

Platelet Rich Plasma and Exercise for Pain Relief in End Stage Knee Osteoarthritis

Abdullah Ahmed Mohammad^{1*}, Hayder Ghali Wadi Algawwam², Huda Ihsan KhairuAllah³, Nuha Abdulwahab Muhammed Ali³, Safwat Abbas Ali⁴

¹Department of Family Medicine, AL-Mansor Primary Health Center, Kirkuk, Iraq.

²National TB Control Program, Iraq.

³Department of Rheumatology & Medical Rehabilitation, Azadi Teaching Hospital, Kirkuk, Iraq.

⁴Department of Anesthesia and Intensive Care, Medicana International Hospital, Istanbul, Turkey.

*Correspondence to: Abdullah Ahmed Mohammad (E-mail: abduhahmohamad796@gmail.com)

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Abstract

Objective: To evaluate the efficacy of exercise and intra-articular ozonized platelet rich plasma (IA-OPRP) injections as management for severe grad IV knee osteoarthritis (KOA).

Methods: Over 18-month period (January 1, 2018–July 31, 2019), 33 patients (21 females and 12 males) with 58 grade IV osteoarthritic knees were retrospectively studied. Severity of KOA was assessed according to the clinical features and Kellgren & Lawrence grading scale. All patients underwent 8-weeks simple exercises followed by 4 sessions of IA-OPRP. OPRP was prepared by centrifuging patients' own blood and activated by passing 1 ml of ozone for each 1 ml of platelet rich plasma. A questionnaire was used to categorize the pain severity into mild, moderate, and severe and the response to therapy was graded as excellent, good, fair, and poor.

Results: The mean age was 63.7 years. The top co-morbid condition were overweight and obesity ($n = 28$, 84.8%) whereas diabetes and hypertension ranked second ($n = 15$ each, 45.4%). All patients had severe pain of grad IV knee OA. Overall, exercise and four IA-OPRP injections yielded good-excellent results in (72.4%) of the treated joints ($P < 0.01$) with no significant sex-related difference in pain response ($P > 0.01$).

Conclusion: Exercise and IA-OPRP seems to be a safe, effective and cheap method for relieving the chronic pain of severe knee OA.

Keywords: Osteoarthritis, knee joint, pain, exercise, ozone, platelet-rich plasma

Introduction

Osteoarthritis is a common, age-related disorder of the synovial joints, involving the synovium, articular cartilage and subchondral articular bone, associated with pain and significant disability besides an increased medical and economic burden to the society.¹

The knee joint is affected by osteoarthritis (OA) more than other joints such as the hand and hip with increase incidence of knee OA (KOA) among young adults in the past decade.² Disability and chronic pain due to KOA is the leading cause in developed nations and United States.³

Maladaptation of a joint and its periarticular structures contribute to the pathogenesis of OA. Aging, obesity and previous connective tissue injuries appear to increase the likelihood of symptomatic OA. Though KOA, until recently, was considered a non-inflammatory disorder, there is a growing evidence that inflammation contributes significantly to OA and is the key regulator of its pathogenesis.⁴

However inflammatory disease of the entire synovial joint comprising structural, functional change and mechanical degeneration of articular cartilage including the subchondral bone, periarticular ligament and the synovium, meniscus (in the knee) as recent evidence suggested.⁵

Joint pain, restriction of joint motion, stiffness and cracking or crepitus within the joint space the main clinical symptoms of KOA.¹ Both clinical and radiographic findings are important in the diagnosis and management of OA as radiological features alone lead to over and unnecessary use of drugs in the elderly population.⁶

The easiest and most cost-effective radiological modality for diagnosing and follow-up of KOA is conventional radiographic image analysis in which a decreased joint space reflects joint cartilage reduction, non-homogenous joint space narrowing over the entire width of the joint represent a typical finding accompanied by an increased subchondral sclerosis, joint effusion and intra-articular free bony bodies. In addition, the development of subcortical cysts, periarticular osteophytes and new bone formation are characteristic for the diagnosis of KOA.⁷

