

# Efficacy of intra-articular injection of activated platelet rich plasma as pain management method in chronic knee pain

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**Objective** The aim of this retrospective study is to evaluate the efficacy of intra-articular platelet rich plasma (IA-PRP) in managing the chronically painful knees with osteoarthritis (OA) in a private clinic in Kirkuk, Iraq.

**Methods** Over an 18-month period (July 1, 2016–December 31, 2017), 76 patients (57 females) visited us because of painful knees due to OA. About 124 knees received IA injections of ozonized PRP (OPRP). The PRP was prepared by centrifuging patients' own blood and activated by passing 1 ml of ozone for each 1 ml of PRP. A questionnaire was used to categorize the pain into mild, moderate, and severe and the response to therapy was graded as excellent, good, fair, and poor.

**Results** The mean age was  $53.6 \pm 1.7$  years. 59.2% of females had a moderate pain. Overall, IA-PRP injection yielded excellent–good results in (88.7%) of the treated joints. More than half ( $n = 53, 66.3\%$ ) of the well-responded joints received 1–4 doses of IA-OPRP.

**Conclusion** IA-PRP seems to be an effective, safe, and cheap method for relieving the chronic pain of knee OA.

**Keywords** chronic knee pain, osteoarthritis, pain management, platelets rich plasma, Iraq

## Introduction

Osteoarthritis (OA) is one of the most common disabling joint diseases of the older adults in the world. It is a major cause of chronic pain in this age group. The incidence of knee OA is more than that of the hip or hand joints and there is an increase in the number of the newly diagnosed cases in the past decade particularly in younger adults.<sup>1</sup>

The pathophysiology of the disease is complex and multi-factorial. Synovial inflammation, peripheral and central nervous system sensitization and other factors may all contribute.<sup>2</sup> The precise mechanism of chronic pain and disability in OA of knee joint is not so clear. Various articular and extra-articular structures can be affected by the disease. The bone, synovial membrane, joint capsule, ligaments, and meniscus as well as ligaments and tendons outside the joint may be diseased and hence, generate the chronic pain.<sup>3</sup>

In the last few years, studies concentrated on finding new biochemical treatment methods for joints OA. Platelet rich plasma (PRP) was one of the major foci of research as a novel promising therapy. PRP is one of the most up-to-date issues in regenerative medicine for many degenerative conditions. It is currently used as intra-articular (IA) injection for management of chronic knee pain resulting from injured or degenerated cartilages.<sup>4</sup>

Platelet-rich plasma is a fraction of plasma characterized by high levels of multiple growth factors. PRP isolated from autologous blood may be useful as a source of anabolic growth factors for stimulating chondrocytes to engineer cartilage tissue.<sup>5</sup> Studies have shown that PRP supplementation to a cell culture of human OA chondrocytes can maintain the chondrocyte differentiation and thus cartilage regeneration unlike platelet poor plasma.<sup>6</sup>

The aim of this study is to clinically evaluate the efficacy of IA injection of PRP activated by ozone (OPRP) as pain management method for chronic pain resulted from knee joint OA.

## Patients and Methods

This is a retrospective study of a group of patients with different degrees of chronic knee pain (>6 months) as a result of unilateral or bilateral knee joint osteoarthritis. The diagnosis was based on clinical and radiological features. In this study, “the authors used a symptom-based patient-directed questionnaire to assess the outcome after ozone therapy. The questionnaire was similar to that described by Bhattacharya et al. in their study of thoracic outlet compression but slightly modified. The questionnaire asked patients to grade their perception of symptomatic relief using the terms “Excellent” for complete relief of symptoms, “Good” for relief of most major symptoms, “Fair” for relief of some symptoms, but persistence of others and “Poor” for no improvement.”<sup>7</sup>

Pain management was done with intra-articular injection of OPRP, 20 cases in the Department of Family Medicine/ Azadi Teaching Hospital/Kirkuk/Iraq and 54 cases in authors private clinic/ Kirkuk/ Iraq over the period (July 1, 2016–December 31, 2017). There were 76 patients (57 females and 19 males) with a total number of 124 knees received different number of sessions of IA-OPRP therapy. The study was approved by the Medical Ethical Committee of Kirkuk Health Directorate; the reference number of the approval is 33587 in 15/11/2018.

