; p < 0.001). A significant improvement in Doppler activity (p = 0.04) and synovial thickening (p < 0.001) was found after 6 months of PRP. A significant correlation was found between age of patients, body mass index and disease duration with the VAS (r = 0.55, p < 0.001 and r = 0.29, p = 0.03 and r = 0.71,
1. Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis in the world. With the progressive ageing of the population, it becomes a major problem of public health. Osteoarthritis is a degenerative affection characterised by many disorders leading to structural and functional defect of one or several joints [1]. The combination of biochemical markers with clinical and radiographic data was most helpful to improve the diagnostic and prognostic values on assessment of patients with early knee OA and in determining disease progression [2].

The management of chondral disease is challenging because of its inherent low healing potential. In fact, the regeneration ability of cartilage is limited due to its isolation from systemic regulation and its lack of vessels and nerves [3]. Intra-articular injection of Human umbilical cord blood as a new source of mesenchymal stem cells was found effective for cartilage repair in rats with osteoarthritis [4].

A variety of agents, such as nonsteroidal anti-inflammatory drugs, glucosamine, chondroitin-sulphate, hyaluronic acid, and glucocorticoids have been proposed as non-invasive solutions for pain treatment, improvement in function, and disability, and ultimately modification of severe chondral degeneration and osteoarthritis with varying success rates [5].

Glucosamine, chondroitin-sulphate, and intra-articular hyaluronic acid have not been clearly demonstrated to be effective, and due to the continuing controversies and lack of common accepted beneficial evidence they should not be considered ideal procedures for the treatment of chronic chondropathies or osteoarthritis [6].

The field of using platelet rich plasma (PRP) in clinical and basic science research is growing. There is experimental evidence for positive effects of PRP in the context of soft tissue healing, ligament and bone regeneration, and inflammation reduction [7–10]. In another study on Egyptian patients with lateral epicondylitis and with plantar fasciitis, PRP was found promising and effective in both [11].

The aim of this work was to evaluate the effect of 6-monthly intra-articular injection of PRP on the functional status of the knee joint as measured by the International Knee Document Committee scale (IKDC), on the visual analogue scale for pain (VAS) and on the ultrasonographic finding of the OA knee. Assessment of its safety as a new line of treatment in knee OA was taken into consideration.

2. Patients and methods

2.1. Patients

The study was carried out on 20 patients with mild to moderate primary knee OA, recruited from Rheumatology and Rehabilitation outpatient clinics in Zagazig University Hospitals, during the period from May 2012 to March 2013. They were diagnosed according to The American College of Rheumatology (ACR) classification criteria of OA [12]. The study was approved by the local ethics committee and by the Institutional Review Board (IRB) of the institution. An informed written consent was taken from all the participants. Inclusion criteria for patients selection included history of chronic (at least 4 months) pain or swelling of the knee, not responding to NSAIDs and/or physical therapy and radiographic findings of minimal (grade 1: definite osteophyte, unimpaired joint space) to moderate (grade 2: moderate diminution of joint space) OA of the knee joint, according to Kellgren-Lawrence scale [13]. Exclusion criteria were systemic disorders, such as diabetes, rheumatoid arthritis, major axial deviation (varus more than 5 deg, valgus more than 5 deg), haematological diseases (coagulopathies), severe cardiovascular diseases, infections, immunosuppression, patients on therapy with anticoagulants-antiaggregants or use of NSAIDs within 5 days before blood donation.

2.2. Clinical, functional and radiological assessment

At the first visit all patients were subjected to full history taking, general examination and complete knee joint examination. The severity of pain was assessed by VAS [14]. Patients were asked to complete the International knee documentation committee (IKDC) osteoarthritis scale in order to evaluate the function of the affected knee [15]. Plain X-ray of the affected knee, anteroposterior and lateral views were done for grading of knee OA which was done according to the Kellgren–Lawrence grading system [13].

Sonographic Doppler examination was performed on the affected knee with 5.12 MHz linear array transducer (Medison R3). Patients were supine on an examination bed, with the knee flexed as much as possible [16]. Ultrasonography reports included comment on increased vascularity (Doppler activity), synovial hypertrophy, cartilage thickness, regularity of the cartilage margins and effusion.