Classification of the severity of osteoarthritis (OA) depends on clinical and radiological features. The radiological features depend on Kellgren and Lawrence system which is a common method of classifying the severity of OA using five grades: Grade 1 (doubtful): doubtful joint space narrowing and possible osteophytic lipping; Grade 2 (minimal): definite osteophytes and possible joint space narrowing; Grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends and Grade 4 (severe): large osteophytes, marked narrowing of joint space, severe sclerosis and definite of bone end.⁸

Osteoarthritis of the knee joint is a progressive degenerative process, unlikely to regress. Hence, the management target is symptomatic control. Currently, the recommend available treatment options have been developed and standardized by multiple academic and professional societies with different guidelines.⁹

Controlling the pain of KOA and improving the functionality and quality of life is the goal. Exercise is a simple

and effective method which is tolerated by patients. High impact activities should be avoided. Favorable effect of exercise on patients with KOA have been shown with different modalities.⁹

Exercise training improves muscle strength, functional performance and pain in all grades of KOA as Knoop et al. reported.¹⁰ End-stage knee or hip OA waiting for total joint replacement exercise therapy was feasible and safe.¹¹ Education, weight loss (if overweight or obese), exercise (strength training and aerobic exercises) and walking aids are widely accepted as first-line treatment for KOA as self-management and better to initiate early as possible to improve pain, joint motion and quality of life.¹²

Pharmacological management in KOA includes non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, celecoxib and combination of glucosamine and chondroitin help relieve joint pain when compared with placebo as shown in a meta-analysis published in 2015.¹² Intra-articular hyaluronic, intra-articular steroids also considered as pharmacological treatment.⁵

Platelet rich plasma for KOA prompted as new treatments as a recent technological advancement.⁴ PRP is a promising option for treatment of KOA associated with cartilage damage OA and it is widely used in clinical studies. Genicular nerve block and radiofrequency ablation (RFA) now used as pain management for sever KOA pain and after total knee replacement pain.¹² Ozone (O₃) is a form of oxygen in which three atoms bind together instead of the two atoms of O₂, and in this study used as PRP activator, anti-inflammatory activity and analgesia effects.¹³ The objective of this study is to evaluate the efficacy of exercise and intra-articular ozonated platelet rich plasma (IA-OPRP) injections as management for sever grad IV knee osteoarthritis (KOA).

Patients and Methods

This is a retrospective study of a group of patients with end stage grade 4 (bone on bone) knee OA according to the Kellgren and Lawrence classification with clinical features of chronic knee pain as a result of unilateral or bilateral knee joint osteoarthritis. In this study, "The authors used a symptom-based patient-directed questionnaire to assess the outcome after exercise and ozonized platelet rich plasma intraarticular injection". 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.²

Pain management was carried out with exercises of two muscles group quadriceps and calf muscles one time daily for 15–20 minute for eight weeks duration. X-ray (anteroposterior and lateral views) were taken before and after 8 weeks of exercise. In this study patients underwent simple exercises because most of them were old age with pain and limitation of movement.

Exercises

1. Quadriceps exercise: from sitting position elevation of the leg straight and count to 10 seconds then rest for 10 seconds

and repeat 10 times once daily for first week and increase time in each session from 10–30 seconds from second week to 8th weeks, as shown in **Figure 1**.

2. Calf stretch: patients stand against the wall bending the front leg and stretching the other for one minute each leg once daily from second week increase to two minutes once daily and continue for two minutes daily for 8 weeks if unable to stand do it passively with sitting position. As shown in **Figure 2**.
3. Exercises after each dose stopped for 3 days then continued in the 4th day, after complete the OPRP sessions exercises continued lifelong.
4. All the patients were followed up for six months.

Intra-articular injection of OPRP were carried in the authors private clinic/Kirkuk/Iraq over the period (January 1, 2018–July 31, 2019). There were 44 patients of which, 11 could not be included in the trial (7 patients were noncompliant to exercises, 4 drawn after exercises before injection), therefore, 33 patients were included (21 females and 12 males) with a total number of 58 knees received 4 sessions of IA-OPRP for each joint.