Longevity resources EXT50 Ozone Generator (Fig. 1A) with oxygen tank and CGA870 Oxygen Regulator (Fig. 1B) were used. Preparation of OPRP was described in a previous publication of the first author.<sup>8</sup> It was done by withdrawing “an autologous blood from the patient's own vein by a 50-ml syringe. The withdrawn blood was then placed in aseptic tubes, each one filled with 9-ml blood and 1-ml 3.8% sodium citrate as an anticoagulant. The tubes were then placed in 80-2 Electronic Centrifuge (Fig. 1C) at 1500 rpm for 10 min separating the sample into three parts; the upper one made of plasma, the middle (Buffy coat) made of white blood cells while the lower part made of red blood corpuscles. The upper

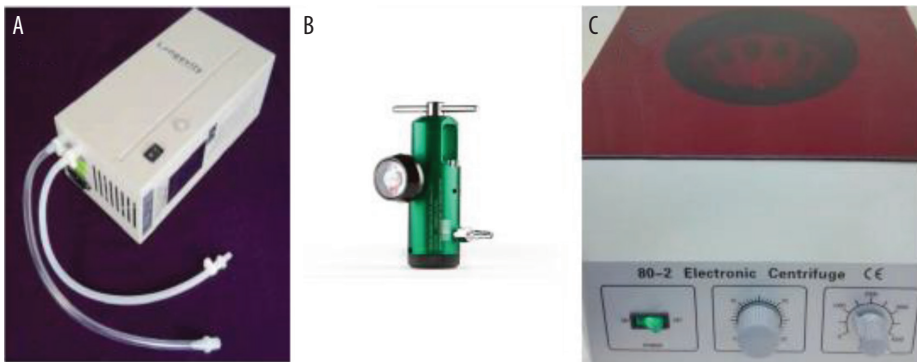


Fig. 1 (A) Longevity resources EXT50 ozone generator, (B) CGA870 oxygen regulator, (C) 80-2 Electronic Centrifuge.

two thirds of plasma were then discarded while the lower third was transferred to another aseptic tube and placed in a centrifuge again. After 15-min centrifugation at 3000 rpm, the upper half of the sample was discarded while the lower half formed the PRP. Platelet rich plasma was then activated by passing 1 ml of ozone for each 1 ml of PRP and injected into the knee joint spaces”. Patients with a bleeding tendency or those receiving anticoagulant therapy were excluded from the study.

Body mass index (BMI) of the patients was calculated by the equation: Weight in kg/(Height in m)<sup>2</sup> and accordingly, the patients were classified as having a healthy body weight (18.5–24.9), overweight (25–29.9), obesity I (30–34.9), obesity II (35–39.9), and obesity III (≥40).<sup>9</sup> Statistical analysis was performed using z-test for two population proportions.

### Results

There were 76 patients (57 females and 19 males) with a female: male ratio of 3:1. The age ranged between 26 and 80 years with a mean of 53.6 ± 1.7. Figure 2 displays the age and sex distribution of the studied patients.

Most of the patients were in the 5<sup>th</sup>–7<sup>th</sup> decades of life (n = 55, 72.4%). Figure 3 shows the patients job distribution.

Most of the female patients were housewives (n = 46, 80.7%) while most males were free workers and government employees (n = 15, 78.9%). Table 1 shows the co-morbidities encountered in the studied patients.

The top co-morbid condition was obesity as most of the patients (n = 69, 90.8%) were either overweight or obese. Hypertension (HT) and diabetes mellitus (DM) ranked second. Thirty patients (39.5%) had HT either alone or in combination of other conditions while 11 patients (14.5%) had DM either alone or in combination of other conditions. Worthy no note that 28 patients (36.8%) had a unilateral disease while 48 (63.2%) had a bilateral knee involvement. The distribution of patients according to their BMI is shown in Fig. 4.

Most of the patients (n = 69, 90.8%) were either overweight or obese, while the minority (n = 7, 9.2%) had a healthy body weight. Figure 5 shows the results of chronic knee pain classes according to gender and severity.

Most females had either moderate (n = 58, 59.2%) or severe chronic pain (n = 29, 29.6%) while males were almost equally divided between the three pain severity grades. Figure 6 shows the different degrees of response of chronic knee joints pain to IA injection of OPRP vs. different degrees of chronic knee joint pain.

