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Efficacy of intra-articular autologous platelet rich plasma injection in primary knee osteoarthritis; a quasi-experimental study

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Abstract

Objectives: To observe the efficacy of platelet rich plasma on pain improvement in knee osteoarthritis patients, and to explore the impact of various facotrs on pain reduction with such a treatment.

Method: The quasi-experimental study was conducted at the Armed Forces Institute of Rehabilitation Medicine, Rawalpindi, Pakistan, from October 2017 to April 2018, and comprised patients with primary knee osteoarthritis. The sample was sub-grouped into "normal", "overweight" and "obese" on the basis of body mass index. Two age-based sub-groups were also formed at ≤60 years and >60 years. Three injections of calcium gluconate activated 2.5ml platelet rich plasma were given in the knees at an interval of two weeks each. The pain score was calculated using the numerical rating scale at the 6th week. Data was analysed using SPSS 20.

Results: Of the 50 patients, 26(52%) were females and 24(48%) were males. The overall mean age was 59.6±9.6 years (range: 42-75 years), with 22(44%) aged ≤ 60 years. There were 21(42%) patients who were overweight, 7(14%) had normal weight and 22(44%) were obese. There was significant pain reduction post-treatment compared to the baseline ($p<0.001$). The reduction in pain was not

significantly related to gender, age, knee osteoarthritis grade, or body mass index ($p>0.05$).

Conclusions: Platelet rich plasma significantly improved pain in knee osteoarthritis patients regradless of all age, gender, grade and body mass index.

Key Words: Intra-articular injections, Primary knee osteoarthritis, Platelet rich plasma, Efficacy.

Introduction

Knee osteoarthritis (KOA) is one of the commonest types of arthritis affecting quality of life (QOL) and functional status, and putting financial burden. The goals of treatment in OA include alleviation of pain, improved mobility, and delay in disease progression.[1] Many conservative therapies for KOA, like massage, exercises, analgesics, herbal medicines, nutritional supplements, walking aids, homeopathic medicines, manipulation, faith healing etc. are in practice.[1,2] Conservative therapies may improve symptoms to some extent, but do not reliably succeed in controlling pain, progress of disease, improvement of functional outcome, and QOL. More recently, new approaches in KOA treatment are increasingly being used with an aim of stimulating cartilage healing processes and halting disease progression.[3] These include administration of growth factors, artificial chondrocytes and cytokine inhibitors.[3-5]

Platelet alpha granules contain significant amount of growth factors. For this reason, autologous platelet rich plasma (PRP) application has emerged as a treatment option for KOA.[3-5] PRP contains several growth factors and cytokines that are capable of stimulating cellular growth, tissue regeneration and collagen synthesis. It is prepared by centrifugation of blood and contains large number of platelets in a small plasma volume.

Various studies have explored the effectiveness of PRP in KOA patients. So far, solid evidence is lacking for the efficacy of PRP and the current treatment guidelines neither recommend nor prohibit the use of PRP in symptomatic KOA.[6]

The current study was planned to assess the effect of PRP on pain improvement in primary KOA patients, and to observe the impact of gender, body mass index (BMI), age and KOA severity on pain reduction produced by PRP treatment.

Patients and Methods

The quasi-experimental survey was conducted at the pain clinic of the Armed Forces Institute of Rehabilitation Medicine (AFIRM), Rawalpindi, Pakistan, from October 2017 to April 2018. After approval from the institutional ethics review committee, patients fulfilling the KOA criteria of the American College of Rheumatology ACR)[7] were selected using consecutive sampling. Those included had knee pain for at least four months, not responding to non-steroidal anti-inflammatory drugs (NSAIDs) and/or physical therapy, and radiographic findings of grade-1→ 3 OA changes according to the Kellgren-Lawrence scale.[8] Patients with systemic or local infection, rheumatoid arthritis (RA), history of direct trauma to the symptomatic knee joint, uncontrolled diabetes mellitus (DM), coagulopathies, immunosuppression or those taking anticoagulant therapy were excluded.

After taking informed consent, all patients were subjected to detailed clinical evaluation on the first visit. Height and weight were recorded in meters and kilograms respectively. All the subjects were requested to put on light clothes and remove their shoes. The weight after an overnight fast was measured using Tanita HA-650 Precision Bathroom Scale (Tanita Corp., Tokyo, Japan). The height was measured using a simple height measurement scale. The BMI was calculated by dividing the weight in kilograms by height in meters squared.

On the basis of BMI, the sample was grouped into “normal”, “overweight”, and “obese” on the basis of the recommendations for South Asians by the National Institute of Health and Care Excellence of the United Kingdom and by the American Diabetes Association for all Asian ethnic groups.[9]

Pain severity was measured using the Numerical Rating Scale (NRS)[10] and graded 0→10. Anteroposterior and lateral X-rays, only of the affected knee joint in

standing position, were done for grading KOA according to the Kellgren–Lawrence grading system[8].

A 20ml blood sample was taken under aseptic conditions from antecubital veins and 2.5ml of PRP was prepared after double centrifugation. About 0.5ml of 10% calcium gluconate was added to each injection for platelet activation. For the knee joint injection, medial or lateral retropatellar approaches were used depending upon the ease on the part of the investigator. Using sterile techniques, skin over the target area was prepared with Povidone-Iodine 10% w/v, allowed to air-dry, and then wiped with methylated spirit (mixture of 95% ethyl alcohol and 5% methyl alcohol) prior to needle placement. A 1¼-inch 21-guage needle was used for the injection. Three injections of PRP were given in knees at an interval of 2 weeks each. Antibiotics were not given after the injection as they were not required after good asepsis. After injection, the patients were instructed to minimise mobility of the injected joint, do ice fomentation of the injected knee for 10-15 minutes three times a day for two days, avoid NSAIDs during the study period, and report any complication, like swelling, fever, persistent redness >48 hours, etc, without waiting for completion of the study period. The pain score was calculated on NRS at the 6th week and the patients were asked about any complications.