Inclusion Criteria

All Patients with grade 4 knee OA according to clinical features and the Kellgren and Lawrence classification, who were unfit for surgery or refused surgery.

Exclusion Criteria

Medical history of bleeding tendency, patients on anticoagulants, age more than 80 years old and noncompliant to exercise.

Body mass index (BMI) of the patients was calculated by the equation: Weight in kilogram/(Height in meter)² 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).¹⁴

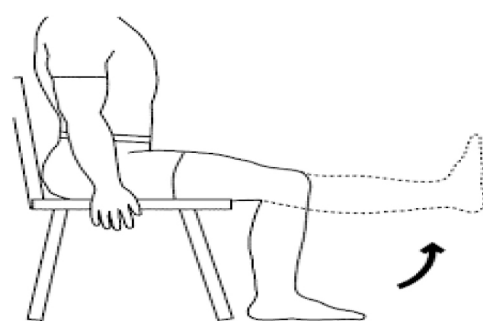


Fig. 1 Quadriceps exercise.

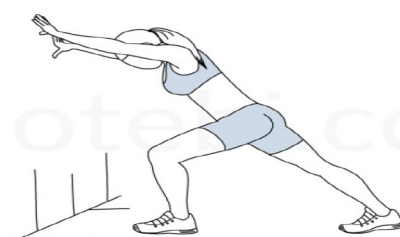


Fig. 2 Calf stretching exercise.

Longevity resources EXT50 Ozone Generator with oxygen tank and CGA870 Oxygen Regulator were used. Preparation of OPRP was described in a previous publication of the first author.¹⁴ It was done by withdrawing “an autologous blood from the patient’s own vein mixed with 3.8% sodium citrate as an anticoagulant. The tubes were then placed in 80-2 Electronic Centrifuge. The end results of this procedure are PRP. Platelet rich plasma was then activated by passing 1 ml of ozone in a concentration of 68.7 gammas for each 1 ml of PRP and injected into the knee joint spaces.² Statistical analysis was performed using z-test for two population proportions.

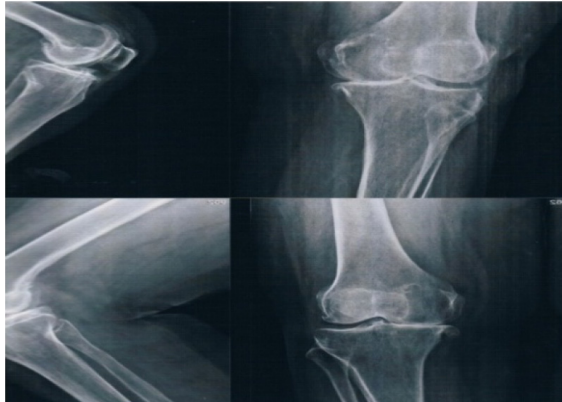


Fig. 3 Bilateral knees X rays AP and lateral views of one patients (first) included in this study shows osteoarthritis Kellgren and Lawrence grade IV classification (before exercise).



Fig. 4 Bilateral knees X rays AP views shows improvement in both joint space of the same (first) patient after eight weeks of exercises and before intra-articular injections.



Fig. 5 Bilateral knees X rays AP view of another (second) patients included in this study shows osteoarthritis Kellgren and Lawrence grade IV (before exercise).

Results

There were 33 patients (21 females and 12 males) with a female: male ratio of 1.75:1. Figure 7 displays the sex distribution of the studied patients.

The age ranged between 49 and 80 years with a mean of 63.7. Figure 8 displays the age distribution of the studied patients. Most of the patients were in the 6th and 7th decades of life ($n = 27, 81.81\%$).

Most of the female patients were housewives ($n = 15, 45.4\%$) while most of the males were free worker ($n 9 = 27.2\%$). As shown in Figure 9.

