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A STUDY OF INTRA ARTICULAR PLATELET RICH PLASMA THERAPHY IN THE TREATMENT OF KNEE OSTEOARTHRITISN.V

Orthopaedics

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ABSTRACT

To evaluate the role of Autologous Platelet Rich Plasma in the treatment of patients presenting with primary osteoarthritis and to analyze whether it could be a cost effective disease modifying measure.

METHODS: The patients attending the OPD of Orthopaedics Department at with complaints of bilateral knee pain were screened and those diagnosed as bilateral or unilateral Knee Osteoarthritis were chosen for the study.

The Patients, classified either grade 0 to 4 on the Kellgren-Lawrence grading scale or grade 1 to 4 on the Ahlback scale, were included in the study after prior well informed written consent.Hundred Patients were chosen and randomly divided into two groups of fifty each. Group I received intra articular injection Platelet Rich Plasma in to knee served as study group. Group II received normal saline and served as control.Randomization ensured that both the groups were comparable with respect to age, sex, height, weight, body mass index and pre injection WOMAC score.

RESULT : Our study relied on injecting a highly concentrated mix of platelets into joint cavity and observing the patients for reduction in symptoms of pain, stiffness and improvement in physical function .our study has revealed a consistent reduction in pain and stiffness and a clear improvement in lifestyle of the patients.

CONCLUSION: Our study has thrown up an interesting choice of treatment modality using Platelet Rich Plasma in the treatment of Knee Osteoarthritis and it has proved efficacious in the observation period of six months.

KEYWORDS

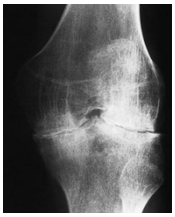
INTRODUCTION

Osteoarthritis (OA) represents a failure of the di-arthrodial, synovial lined joint. Among the elderly, knee Osteoarthritis is the leading cause of chronic disability[1]. Because of the increased lifespan and obesity the prevalence of osteoarthritis is in the rise in India.

Osteoarthritis is age related, affecting more than 80% of people over the age of 55. OA in weight-bearing joints is strongly linked to body mass index. As life expectancy increases, and the rate of obesity reaches epidemic proportions, OA has become increasingly common. The pathogenesis involves an imbalance between normal cartilage derivative and repair mechanisms, which results in net cartilage loss, hypertrophy of bone, and osseous outgrowths called osteophytes. OA has a predilection for finger joints, knees, hips, shoulders, and the spine. Occurrence in an atypical joint, such as an elbow, can usually be traced to prior trauma, a congenital joint abnormality, underlying systemic disease, or a chronic crystalline arthropathy. The heterogeneity of OA arises from the many factors that can contribute to cartilage damage. Symptomatic OA of the knee which is described as having pain during most days of a month along with radiologic evidence of arthritis has a prevalence of 22% to 39% in India[3,4]. Osteoarthritis is a chronic disorder of synovial lined joints where there is progressive softening and disintegration of articular cartilage accompanied by new growth of cartilage and bone at the joint margins, cyst formation and sclerosis at subchondral regions of bone, mild synovitis and capsular fibrosis.[5] Osteoarthritis differs from simple wear and tear in that it is asymmetrically distributed, often associated with abnormal loading rather than frictional wear.[6] It is not an inflammatory disorder although at times there are local signs of inflammation. In its most common form osteoarthritis is unaccompanied by any systemicillness.[7]

THE CARDINAL SIGNS OF OSTEOARTHRITIS

- Narrowing of the joint space
- Marginal osteophytes
- Sub chondral cysts
- Bone remodeling



PREPARATION OF PRP

PRP is obtained from the sample of blood drawn at the time of treatment from patient. 30 cc of venous blood drawn can yield upto 3-5 cc of PRP depending on the platelet count of that individual, and depending on the device used, and the technique employed at the time of preparation. The blood drawn is transferred into anticoagulant tube, such as citrate dextrose to prevent platelet activation prior to its use.

Iemployed a specialized 'table top cold centrifuge' device. Preparation-related costs are significantly lower than with commercial kit.

