Evaluation of the Effect of Intra-Articular Injection of Platelet Rich Plasma in Treatment of Primary Knee Osteoarthritis

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Abstract: Two hundred consecutive patients with symptomatic primary knee osteoarthritis (KOA) were included in this study. All patients met the European League against Rheumatism (EULAR) 2010 criteria for diagnosis of primary KOA.100 patients received treatment withintra articular injection of platelet retched plasma (PRP) and 100 patients received treatment with NSAIDs as control group. Clinical data were collected at baseline and after three months of treatment with (PRP) or NSAIDs. To assess results some measures were used, the VAS-pain score, tenderness score, the IKDC score, KL-grade, and the synovial vascularity using plain X ray and musculoskeletal ultrasound. The study revealed that, there were no significant differences between the two groups at baseline, after 3 months of treatment there were significant differences between the two groups. The VAS-pain score was significantly lower in the PRP-treated group than in the control group (4.2 ±1.6 versus 4.7 ±1.5 respectively, p=0.025). The tenderness score in the PRP-treated group was 1.9 ±0.8 vs. 2.3 ±0.6 in the control group (p<0.001). The IKDC was significantly higher in the PRP-treated group compared to the control group (73.9 ±11.4 versus 63.6 ±12.3 respectively, p<0.001). In addition, the average KL grade of the control group was significantly higher than that of the PRP-treated group (1.64 ±0.61 versus 1.48 ±0.52 respectively, p=0.048). So, treatment were significantly better in the PRP-treated group in comparison to the control group.

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1. Introduction

Osteoarthritis (OA) is one of the most prevalent conditions resulting to disability particularly in elderly population. OA is the most common articular disease worldwide and a leading cause of chronic disability ***(Grazio and Balen, 2009)***. It was expected to affect 67 million Americans by 2030. OA one of degenerative joint disease, and represents a painful chronic condition that can affect any synovial joint ***(Buckwalter JA and Martin JA*, 2006).**

Knee OA (KOA) affected patients at earlier age groups particularly in obese women. The incidence of KOA increased with age, longer lifetime and higher weight ***(Bliddal and Christensen, 2009)***. The disease was not localized incartilage alone but it considered as a chronic disease of the whole joint. It may include articular cartilage, meniscus, ligament, and peri-articular muscle ***(Hayami., 2008).*** *it may* arising from the biochemical breakdown of articular cartilage in the synovial joints ***(Abramson and Attur, 2009; Martel-Pelletier and Pelletier, 2010).*** OA is characterized by a progressive loss of articular cartilage accompanied by new bone formation and, often, synovial proliferation that may culminate in pain, loss of joint function, and disability ***(Abramson and Attur, 2009)***. A healthy joint requires a perfected balance between molecular signals regulating homeostasis, damage, restoration, and remodeling. Different factors are able to impair the maintenance of homeostasis in a joint that has been damaged, and they may progressively lead to OA ***(Hunter and Felson, 2006; Heijink et al., 2012)***.

A wide spectrum of treatments is available, from non-pharmacological modalities to dietary supplements and pharmacological therapies, which aimed to restore joint homeostasis and providing clinical improvement (***Kon et al., 2012)***. When these strategies fail, a trial of corticosteroid injections may be pursued or recently using PRP intra- articular injection.

Platelet-rich plasma (PRP) is a fashionable treatment, offering the possibility to deliver a high concentration of autologous growth factors and bioactive molecules in physiologic proportions, with low costs and in a minimally invasive way. This explains the wide application of this blood derivative to several tissues and heterogeneous pathologies in different fields of medicine ***(Kon et al., 2011)***. PRP

when injected to injured tissues, endogenous thrombin and/or intra-articular collagen lead to activated platelets. The later promotes secretion of growth factors which some of them act as anti-catabolic and anti-inflammatory agents. Also, platelet growth factors stimulate synovial fibroblasts to synthesize hyaluronic acid (**Anitua E et al.,2007**).