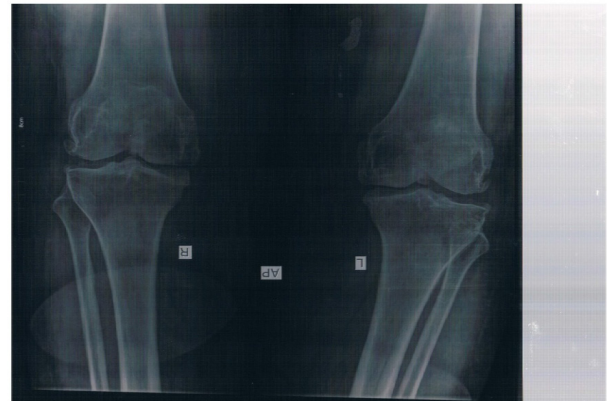


Fig. 6 Bilateral knees X rays AP views shows improvement in both joint space of the same (second) patient after eight weeks of exercises.

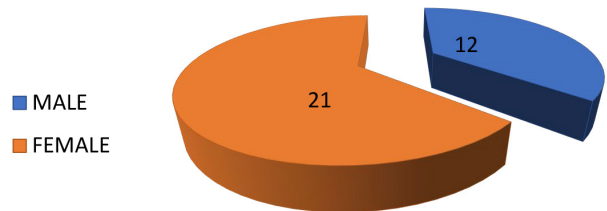


Fig. 7 Patients sex distribution.

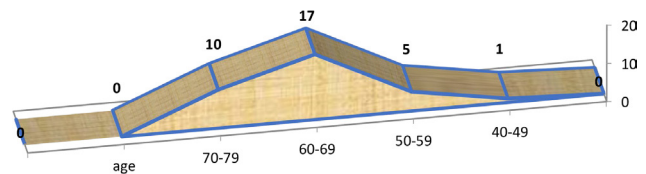


Fig. 8 Displays the age distribution.

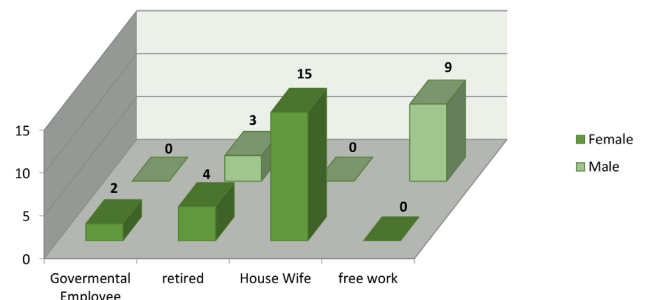


Fig. 9 Displays the job distribution.

Most of the patients were overweight or obese (n : 28, 84.8%) while the patients with a normal body weight were (n : 5, 15.1%) as shown in Figure 10.

The top co-morbid condition was either overweight or obese (n : 28, 84.8%). Diabetes with hypertension ranked second (n : 15, 45.4%) as shown in Figure 11.

As shown Figure 12 (n : 42, 72.4%) of knee injections had either excellent or good response to treatment, while 16 (27.5%) patients had either fair or poor response to treatment. The difference between the 2 groups was statistically significant ($P < 0.01$).

Figure 13 shows sex response to treatment. 27 out of 37 female knee joints injections (72.9%) had good or excellent response while 15 out of 21 males (71.4%) had good and excellent response. There was statistically no significant difference between the 2 groups ($P > 0.01$).

Discussion

KOA is of high prevalence and a leading cause of disability in elderly worldwide. It is the 11th leading cause of global

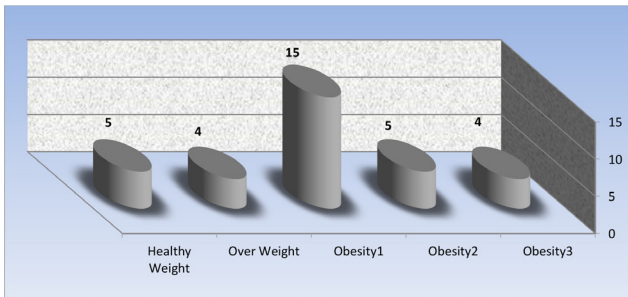


Fig. 10 Patients BMI distribution.