Ultrasonographic detection of cartilage degeneration of the osteoarthritic knee was done according to Saarakkala et al. [17], in which they recommended supine position and the knee was fully flexed. First, the intercondylar notch area, including femoral condyles just above the patellar bone (later called sulcus), was depicted. Subsequently, the cartilage in medial and lateral femoral condyles were fully scanned by sweeping the full surfaces of the cartilage from proximal to distal with the probe always in transverse position. The ultrasound beam was kept perpendicular to the surface of the femur all the time. They evaluated the cartilage and gave the following grades: Grade 0: a monotonous anechoic band having sharp hyperechoic anterior and posterior interfaces. Grade 1 (Mild degenerative changes): loss of the normal sharpness of cartilage
interface and/or increased echogenicity of the cartilage (one point for each observation site, thus maximum of three points if the findings were present in both condyles and in the sulcus). **Grade 2A** (Moderate degenerative changes): in addition to above changes, clear local thinning (less than 50%) of the cartilage was observed. **Grade 2B**: degenerative changes were: local thinning of the cartilage more than 50% but less than 100% (two points at each observation site, maximum of six points). **Grade 3** (Severe degenerative change): 100% local loss of the cartilage tissue (three points, maximum of nine points).

Synovial hypertrophy was judged according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials Ultrasonography Task force which reported the US definition of synovial hypertrophy as “abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular tissue that is nondisplaceable and poorly compressible and which may exhibit Doppler” [18].

All patients were injected intra-articularly with about 5 ml of PRP for each affected joint, at 1 month intervals, for 6 injections. Injection was performed with the patient in the supine position, with the knee fully extended, using the lateral approach. After injection, patients were instructed not to use the injected leg for 24 h, use ice packs over the injected joint and not to use NSAIDs during this period [19].

### 2.3. Platelet – rich plasma preparation

The procedure consisted of 30 ml of venous blood samples taken from every patient and collected in sterile sodium citrated tubes. Platelet concentrates rich in growth factors were obtained by the following technique: The tubes with citrated blood were centrifuged at 1800 rpm for 15 min to separate erythrocytes, and at 3500 rpm for 10 min to concentrate platelets [20]. By this method, 5 ml of PRP were obtained and injected immediately without storage. It has been stated that fresh-ly harvested PRP might preserve all the platelet functions better [19].

### 2.4. Follow up assessment

After 6 months, all patients were re-evaluated by physical examination, assessment of VAS for pain, IKDC score and musculoskeletal Doppler ultrasonography.

**Statistical analysis:** Data of the patients were entered on the Statistical Package for Social Science (SPSS). Quantitative data were presented as mean and standard deviation, while the qualitative data were presented as number and percentage. Paired t-test and chi square test were used to assess differences between quantitative and qualitative data at baseline and after 6 PRP injections. Spearman’s correlation coefficient analysis was performed to identify factors associated with better functional outcomes. A statistically significant cutoff value was set at $p < 0.05$.

### 3. Results

#### 3.1. Clinical data of patients

This study was carried out on 20 patients who were suffering from mild to moderate primary knee OA diagnosed clinically, by plain X-ray and Doppler musculoskeletal ultrasound. There were 14 (70%) females and 6 (30%) males. Their age ranged from 40 to 70 years with a mean of 50.4 ± 8. Thirteen patients were overweight with body mass index ranged from 22–35, with a mean of 28.4 ± 7.7. Five patients were of normal weight and two were obese. Their disease duration ranged from 19–30 months, with a mean of 24 ± 5. Seventy percent of patients had moderate OA (grade 2) and 30% had minimal OA (grade 1), according to Kellgren-Lawrence scale. There were statistically significant differences in the number of patients with crepitus, tenderness at the joint line and limited ROM at base line and after 6 monthly injections of PRP ($p < 0.05$) (Table 1).

#### 3.2. Pain and functions of the affected joints

Table 2 shows clinical and functional changes of affected joint after 6 PRP injections. There was a highly statistically significant improvement in the duration of inactivity stiffness; VAS score and IKDC score ($p < 0.001$).

#### 3.3. Changes in ultrasonographic findings

Patients did not show any significant changes in the ultrasonographic grading of cartilage degeneration after PRP injections. While there was a significant decrease in the number of patients having increased Doppler activity after 6 PRP injections ($p = 0.04$), as 35% showed activity at baseline while only 10% showed it after 6 PRP injections. There was a highly significant decrease in the number of patients having synovial hypertrophy. Only 5 cases (25%) had synovial hyperplasia after 6 PRP injections, compared to 15 cases (75%) at baseline (Table 3).