PRP contains other molecules such as vascular endothelial growth factor (VEGF) which does not take part or might even jeopardize cartilage homeostasis and regeneration ***(Tschon et al., 2011; Mifune et al., 2013)***. Thus, it is mandatory to investigate whether the overall effect of PRP is also beneficial for the peculiar requirements of cartilage tissue before an indiscriminate human application.

Subjects and Methods

This study included 200 consecutive patients with mild to moderate primary KOA in the period from April 2016 to April 2017. All patients met the European League against Rheumatism (EULAR) 2010 criteria for diagnosis of primary KOA (Table 1) ***(Zhang et al., 2010)*** and patients must had radiological changes in studied knees by plain x-ray. The patients were recruited from Rheumatology and Rehabilitation outpatient clinic in AL-Azhar University Hospital, Damietta.

Preparation of PRP

The procedure consisted of a 30-ml venous blood sample for every knee treated. Then, 2 centrifugations (the first at 1480 rpm for 6 minutes to separate erythrocytes, and a second at 3400 rpm for 15 minutes to concentrate platelets) produced a unit (4 ml) of PRP ***(Mazzucco et al., 2009)***. The 4 ml of PRP that was obtained is injected immediately without storage. It has been stated that using freshly harvested PRP might preserve all the platelet functions better ***(Filardo et al., 2012).***

Treatment and evaluation

The selected patients who met the inclusion criteria were subdivided into two 2 groups: one group received intra- articular PRP, and the other group received NSAIDs as control group. Before intra-articular injection complete blood count preformed on PRP sample to select the platelet concentration. During treatment rest or mild activities were advised.

Demographic data including patient age, sex, OA grade according to the Kellgren-Lawrence (K-L) classification, and IKDC were collected onall patients. Clinical and biological data were compared at baseline and after three times to identify parameters, which affected responses.

Statistical analysis

All statistical analyses were performed using SPSS (SPSS, Chicago, IL). Continuous data were expressed as mean ±standard deviation (SD), while categorical data were expressed in number and percentage. 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 $p<0.05$.

3. Results

The mean age of the KOA patients in the PRP-treated group was 59.1 ±7.5 years and 59.7 ±8.4 years in the control group. As regards the sex distribution between the two groups, the females and males represent 56% and 44% in the PRP-treated KOA group and represent 57% and 43% of the KOA control group.

Clinical Results

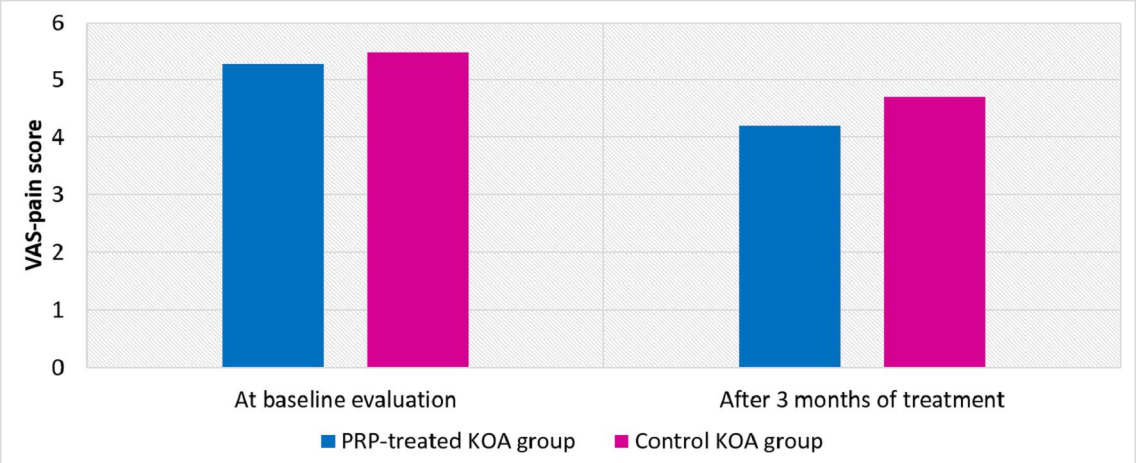

Fig.1. The VAS-pain between the between the PRP-treated group and control group at baseline and after 3 months of treatment