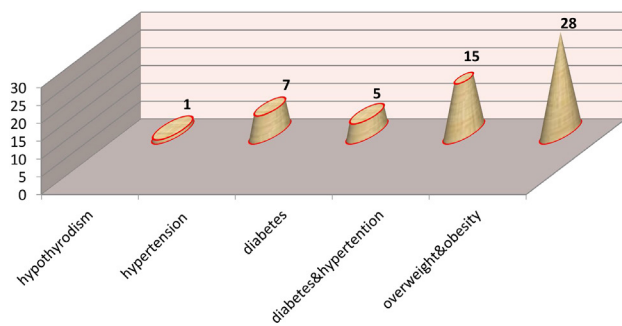


Fig. 11 Shows the co-morbidities encountered in the studied patients.

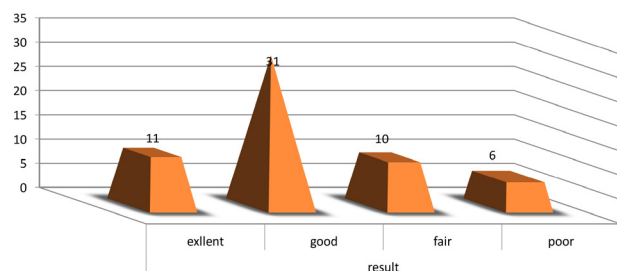


Fig. 12 Distribution of patients according to response to treatment.

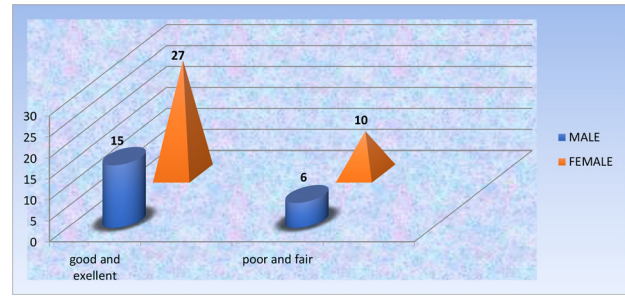


Fig. 13 Distribution of patients' sex according to response to treatment.

disability. There are no disease-modifying interventions for KOA.¹⁵ Routine clinical examination and AP, lateral plain radiography of symptomatic knee are gold standard for diagnosing KOA because wide availability, safe and cost-efficient.¹⁶ Aquatic exercise suggested for patients with functional or mobility limitations had moderate quality evidence in knee and hip OA.¹⁷ Literature documented those KOA are results of Quadriceps muscle impairment.¹⁰ Lower limb rehabilitation program for short term reduce knee pain and stiffness only, but not BMI nor physical function.¹⁸

Women suffer from quadriceps weakness with early radiographic and cartilaginous evidence of OA, exercises show improve quadriceps strength may minimize symptoms or prevent the onset of symptoms.¹⁹ Patients with KOA therapeutic exercise can be recommended as treatment at home.²⁰

Analgesic, weight loss and exercise in order to reduce pain and improve function are recommended as non-surgical treatments for KOA.²¹ Physiotherapists are important to assist in managing their OA and prescribing exercises.²²

PRP characterized by high levels of growth factors isolated from autologous blood which stimulate the chondrocytes regeneration to reestablish cartilaginous tissues in knee joint as valuable source of anabolic growth factors also considered as biological effective treatment for fast healing and regeneration of musculoskeletal tissue.²³