In this study, nine patients (45%) reported decreased use of NSAIDs and/or physical therapy after 6 PRP injections. Regarding complications, 5 patients (25%) experienced slight pain at the site of injection which lasted for one week and only one patient (5%) experienced marked pain. Two patients (10%) had skin discoloration in the form of bruising. No reported cases suffered from infection or allergic reaction.

#### 3.4. Factors associated with improvement after PRP injections

The BMI showed a significant correlation with VAS and a highly significant negative correlation with IKDC score after 6 PRP injections. Patient’s age and disease duration had a

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Difference between clinical data of knee osteoarthritis patients at base line and after 6 PRP injections.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data N (%)</td>
<td>Base line</td>
</tr>
<tr>
<td>Hotness</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Tender joint line</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Crepitus</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Effusion</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Backer cyst</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Limited ROM</td>
<td>7 (35)</td>
</tr>
</tbody>
</table>

ROM: range of motion.

* Significance at $p < 0.05$. 

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**Notes:**

- **Grade 2A** (Moderate degenerative changes): In addition to above changes, clear local thinning (less than 50%) of the cartilage was observed.
- **Grade 2B**: degenerative changes were: local thinning of the cartilage more than 50% but less than 100% (two points at each observation site, maximum of six points).
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The BMI showed a significant correlation with VAS and a highly significant negative correlation with IKDC score after 6 PRP injections. Patient’s age and disease duration had a
highly significant correlation with VAS, while they showed a negative correlation with the IKDC score (Table 4).

4. Discussion

Osteoarthritis is a major public health problem which causes pain and disability in one third of all affected patients [21]. It is one of the crucial musculoskeletal disorders characterised by the imbalanced homoeostasis and destruction of the articular cartilage, in which pro-inflammatory cytokines are important catabolic regulators during OA cascade [22]. Platelet-rich plasma (PRP) is a natural concentrate of autologous growth factors from the blood. It allows in a simple, low cost and minimally invasive way to obtain a concentration of many growth factors [23]. The application of PRP to treat OA of the knee can be considered a relatively new therapeutic indication [24]. This study has been carried out on 20 patients suffering from mild to moderate OA. They were injected in their knees by PRP for six injections at monthly-intervals.

In our patients, a statistically significant improvement was observed regarding most of the clinical aspects, such as, tenderness in joint line, crepitus and range of motion. There was, also, improvement in the number of patients having hotness, effusion and Baker’s cyst, but this improvement did not reach a statistically significant level.

In this study, there were highly statistically significant improvements in the patient’s perception of pain, knee function and quality of life, represented by the duration of inactivity stiffness, VAS and IKDC score. Better results were achieved in younger patients and those with short disease duration. This could be explained by the high percentage of living and vital cells and therefore the high response potential to the growth factors. BMI showed a significant correlation with VAS and a highly significant negative correlation with IKDC score after 6 PRP injections.

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 of VAS and knee injury OA outcome in 60% of patients at follow-up [25]. The same results were reported by Wang and colleagues [26]. More recently, improvement in all WOMAC parameters [27,28], pain scores, clinical and functional scores [29] was reported after three injections of PRP. Intra-articular PRP injections had a better response in younger patients [23,24], more active patients [30] and those with low grade OA [31]. It has been reported that better response rates are evident in OA patients treated with PRP injections than in those treated with hyaluronic acid [24,30,32], although a recent study reported that they have the same efficacy [31].

Regarding musculoskeletal Doppler ultrasound findings there was a highly significant improvement in synovial hypertrophy and a significant improvement in Doppler activity (p = 0.04). But, there were no significant changes in the ultrasonographic grading of cartilage degeneration after PRP injection.

Table 2  Effects of PRP injection on pain and function of affected joints in patients with knee osteoarthritis.

<table>
<thead>
<tr>
<th>Score</th>
<th>Base line</th>
<th>After 6 months</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivity stiffness (min)</td>
<td>18.7 ± 6.5 (15–30)</td>
<td>8.3 ± 2.4 (4–10)</td>
<td>20.3</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>VAS (cm)</td>
<td>5.9 ± 1.3 (4–7)</td>
<td>3.9 ± 1.1 (2–4)</td>
<td>13.1</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>IKDC</td>
<td>40.9 ± 10.4 (30–40)</td>
<td>74.3 ± 10.2 (64–85)</td>
<td>21.5</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

VAS: visual analogue scale, IKDC: international knee documentation committee.