COMPARISON OF STUDIES OF PREPARATION

PRP is prepared by centrifugation varying the relative centrifugal force, temperature and time. It has been seen that the two-step procedure renders the highest output. Preparation procedures are also relevant, as shown by studies of the chondro-inductive and osteoinductive potential of PRP.[40]

There are numerous protocols in the current literature that describe the optimal conditions for centrifugation However, these various protocols have been optimized with respect to different variables of the process, such as volume and sampling of processed WB, number of spins, time period of centrifugation, and range of centrifugal acceleration. Considering the complexity of an autologous product such as PRP and the need for quality control in clinical applications, it is crucial to demonstrate procedure's ability to reproduce consistent results.

Kahn et al.[41] Determined that a centrifugal acceleration of 3731×g for a period of 4 min was the optimal condition for obtaining the highest platelet concentration from 478 mL of WB. The highest platelet recovery efficiency obtained by Slichter and Harker42 was 80%, using a sample of 250-450 mL of WB centrifuged at 1000×g for a period of 9 min. It was observed that a subsequent centrifugation step of 3000×g for a period of 20 min decreased the platelet viability. Landesberg et al. obtained PRP samples that had approximately 3.2 times the concentration of the WB baseline. The centrifugation procedure processed 5 mL of WB for two spins at 200×g for 10 min per spin.43 Jo et al. examined the effect of the centrifugation time and gravitational force (g) on the platelet recovery ratio of PRP. Two-step centrifugations for preparing PRP were used in 39 subjects. WB was centrifuged from 500×g to 1900×g at 200×g increments for 5 min and from 100×g to 1300×g at 200×g Bausset et al. found that a centrifugation of 130×g or 250×g for a period of 15 min was optimal when performing a procedure that involved two spins. A platelet

concentration factor of 3.47 was obtained from the 8.5 mL WB processed, and 2.0 mL of plasma was processed in the second spin step.[44] Tamimi et al.[45]compared two methods for obtaining PRP: Double centrifugation (ACE system;Surgical Supply and Surgical Science Systems, Brockton, MA, USA) and single centrifugation (Nahita System; Nahita, Navarra, Spain). Three test tubes of 8.5 mL WB each were introduced into an ACE centrifuge machine and subjected to a force of 160×g (1300 rpm) for 10 min. For second centrifugation, 400×g force (2000 rpm) for 10 min was applied. For Nahita system blood was extracted into 3.5-mL citrated tubes (Venojet; Terumo MR, Tokyo, Japan) containing 0.5 mL of trisodium citrate, citrate, and ACD as anticoagulants. Test tubes were centrifuged with a 280×g force (1500 rpm) for 7 min. Platelet concentration from the ACE and Nahita systems were (336%) and (227%), respectively Mazzocca et al.[46] analyzed three protocols for preparing PRP samples with different compositions:A low platelet (382 × 10 /mm) and low WBC (0.6 × 10 /mm) process with one spin step at 1500rpm for 5 min (10 mL WB); a high platelet (940 × 103/mm) and high WBC (17 × 103/mm) process with one spin step at 3200 rpm for 15 min (27 mL WB); and a double-spin process (1500 rpm for 5min and 6300 rpm for 20 min) that produced a higher platelet concentration (472 × 103/mm) and lower WBC (1.5 × 103/mm). Anitua et al.[47]used only one centrifugation spin step and collected the volume immediately above the erythrocyte layer. Blood was collected on sterile tubes (4.5 mL) containing 3.8% (w/v) trisodium

citrate, then centrifuged at 460×g for 8 min (PRGF System1, B.T.I. Biotechnology Institute, Vitoria-Gasteiz, Spain). This protocol obtained a platelet concentration factor of 2.67 above the baseline value.

In this study we modified Mazzocca et al method for the preparation of the prp

SELECTION OF THE PATIENTS FOR SURGERY

INCLUSION CRITERIA

- patients with knee OA K-L Score 2 and more
- with pain greater than 3 on VAS Scale;
- older than 18 years of age;
- who have failed any other conservative treatment (analgesics, NSAIDs, steroidal/ hyaluronic acid/Ozone injections, visco-supplementation and/or physical medicine);unwilling or not available for knee arthroplasty replacement.