The best response was observed among patients with moderate pain in whom an excellent response was achieved in

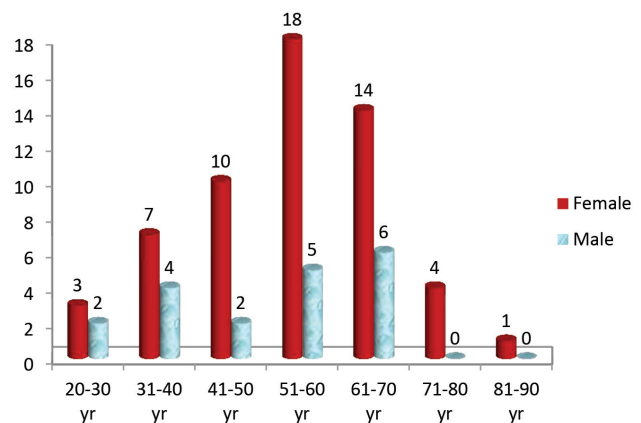


Fig. 2 Patients age and sex distribution.

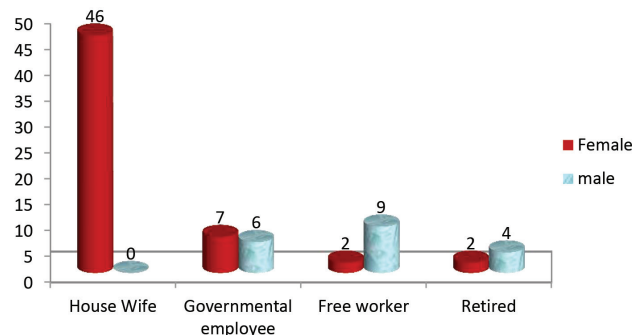


Fig. 3 Patients job distribution.

Table 1. The co-morbid conditions

Co-morbidity	Sex		Total
	Females	Males	
Overweight or obese	52	17	69
HT	17	2	19
DM and HT	6	3	9
DM	1	0	1
DM, HT, and CAD	1	0	1
HT and CAD	1	0	1
CAD	0	1	1
Bronchial asthma	0	1	1
Gall stones	1	0	1

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease.

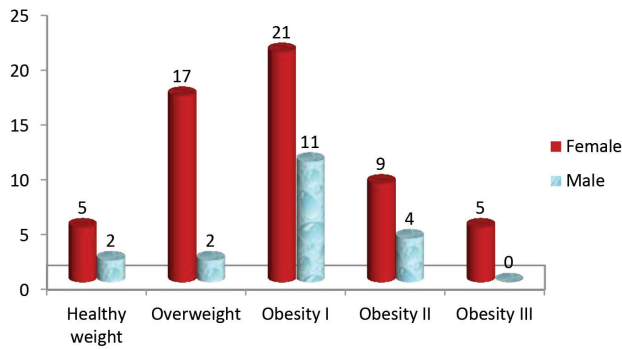


Fig. 4 Patients distribution according to BMI categories.

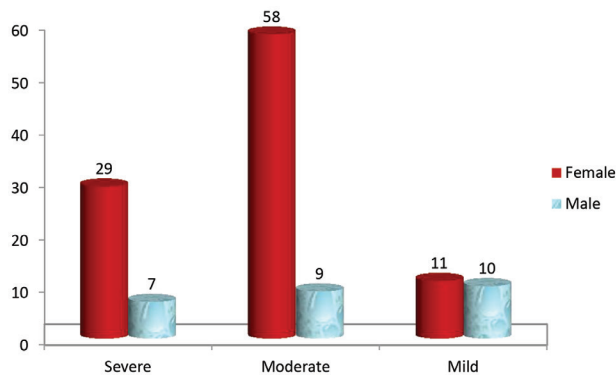


Fig. 5 Pain severity vs. gender.

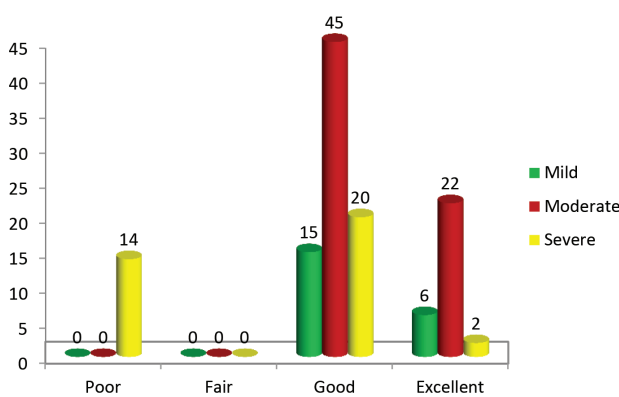


Fig. 6 Response to IA-OPRP vs. pain severities.