The findings were recorded and the data was analysed using SPSS 20. Quantitative data was presented as means and standard deviations, while the qualitative data was presented as frequencies and percentages. The sample was divided into two age-based groups ≤60 years and >60 years to check the effect of age on pain reduction. Paired sample t-test was used to assess differences between pain scores at baseline and at 6 weeks. Analysis of variance (ANOVA) was used to evaluate the influence of gender, age, BMI and KOA severity on mean reduction in pain score among the sub-categories of these variables. $P<0.05$ was considered statistically significant.

Results

Of the 50 patients, 26(52%) were females and 24(48%) were males. The overall mean age was 59.6±9.6 years (range: 42-75 years), with 22(44%) aged ≤ 60 years.

There were 21(42%) patients who were overweight, 7(14%) had normal weight and 22(44%) were obese. Further, 10(20%) patients had grade-2 KOA, while 20(40%) each had grade-1 and grade-3 condition. There was significant pain reduction post-treatment compared to the baseline ($p<0.001$) interms of all the variable studied (Table). The reduction in pain was not significantly related to gender, age, KOA grade or BMI ($p>0.05$).

None of the patients reported any complications.

Discussion

PRP is in use for therapeutic purposes for the last 20 years, but in musculoskeletal problems, particularly in OA, the treatment has been started in recent years. PRP has clearly demonstrated its supremacy in comparison to hyaluronic acid, saline placebo, ozone, and corticosteroids in various clinical trials.[11-13] The supremacy was not only in pain relief, but also in mobility and functional improvement based on various OA index scores. The current also found a significant improvement in knee pain at six weeks following 2-weekly injections of 2.5ml PRP.

Studies have found favourable results for PRP, though the number of injections and the amount of PRP injected differed.[4,5,14,15]

The current study did not find the influence of gender, age, BMIor KOA grades on pain reduction produced by PRP injections. Studies have reported similar findings.[16-18] However, a few studies have found some association with these demographic factors. Kon et al.[19] observed superior effectiveness of PRP in patients with male gender, younger age, low BMI, and lower KOA grades. Hassan et al.[4] found a significant correlation of age, BMI and disease duration with the pain score. Filardo et al. reported a better response in people with low BMI and low KOA grade, while Frizziero et al. reported better responses in younger ages, lower KOA grades, and male gender.[20,21] Poor responses to PRP injection in older age and high grades of KOA is expected as there are fewer living or active cells to respond to the growth factors released by PRP.[17,18]

How PRP improves pain and inflammation in the knee joint and whether it causes remodelling of joint's internal structure is still not fully understood. It is proposed that PRP acts at various structures of the joint to change natural homeostatic processes in the joint. At the level of cartilage, it improves chondrocyte proliferation and synthesis of prostaglandin II, collagen, and matrix molecules.[22] PRP contains insulin-like growth factor-1 that may down-regulate the expression of programmed cell death[4] and thus influences the apoptotic pathways of chondrocytes.[23] At the level of synovium, PRP reduces release of some matrix metalloproteinases (MMP) through interleukin-1 (IL-1)-mediated pathway, and increases hyaluronic acid secretion,[24] creating a more favourable situation for angiogenesis.[22]

The reduction in joint inflammation and pain is attributed to inhibition of gene expression of IL-1ß, cyclooxygenase-2 (COX-2), and MMP-2 and inhibition of release of nuclear factor kappa B (NF-κB) and COX-2, the principal actors of the inflammatory cascade.[22,25] PRP also prevents monocyte-like cell chemotaxis.[22] Lee et al.[26] also noticed an increase in cannabinoid (CB) receptors CB1 and CB2 involved in analgesic and anti-inflammatory pathways. Thus, multiple effects of PRP exist that redesign the natural homeostatic mechanisms in knee joints.

The current study is limited by its small sample size and the absence of a control group. Moreover, it did not include the evaluation of bodily function and QOL. Nevertheless, the study is one of the very few that have been carried out in Pakistan on the subject.

Conclusion

PRP significantly improved pain in patients with grade 1→3 KOA at 6 weeks and the pain reduction was independent of gender, age, BMI and KOA grade.

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Table: Reduction in pain according to Numerical Rating Scale (NRS) among different subgroups of study variables

Variables		NRS Base line	NRS at 6 weeks	P-Value
		Mean ± SD	Mean ± SD	
Gender	Male	6.62 ± 1.36	2.92 ± 1.85	<0.001
	Female	7.08 ± 1.35	3.5 ± 1.74	<0.001
Age-group	Age ≤ 60 years	6.82 ± 1.4	2.82 ± 2.4	<0.001
	Age > 60 years	6.86 ± 1.41	3.5 ± 1.2	<0.001
Kellgren-Lawrence scale Grades	Grade-1	5 ± 0.67	1.4 ± 1.08	0.011
	Grade-2	6.8 ± 1.2	3.1 ± 1.97	<0.001
	Grade-3	7.8 ± 0.62	4.2 ± 1.10	<0.001
Body Mass Index (BMI)	Normal-weight	6.43 ± 1.4	3.14 ± 2.7	0.013
	Overweight	6.52 ± 1.6	2.76 ± 1.6	<0.001
	Obese	7.27 ± 1	3.64 ± 1.7	<0.001

SD: Standard deviation.