EXCLUSION CRITERIA

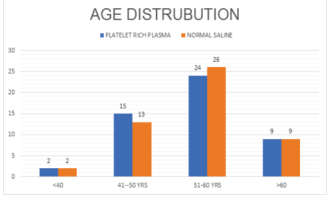
- Immunosuppressed patients
- Patients with secondary osteoarthritis
- Patients with connective tissue disorders
- Patients with inflammatory disorder of joints
- Patients who have received steroid injections within past 6months
- Patients with hemoglobin less than 10mg%
- Patients with tumors, metabolic diseases of bone
- Patients with coexisting backache

OUTCOME ANALYSIS:

The study group and the control group are advised to follow up at 6 weeks, 3 months and 6 months .Outcome analysis for the efficacy was done for reduction in pain, reduction in stiffness and improvement in physical function using WOMAC scale. The Patients were also assessed for reduction in pain using Visual analog scale both at pre injection and at 6 months post injection

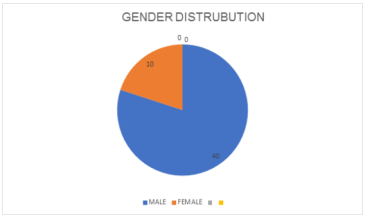
STATISTICALANALYSIS

Age Distribution



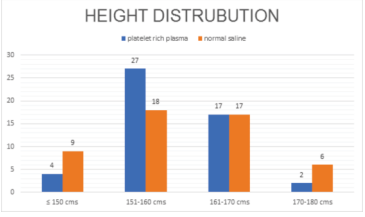
Age Distribution	Platelet Rich Plasma	Normal Saline
N	50	50
Mean	53.14	53.68
SD	6.97	6.45
P value UnpairedtTest	0.6885	

Gender Distribution



Gender Distribution	Platelet Rich Plasma	%	Normal Saline	%
Male	40	80.00	40	80.00
Female	10	20.00	10	20.00
Total	50	100	50	100
P values Chi SquaredTest		0.0000		

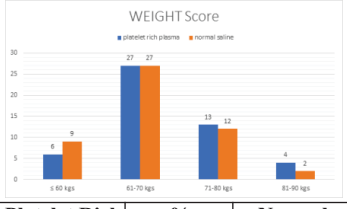
Height Distribution



Height Distribution	Platelet Rich Plasma	%	Normal Saline	%
≤ 150 cms	4	8.00	9	18.00
151-160 cms	27	54.00	18	36.00
161-170 cms	17	34.00	17	34.00
170-180 cms	2	4.00	6	12.00
Total	50	100	50	100

Height Distribution	PlateletRich Plasma	Normal Saline
N	50	50
Mean	159.66	159.68
SD	6.63	8.39
P value UnpairedtTest	0.9895	

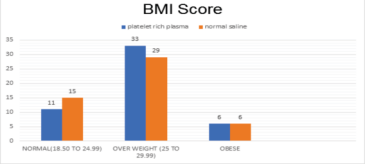
Weight Distribution



Weight Distribution	Platelet Rich Plasma	%	Normal Saline	%
≤ 60kgs	6	12.00	9	18.00
61-70 kgs	27	54.00	27	54.00
71-80 kgs	13	26.00	12	24.00
81-90 kgs	4	8.00	2	4.00
Total	50	100	50	100

Weight Distribution	PlateletRich Plasma	Normal Saline
N	50	50
Mean	68.62	67.66
SD	6.84	6.63
P value UnpairedtTest	0.4777	

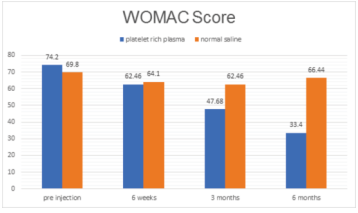
BMI Distribution



BMI Distribution	Platelet Rich Plasma	%	Normal Saline	%
Underweight (≤ 18.49)	0	0.00	0	0.00
Normal (18.50 to 24.99)	11	22.00	15	30.00
Overweight (25 to 29.99)	33	66.00	29	58.00
Obese	6	12.00	6	12.00
Total	50	100	50	100

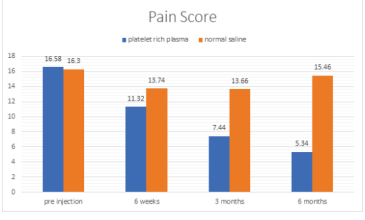
BMI Distribution	PlateletRich Plasma	Normal Saline
N	50	50
Mean	26.97	26.64
SD	2.70	2.92
P value UnpairedtTest	0.5507	