Clinical outcome scores include VAS-pain score, tenderness score and the IKDCscore between the two groups at baseline evaluation and after 3 months are shown in Table 2. At baseline evaluation, there were no significant differences between two groups. Whereas, the clinical outcomes scores after 3 months of treatment were significantly better in the PRP-treated group in comparison to the control group. The VAS-pain score was significantly lower in the PRP-treated group than in the control group, Fig.1. The tenderness score in the PRP-treated group was 1.9 ±0.8 compared to 2.3 ±0.6 in the control group ($p<0.001$), Fig.2. The IKDC was significantly higher in the PRP-treated group compared to the control group, Fig.3.

On the other hand, the average plain x-ray KL grade did not differ significantly between the two-studied groups at baseline evaluation. Whereas, after three months of treatment the control group had significantly higher average KL grade than that of the PRP-treated group, P=0.048) (Fig.4). In addition, table 3 deals with US examination findings between the PRP-treated group and control group at baseline and after 3 months of treatment. No significant differences were found were found the two-studied group at baseline regarding to Synovial vascularity, Synovial hypertrophy, and Cartilage grade. Whereas, after treatment all these parameters were better.

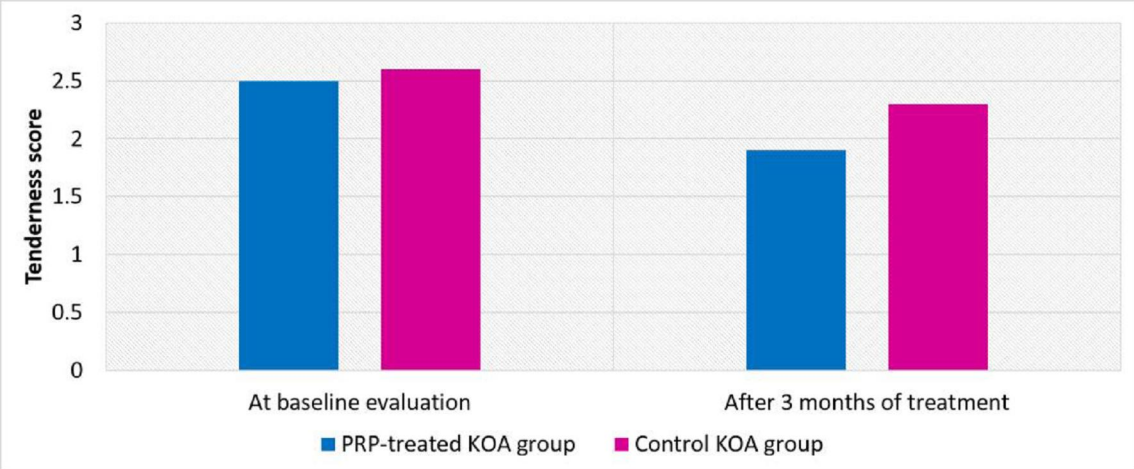

Fig.2. The tenderness score between the between the PRP-treated group and control group at baseline and after 3 months of treatment