In the current study, 33 patients with total 58 grade IV knee joints osteoarthritis according to K&L classification were involved. Sex distribution shows about two thirds of patients were females (21 females and 12 males) with a female: male ratio of 1.75:1. Which is in concordance to result that demonstrates females generally at a higher risk and more severe KOA specially after menopause as regarded the incidence and prevalence higher in females.²⁴ The incidence and severity of KOA is highest among women of African-Americans aging US population and of clinical concern because of the more severe knee OA and its impact on quality of life and independence as the Studies sponsored by the Centers for Disease Control and Prevention and the National Institutes of Health. More effective, sex-specific treatment strategies will possibly emerge, by improving our knowledge of the mechanisms responsible for sex differences in the perception of pain in OA, although the neural and other mechanisms underlying these differences in pain between men and women with knee OA are unknown.²⁵ While no difference found in the distribution of males and females in a study published at 2010.²⁶

The results of age group in this study were ranged between 49 and 80 years and peak in 6th decade with a mean of 63.7. Which is in concordance with a study from China; sever

radiographic OA was more prevalent among patients > 65 years old in the Framingham study.²⁷

Job distribution most of the female patients were housewives ($n = 15, 45.4\%$) while most of the males were free worker ($n = 9 = 27.2\%$). Certain occupations were shown to increase the risk for knee OA as published in Scientific Reports in 2021.²⁸

Regarding BMI in this study most of the patients were overweight or obese ($n: 28, 84.8\%$), All measures (Body mass index (BMI), waist circumference, waist-hip ratio (WHR), weight and percentage of body fat (BF%) of overweight were associated with the incidence of knee osteoarthritis, with the strongest relative risk gradient observed for BMI.²⁹

The top co-morbid condition was either overweight or obese ($n: 28, 84.8\%$), diabetes with hypertension ranked second ($n: 15, 45.4\%$), a greater number of co morbidities is associated with worsening health. Most (62%) people with OA have at least one other co morbid condition as a recent study from Denmark reported.³⁰ Females had a significantly higher rate of co morbidities compared with males, meeting the OA case definition had at least one of the eight selected co morbidities, hypertension was the most frequent co morbidity followed by depression COPD and diabetes.³¹

In this study ($n: 42, 72.4\%$) of knee injections had either excellent or good response. There was statistically significant difference between the 2 groups ($p < 0.01$) and in concordance to study published in 2021 in which patients with grade IV OA who received four PRP injections there was a gradual decrease in pain score from 8.5 in the initial visit to an average of 6.5 in the first follow-up (P -value = 0.000) and a further decrease of average score of 4.25 in the second follow-up (P -value = 0.000), followed by a slight increase to 5.25 in the third follow-up.³² Treatment strategy of PRP in association with HA injection to treat severe KOA shows improvement confirmed by x-ray of the knees which indicated the regeneration of the articular cartilage.³³ significant increase in cartilage thickness was found at the intercondylar area (ICA) at 6 months relative to baseline assessment following PRP. Treatment with PRP injections can

reduce pain and improve knee function in patients with various degrees of articular degeneration.³⁴ Intra-articular injections of PRP improve quality of life in patients with KOA by decreasing the pain and stiffness through the promotion of IGF-1 expression.³⁵ PRP as compared with corticosteroids, HA, and placebo in meta-analysis of randomized controlled trials (level of evidence I), PRP demonstrated the best overall result for patients with KOA at 3, 6, and 12 months.³⁶ PRP and erythropoietin, with beneficial effect in the short, medium and long term for of pain reduction and function improvement and better as comparison with prolotherapy, local anesthetic infiltration, HA, ozone and radiofrequency.³⁷⁻³⁸

There was no sex difference as regard to OPRP injections in both female and male as a response both were equal good and excellent respectively 27(72.9%), 21(71.4%). Figure 13 with no statistical significant difference, which is in concordance to study published in 2021 the efficacy of platelet-rich plasma therapy was not affected by age, sex, body weight, or platelet count.³⁹

Conclusion

Simple life long exercise and platelet-rich plasma therapy is a simple and minimally invasive intervention which is feasible to deliver in primary care to manage severe osteoarthritis of the knee joint, particularly in elderly, or those unfit or refusing surgery. Well-designed randomized controlled trials are needed to measure outcomes, durability of effect and cost effectiveness.

Conflict of Interest

None declared.

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