WOMAC Score



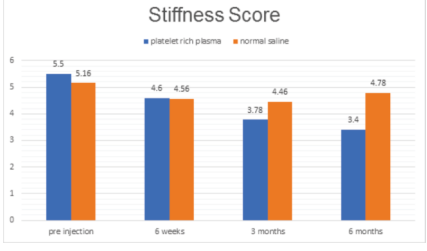
WOMAC Score		Preinjection	6 weeks	3 months	6 months
PlateletRich Plasma	N	50	50	50	50
	Mean	74.20	62.46	47.68	33.40
	SD	4.85	6.60	8.15	7.59
Normal Saline	N	50	50	50	50
	Mean	69.80	64.10	62.46	66.44
	SD	4.68	5.50	5.44	5.01
P value Unpaired t Test		0.1804	0.0000	0.0000	0.0000

Pain Score



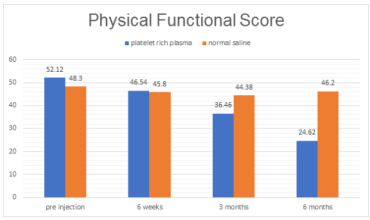
Pain Score		Preinjection	6 weeks	3 months	6 months
Platelet Rich Plasma	N	50	50	50	50
	Mean	16.58	11.32	7.44	5.34
	SD	3.08	2.76	1.93	1.42
Normal Saline	N	50	50	50	50
	Mean	16.30	13.74	13.66	15.46
	SD	2.39	2.28	2.35	1.94
P value Unpaired t Test		0.6132	0.0000	0.0000	0.0000

Stiffness Score



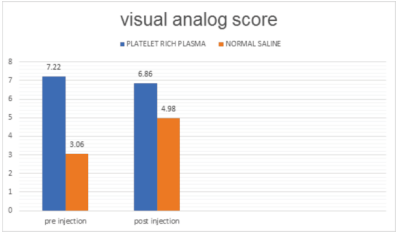
Stiffness Score		Preinjection	6 weeks	3 months	6 months
PlateletRich Plasma	N	50	50	50	50
	Mean	5.50	4.60	3.78	3.40
	SD	1.22	1.20	1.09	1.14
Normal Saline	N	50	50	50	50
	Mean	5.16	4.56	4.46	4.78
	SD	0.93	0.81	0.73	0.84
P value Unpaired t Test		0.1204	0.8453	0.0004	0.0000

Physical Function Score



Physical Function Score		Preinjection	6 weeks	3 months	6 months
Platelet Rich Plasma	N	50	50	50	50
	Mean	52.12	46.54	36.46	24.62
	SD	3.77	4.53	6.49	6.33
Normal Saline	N	50	50	50	50
	Mean	48.30	45.80	44.38	46.20
	SD	3.17	3.91	3.88	3.67
P value Unpaired t Test		0.3840	0.0000	0.0000	0.0000

Visual Analog Score



Visual Analog Score		Preinjection	Post injection
PlateletRich Plasma	N	50	50
	Mean	7.22	3.06
	SD	0.97	1.24
Normal Saline	N	50	50
	Mean	6.86	4.98
	SD	0.81	0.89
P value Unpaired t Test		0.0473	0.0000

DISCUSSION

Osteoarthritis is a disorder of synovial joints characterized by focal loss of hyaline cartilage with proliferation of new bone and remodeling of joint contour, mainly due to uncoupling of balance between cartilage regeneration and degeneration. Osteoarthritis is a dynamic repair process of synovial joints that may be triggered a variety ofinsults.

We in our study had randomly chosen 100 patients with classic findings of Osteoarthritis and divided them in to two groups. Both the groups were comparable on baseline characteristics of age, height, weight, BMI, pre injection WOMAC score. Fifty of these patients were administered an intra articular injection of Platelet Rich Plasma and other fifty received Normal Saline.