** High significance at p < 0.001.

Table 3  Differences in musculoskeletal US findings and grading after 6 PRP – injections in patients with knee osteoarthritis.

<table>
<thead>
<tr>
<th>US findings N (%)</th>
<th>Base line</th>
<th>After 6 months</th>
<th>X²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doppler activity</td>
<td>7 (35)</td>
<td>2 (10)</td>
<td>4.23</td>
<td>0.04*</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6 (30)</td>
<td>7 (35)</td>
<td>0.40</td>
<td>0.53</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (35)</td>
<td>6 (30)</td>
<td>0.37</td>
<td>0.49</td>
</tr>
<tr>
<td>Grade 3</td>
<td>7 (35)</td>
<td>7 (35)</td>
<td>0.60</td>
<td>0.63</td>
</tr>
<tr>
<td>Synovial hypertrophy</td>
<td>15 (75)</td>
<td>5 (25)</td>
<td>4.91</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

* Significance at p < 0.05.
** High significance at p < 0.001.

Table 4  Correlation between patients’ ages, BMI and the severity of pain and functional scores after 6 injections in patients with knee osteoarthritis.

<table>
<thead>
<tr>
<th>Score</th>
<th>Age</th>
<th>BMI</th>
<th>Disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>VAS</td>
<td>0.55</td>
<td>&lt;0.001**</td>
<td>0.29</td>
</tr>
<tr>
<td>IKDC</td>
<td>−0.32</td>
<td>0.03*</td>
<td>−0.96</td>
</tr>
</tbody>
</table>

VAS: visual analogue scale, IKDC: international knee documentation committee.

* Significance at p < 0.05.
** High significance at p < 0.001.
injections. Only one patient had moved from grade 2 to grade 1, meaning that thinning of his cartilage has no longer been evident during musculoskeletal ultrasound examination.

Actually, the role of PRP in the cartilage repair is a matter of debate. A recent study reported that qualitative MRIs demonstrated no change per compartment in at least 73% after PRP injections [29]. But a lot of in vitro studies evaluated the effect of PRP on chondrocytes; Gaissmaier et al., reported that addition of human platelet supernatant may accelerate chondrocyte expansion, even though it can also lead to de differentiation [33]. In another study, an autologous conditioned serum was administered in horses with experimentally induced OA and reported a significant clinical improvement in lameness, decreased synovial membrane hyperplasia, less gross cartilage fibrillation and synovial membrane haemorrhage and increased synovial fluid concentration of interleukin-1 receptor antagonist. They stated that PRP may influence the overall joint homeostasis, reducing synovial membrane hyperplasia and modulating the cytokine level, thus leading to an improvement in the clinical outcome, even if only temporarily and without affecting the cartilage tissue structure and joint degenerative progression [34]. Wu et al. investigated the feasibility of PRP to support chondrogenesis; they found that gelled PRP provided a 3-dimensional environment for seeded chondrocytes and was successfully used to deliver chondrocytes in cartilage defects in a rabbit model [35]. Mitsuyama and colleagues reported that PRP promotes human chondrocyte proliferation, cells expanded with 30% PRP can express chondrocyte phenotype, and can serve as scaffold for autologous chondrocyte implantation that has potential availability for repair of osteoarthritis with chondral defects [36]. Regarding humans, an old case report has been described, where plasma rich in growth factors was used to treat an articular cartilage avulsion in a soccer player. They reported an accelerated and complete articular cartilage healing [37]. Recently, it has been stated that PRP has an anabolic effect on chondrocytes and bone marrow-derived stem cells with resulting increase in the cell proliferation and matrix production, as well as an anti-inflammatory effect via down regulation of known catabolic signalling pathways [38].

Our study showed that this method of treatment is very safe as no complications such as infection or fever occurred among study subjects. Only minor adverse events were detected such as mild pain at injected area and skin bruises. Patel and colleagues reported mild complications such as nausea and dizziness, which were of short duration [27] and these complications were not reported in our patients.

In conclusion, from the presented results it was found that intra-articular injection of PRP is an effective and safe method for treatment of knee OA. Maximal improvement was seen in younger patients and those with shorter disease duration.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgement

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References