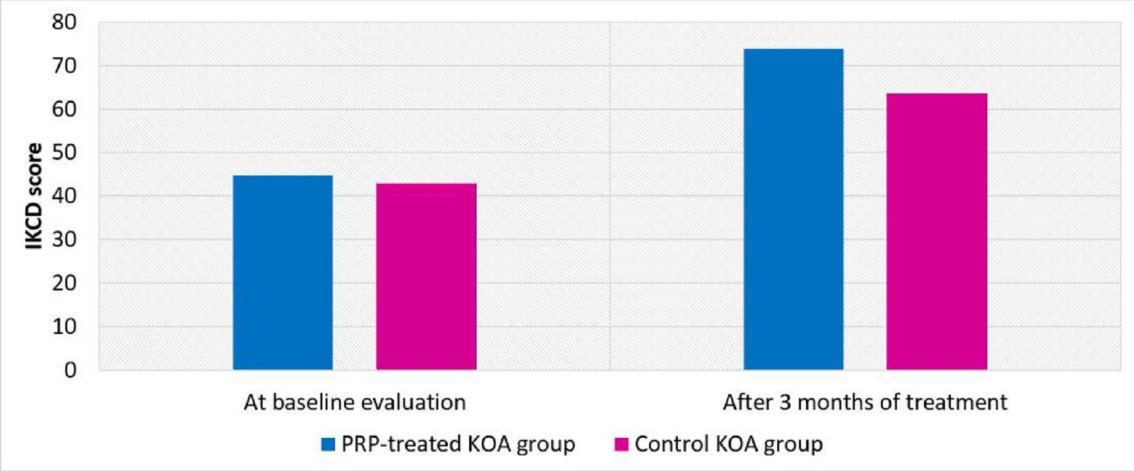

Fig.3. The IKDC score between the between the PRP-treated group and control group at baseline and after 3 months of treatment.

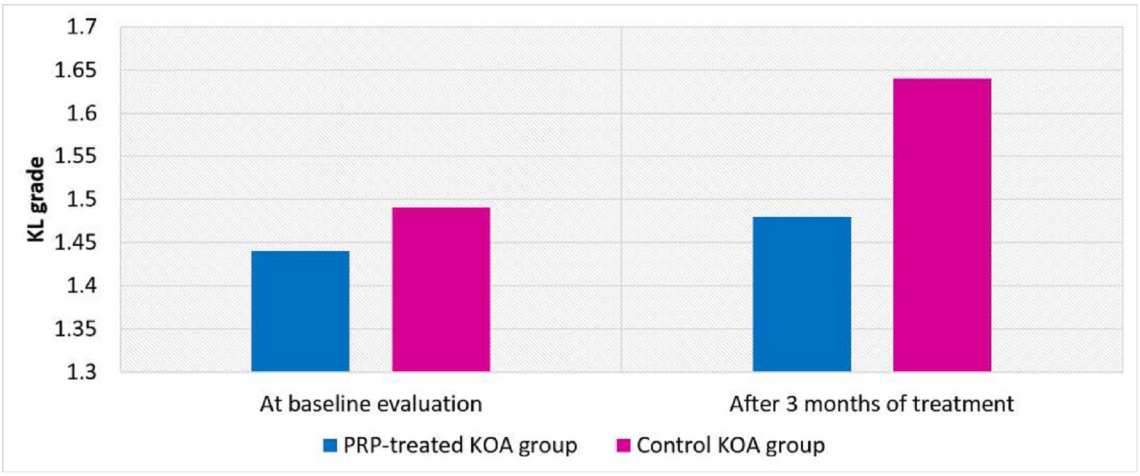

Fig.4. The frequency of KL-grade between the PRP-treated group and control group at baseline and after 3 months of treatment (*P*= 0.048)

Table1(Patient Screening Criteria)

Inclusion Criteria

1. Persistent knee pain.
2. Limited morning stiffness.
3. Reduced function

Signs

1. Joint crepitus
2. Restricted movement
3. Bony enlargement

Exclusion Criteria

1. Age younger than 40 years.
2. Advanced KOA.
3. Any local disease in the involved knee other the primary OA.
4. Morbid obesity.
5. Previous knee surgery.
6. Local sepsis, cellulites or skin ulceration which limits the injection.
7. Vascular insufficiency or neuropathy in the involved lower limb.
8. Systemic disorders, including uncompensated diabetes mellitus, cardiovascular disease, hepatic disease, renal disease hematological diseases or immune-suppression and patients co-agulopathy.
9. Receiving NSAIDs within one week prior to inclusion in the study.
10. Receiving local steroids injection within 6 months prior to inclusion in the study.
11. Receiving physical therapy four weeks prior to inclusion in the study.