The Efficacy of Platelet Rich Plasma in reducing pain ,stiffness and physical function were assessed and scored on WOMAC index for both study and control group. The Results were analysed using unpaired t-test and chi- square test. Age distribution revealed mean age in group I to be 53.14 and the mean age in Group II was 53.68. The p-value derived using unpaired t-test is 0.6885, rendering age factor insignificant.Gender distributions were comparable on both groups with 80 % being male 20% being female. The p-valve using chi square test is 0.000 .The Gender factor was insignificant. The mean height in group I was 159.66 and the mean height in Group II was 159.68. The p-valve using unpaired t test turned insignificant (0.9895). The mean weight, in group I was 68.62 and group II was 67.66 with p- valve of 0.4777(insignificant). The mean BMI was 26.97 in group I and 26.64 in Group II. The p-valve is0.5507(insignificant). Thus the study ensured that all patients were comparable on baseline characters. The Global WOMAC showed a mean of 74.2 at pre injection period which decreased to 62.46 at 6 weeks follow up and 47.68 at 3 months and declining to 33.40 at 6months. The study showed a significant decrease in global WOMAC score, which was also consistent throughout the study period. The Individual variables such as pain, stiffness and physical function were assessed. Mean score for pain showed a

decrease from 16.58 to 11.32 at 6 weeks post injection .Atthe end of 6 months follow up, the mean was5.34.

The mean score for pain in group II showed a marginal decreased from 16.30 to 13.74 at 6 weeks but returned to 15.46 at 6 months follow up. The p-value using unpaired t-test showed significant improvement. Secondary variable stiffness showed significance difference at 3 months follow up and 6 months follow up. The mean ofPhysicalfunctiondecreased from a pre injection score of52.12 to 24.62 at 6 months follow up in Group I. Group II showed a marginal dip in mean scores from 48.30 to 45.80 and to 44.38 at 3 months. The scores leveled at 46.20 at the end of 6monthsVisual analog score showed a decrease in mean of 7.22 to 3.06 which denoted a change of patient's perception of pain from intense, dreadful, horrible pain to mild annoying pain in Group I. Group II showed a marginal dip from 6.86 to 4. 98 on mean, showing insignificant change in pain. In study the most frequent grade of knee OA according to K-L scale was 3º grade (59.2%) followed by 4º(25.9%) and 2º(14.9%). This finding is in accordance with other 4 studies from the meta-analysis of Meheaux,[77] where 2º(40.7%) and 3º grades (37.9%) were the most frequent OA grades, followed by 4º(12.6%) and 1º(8.7%). In the same study, Filardo et al.78reported only average severity of knee OA; where 2ºgrade was again the most frequent.

Similarly, the meta-analysis from Kanchanatawan[79] mainly considers only patients on 1º and 2º K-L grades. Most of the studies from Dai´s meta-analysis considered for treatment 1º-3ºK-L grades, and only some of them (Gomeli´sl and Sanchez´[80]) treated patients with severe OA (K-L 4º grade). This analysis is very important because most of Randomized Control Trialshave demonstrated effectiveness of PRP in decreasing pain and recovering functionespecially for younger patients and milder knee OA,but there is only one study that showed benefit of PRP even for 3º grade in knee OA.Our study contributes to show the efficacy of PRP even in patients with K-L 4º grade. In our study, a PRPinjections has shown effectiveness in improving pain relief, function and rigidity in knee OA patients globally and in all grades of knee OA severity. This is in accordance with most present studies that show moderate quality of evidence supporting the use of PRP on knee OA treatment.PRP is capable to improve pain and function measured by VAS and WOMAC.But, when it comes to see whether PRP is effective in all grades of severity, is still a matter of controversy. Wu et al[81] states that most of trials suggest the efficacy of PRP to improve functional outcomes only for mild knee OA. Spaková concluded that autologous PRP is effective and safe in early knee OA (K-L 1º, 2º and 3º grades).[82]Moreover, Zlotnicki et al [83]state that multiple studies suggest that advanced knee OA implies ineffectiveresponse to PRP injection therapy.83