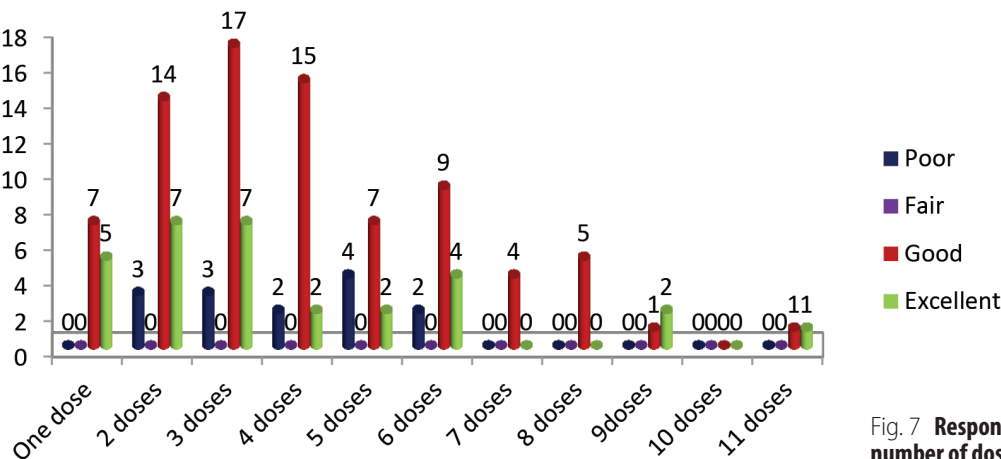


Fig. 7 Response to IA-OPRP injection vs. number of doses.

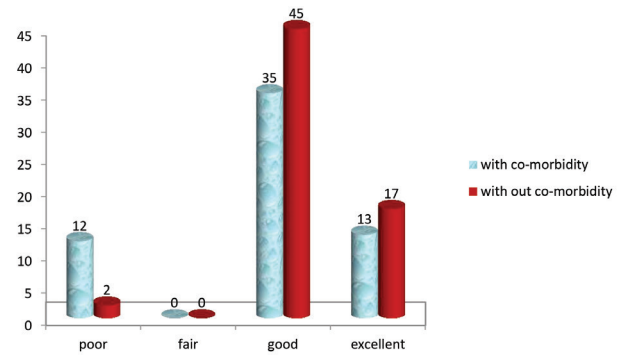


Fig. 8 Influence of different co-morbidities on response of painful knees to IA-OPRP injections.

one third and a good response in two thirds of patients. Likewise, patients with mild pain ( $n = 21$ ) had experienced an excellent response in almost one third and a good response in more than two thirds of patients. In contrast, patients with severe pain had either a good ( $n = 20$ ) or poor response ( $n = 14$ ) but there was no statistically significant difference between the two groups ( $P < 0.05$ ). Figure 7 shows the degree of response of chronic knee pain vs. number of sessions of IA-OPRP.

Almost two thirds of painful knees ( $n = 53$ ) who achieved a good response to IA-OPRP injections required 1–4 treatment sessions. Figure 8 shows the influence of different co-morbidities on the response of painful knees to IA-OPRP injections.

Most of the painful knees which responded poorly to IA-OPRP injections (12/14, 85.7%) had associated co-morbidities particularly obesity (statistically significant at  $P < 0.05$ ). Among the good–excellent responders, a higher proportion had no associated co-morbidities. However, this difference was not statistically significant at  $P < 0.05$ .

## Discussion

Osteoarthritis of the knee joint is a common disease affecting adult patients all over the world. It has a significant impact on the life-style of the individual patient as well as the health resources of the communities. Globally, OA is the eighth leading cause of disability. Knee osteoarthritis is the most common form of arthritis.<sup>10</sup> The disease may affect one or

both knees and may be associated with OA of other joints. The main presentation of this chronic illness is pain. There are different medications used to treat OA and relieve its symptoms particularly pain. Besides these “pain killers” the patient may need additional medications to address one or more of the associated co-morbidities. It is not a surprise that such a patient ought to pay not only the price of these medications but also be at risk of their adverse effects. Therefore, researchers worldwide are developing new approaches that could help OA sufferers yet be safe and cheap. The PRP is just an example.