Table2. Comparison of the US examination findings between the PRP-treated group and control group at baseline and after 3 months of treatment

	KOA Group PRP-treated	Control	Student's t test t	p
At baseline evaluation				
Synovial vascularity	1.81 ±0.86	1.86 ±0.77	1.465	**0.145**
Synovial hypertrophy	1.91 ±0.81	1.94 ±0.85	0.256	**0.798**
Cartilage grade	2.28 ±1.08	2.52 ±1.15	1.519	**0.130**
After 3 months of treatment				
Synovial vascularity	1.59 ±0.78	1.82 ±0.76	2.116	**0.036**
Synovial hypertrophy	1.63 ±0.71	1.89 ±0.84	2.370	**0.019**
Cartilage grade	2.33 ±1.06	2.64 ±1.06	2.065	**0.040**

4. Discussion

Recently, much researches deal with the role of PRP in treatment of many diseases. Herein, we had evaluated PRP in patients with KOA. RPP is an effective treatment, which reduced pain and improved the functional status in patients with KOA. In comparison to conventional NSAIDs treatment, PRP produced significantly better radiological outcome. US examination revealed that PRP improved the synovial vascularity, hyperplasia, and rate of effusion more effectively than conventional NSAIDs treatment. That may be due to the anti-inflammatory effects of PRP, it attributable to the reduction in the trans-activation of NF-κB, the critical regulator of the inflammatory process. Activated PRP has an enhanced concentration of HGF and TNF-α. These growth factors disrupt the trans-activation of NF-κB, which intern contributes to PRP anti-inflammatory effects ***(Dhillon et al., 2014)***.

The present study reveals that at baseline evaluation there were no significant differences between the groups as regards VAS-pain score, tenderness score and IKDC score, these clinical outcomes scores after 3 months of treatment were significantly better in the PRP-treated group in comparison to the control group. These results are constituent with ***Kon et al (2010)*** who reported that there is a significant improvement of all clinical scores at the end of the study compared to baseline values. In addition, ***Filardo et al (2011)*** reported improvement of the evaluated parameters at the end of the injection course and the improvement was stable along one-year follow-up period. It may illustrate by decreasing the expression of inflammatory enzymes COX-2 and COX-4 ***(Bendinelli et al., 2010)*** and decreasing the gene expression of a ADAMTS-4 and prostaglandin-endoperoxide synthase ***(van Buul et al., 2011)***. However, PRP could have pro-inflammatory effect on the human chondrocytes after the initial reduction of COX-2 ***(Pereira et al., 2013).***

van Drumpt et al. (2016) reported that pain, tenderness and functional scores were all significantly improved after the PRP injection in eleven patients with KOA. ***Bottegoni et al. (2016)*** reported that the homologous PRP had produced a significant short-term improvement in pain and IKDC score in comparison to the baseline levels, these findings were in agreement with the findings of the present study. PRP has a dual effect on the chondrocytes' response to inflammatory conditions ***(Dhillon et al., 2014)***.

Also, our study estimated significant improvement of pain, IKDC and VAS pain scores. This is agree with ***Filardo et al (2011),*** PRP injections in patients with KOA can reduce pain and improve knee function and quality of life with short-term efficacy. PRP had significant role in improvement of pain, IKDC and VAS pain scores (***Napolitano et al. 2012).***

In recentsimilar studies, whichcomparedintra-articular PRP with other therapeutic protocol their results are confirm our results. ***Simental-Mendía et al (2016)*** had compared the clinical response of acetaminophen and intra-articular PRP in early KOA and found that treatment with PRP injections produce asignificant better pain score and functional scores (WOMAC). ***Dai et al. (2016)*** PRP is slightly superior to HA in relieving pain and improving the functional scores. However, after one year follow up period, PRP injections is associated with significantly better pain relief and functional outcome compared to the HA injections. The systemic reviews of **Orchard (2016)** and **Sadabad et al. (2016)** also obtained the same conclusions. So, we can recommend the using of PRP as therapeutic protocol for treating KOA.

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