Forogh et al.[84]sustain that some studies have reported an inverse relationship between age and response to treatment; in younger patients the outcome was better than those over 50 years. Fernández-Cuadros et al have stated that age is related to knee OA severity and outcomes are dependent on such variable.[85,86] There is only one study that shows benefit on older patients with even 3º grade knee OA.Our present study shows a clear correlation between age and knee severity and for the first time shows statistical significant improvement of PRP-protocol treatment in all K-L grades, even 4º grade, to the best of our knowledge. There is controversy on PRP processing; therefore, the variability for its clinical responses. However, despite the technique and formulation discrepancies, intra articular PRP injections are effective in degenerative knees.With respect to the number of injections and their frequency, most protocols are different.[87] Almost all of them require three injections without any specific reasons or specific justification. It is believed that the traditional practice of 3 Hyaluronic Acid injections is followed to PRP protocols.[88] In fact, no difference in outcomes for pain and function came from having a single or a double injection of PRP, but both provided superior outcomes compared with saline control. Görmeli et al.[89,90]compared 3 injections of PRP to one injection of PRP (plus 2 saline injections) or 3 Hyaluronic Acid (HA) injections or 3 saline injections. Three PRP injections showed better scores in EQ-VAS and IKDC at 6 months compared to one single PRP injection or HA injection. Gobbi et al.[91] showed significant knee OA improvements up to 1 year after PRP injections. Forogh has stated that one-PRP injection diminished pain for a longer term and improved activities of daily life for a short-time duration, better than corticosteroids.[92] With regard to the quantity of PRP infiltrated, scientist administered volumes that vary from 2 to 8ml, being the most frequent volume 3ml.The same controversy exits with respect to spinning; some authors preferred single spinning,while other prefer double spinning.There is controversy about the necessity to an optimal activation method in clinical practice.By activation, platelets release alpha granules.[93,94]The objective to activate PRP is to ensure that growthfactors are immediately available.[93,94] PRP infiltration technique is safe and only small frequencies of adverse effects are reported (mainly infections and allergic reactions). Pain after injection is greater in PRP when compared to HA infiltration.In our study one out of 50 patients (1.78%) presented severe pain and inflammation which lead the patient to quit treatment protocol.[97] No other adverse effects were reported on this series. This confirms that PRP treatment is safe. Despite positive findings and outcome results, most of those results are inconclusive due to low level-evidence studies, diverse PRP protocols and outcome measures.[21] The present quasi-experimental before-and-after study, tries to solve such weaknesses, by the use of an stablished protocol, the use of validated outcome measures (VAS and WOMAC Index) and a before-and-after follow-up analysis, all of that gives a good level of evidence,that let us postulate PRP as a promising option for knee OA treatment. The importance to show our clinical experience in a series of patients is to provide more clinical evidence of an stablished PRP-treatment protocol on knee OA; because, although there is plenty of current meta-analysis, most of them make reference to only 5 to 6 randomized control trials (RCT). As a resume, activated PRP releases cytokines and growth factors, promoting chondrocyte proliferation and differentiation, modulating inflammation and exerting mesenchymal stem cell proliferation.PRP exerts and anti-inflammatory effect by the inhibition of NF- κβ pathway,but also by a decrease in expressing inflammatory enzymes cyclooxygenase 2 and 4, metalloproteinases and disintegrins. All those combined PRP effects make this treatment as a potential injectable option in the management of knee OA, improving pain relief and function, as it was demonstrated on this study.In recent studyCase control study of 50 patients in 2018 published in JAJS JUNEstudied two groups of 25 patients each. [99]One group of 25 patients was given therapeutic exercises and Acetaminophen for pain relief (control group). Second group of 25 patients (PRP group) was injected with two courses of intra-articular injection of Leucocyte rich PRP with interval of 6 weeks. WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) was recorded pre-intervention, at six months &one year post-intervention in both the groups. Change scores were assessed for statistical significance. No compilations were noted in both groups and none of the cases needed further surgical intervention during the follow up period. Mean changes of total WOMAC, in PRP group showed significantly better improvement than control group ($P < 0.05$) at all time intervals. This study showed that intra articular PRP knee injection combined with therapeutic exercise can be more effective in pain reduction and improvement of stiffness and quality of life, compared with therapeutic exercise alone.