In this study, three quarters of the patients were females mainly housewives ( $n = 46, 80.7\%$ ) and most of them (the females) had either moderate ( $n = 58, 59.2\%$ ) or severe chronic pain ( $n = 29, 29.6\%$ ). Most of the patients ( $n = 55, 72.4\%$ ) were old-aged (5<sup>th</sup>–7<sup>th</sup> decades). Age is the strongest risk factor for osteoarthritis of all joints. Occupational risk factors are important in development of OA. Prolonged or repeated knee bending is a risk factor for knee OA and the risk is higher in jobs which entail knee bending and mechanical loading. This may explain the high proportion of housewives with knee OA in our study. It is of interest to note that only 8% of patients in the study of Muralidhara et al.<sup>10</sup> were housewives while farmers accounted to 70%. Both housewives and farmers are subjected to prolonged or repeated knee bending. Both knee joints may be involved by OA. The disease was bilateral in 48 of our patients (63.2%).

Comorbidity refers to the coexistence of other conditions with a defined index disease. OA is one of the diseases with the highest rate of comorbidity particularly in elderly people. Studies focusing on comorbidity in OA showed that chronic conditions, such as hypertension, cardiovascular diseases, obesity, respiratory diseases and diabetes can be found alongside OA. Obesity, an important health hazard, can be regarded as a comorbidity and has been found to be associated with limitations in activities, body functions, and quality-of-life in OA.<sup>11–13</sup> In this study, significant proportions of patients ( $n = 35, 39.5\%$ ;  $n = 11, 14.5\%$ ) had hypertension and DM respectively (alone or in combination with other co-morbidities) and the vast majority ( $n = 69, 90.8\%$ ) were either overweight or obese. Vasilic-Brasnjevic et al.<sup>12</sup> investigated the influence of the BMI on the radiographic severity of knee OA and found a strong association between the two.

The international literature is full with research papers from different countries that explain the scientific basis and mechanism of action of PRP and its results in relieving the

pain of OA and even providing evidence of cartilage regeneration in this degenerative disease.<sup>1,4–6</sup> PRP is a promising therapeutic modality for damaged cartilage in OA. The active platelets have biologically active proteins that bind to trans-membrane receptors in the target cells. This binding leads to gene expression resulting in cellular recruitment, growth, and morphogenesis and at the same time reduction in inflammation. Sundman et al. (cited in Mohammad<sup>8</sup>) found in their study that PRP stimulates hyaluronic acid (HA) production and reduces cartilage catabolism.

In a previous publication from Iraq, Mohammad used IA-OPRP to treat 40 cases of isolated knee OA with excellent to good results achieved in 27 (67.5%) of them. It was superior to O<sub>2</sub>-O<sub>3</sub> without PRP.<sup>8</sup> In this study, we achieved much better results as 110 of chronically painful knees (88.7%) portrayed an excellent to good results. It is of interest to note that even patients with comorbidities benefited from IA-OPRP injections. Joshi et al. conducted a comparative study of 75 patients with knee OA divided into two treatment groups: IA-PRP and IA-steroid injection. They found that a single IA-PRP injection was effective for relieving pain and improving activities of daily living and quality-of-life in late-stage knee OA. Moreover, patients with late-stage knee OA who were 67 years or older, 1 IA-PRP injection had similar results to 1 shot of corticosteroid.<sup>1</sup> When compared with hyaluronic acid, Di et al.<sup>14</sup> concluded that IA-PRP may be as effective as HA in the treatment of mild knee OA.

In a summary, the results of this study indicate that IA-PRP injection is an effective, safe and cheap treatment modality of the chronic pain of knee OA. Excellent–good pain relief was obtained in 88.7% of the treated joints after a few injections. High success was achieved despite the bad characteristics of our cohort; being elderly, obese, having moderate to severe pain and many co-morbidities as well as a high rate of bilateral disease. The use of PRP in knee OA should be encouraged as it may save the patient using costly drugs with adverse effects. Obesity should always be fought as it is the top comorbidity in knee OA.

## Conflicts of Interest

None declared.

## Funding

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