Recent study done by the Egyptian rheumatologist work aimed to compare the efficacy of intraarticular injection of PRP therapy in the treatment of KOA. There was a remarkable improvement in the VAS, WOMAC and walking 6 min test in the PRP group after 1 and 3 months. This was in agreement with the results of others who found that PRP resulted in a significantly better WOMAC score from 3 to 12 months post-injection. Another study showed that the evaluated parameters significantly improved at 24 months compared with those at 12 months, but still better than those at baseline. In another study on Egyptian KOA patients, Hassan et al. reported a highly significant improvement in VAS and functional assessment scores after 6 months 99 This reduction in pain is due to the capability of PRP to promote the proliferation of chondrocytes, stimulate the production of synovial fluid and limit the inflammatory response. It was reported that intra-articular PRP injection is potent in degenerative knees. Therapy with PRP can potentially adjust the articular inflammatory environment and the progression of OA due to the presence of therapeutic concentrations of interleukin (IL-1ra) and transforming growth factor (TGF-b) in PRP. Intra-articular infiltrations with PRP could avert further degeneration of cartilage by retarding OA progression in early stages of the disease. There was a significant correlation between radiological grades and WOMAC score at baseline and after treatment but as regard to VAS only at the start, while 6- min test there was a negative significant correlation after 1 and 3 months These results are in consonance with those of Duymus et al.100. A meta-analysis emphasized that PRP was effective in mild-moderate grades Chang et al.,[101]

PRP injections had a better response in those with low grade OA. It has been reported that better response rates are evident in OA patients

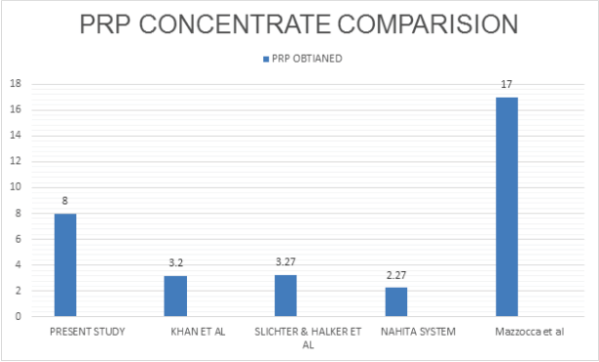
treated with PRP injections than in those treated with hyaluronic acid Others reported a similar efficacy in elderly patients with advanced KOA who received PRP in association with HA injection and showed pain relief and functional improvement. The follow-up standard weight-bearing x-ray images of knees also confirmed the improvement and indicated the regeneration of the articular cartilage. The treatment strategy of PRP in association with HA injection may be useful to treat advanced KOA before these patients receive arthroplasty. In a randomized trial with patients in the different stages of the disease it is difficult to conclude whether this approach can be applied to a specific phase of cartilage degeneration The recent advancement like ozone therapy for OA knee has been started. In those who received ozone therapy, there was a significant improvement of the studied parameters after 1 month and even more after 3 months.[101] These results coincided with those of many authors who stated that ozone diminishes pain and improves function in KOA. This short-term effect on symptoms was thought to be due to the relatively potent anti-inflammatory properties of ozone rather than intra-articular structural improvement. [101] Another study of Mishra et al[103]., described that the effectiveness lasted 6 months. When, PRP and ozone therapies were compared as regards to VAS and WOMAC score, improvement was achieved with PRP rather than with ozone in the treatment of KOA. In particular, ozone gas injection was efficient for only the first month, whereas the effect of PRP injection lasted for at least 3 months. Many studies compared PRP and ozone in terms of efficacy[102] The differences between various studies in the efficacy of ozone therapy in KOA may be related to a number of factors including differences in study populations, severity of disease, and heterogenicity of treatment parameters such as concentration of the ozone, number of settings and different machine design. Use of different outcome measures can also prevent direct comparisons between studies. There are no unanimous criteria for ozone treatment protocols in KOA including number of doses, concentration, volume or frequency 104In contrast, no significant difference between PRP and ozone has been reported [105]. This differences between various studies in the efficacy of PRP due to the application was performed in a single session, other were administered twice at an interval of 2 weeks/month.Duymus et al.106 reported in their study that PRP is superior to hyaluronic acid (HA) and ozone in the treatment of mild-moderate KOA and is becoming increasingly widespread. PRP injection alone was effective for achieving at least 12 months of pain-free daily activities. Also, Shen et al. [107] found that intra-articular PRP injections may be more efficacious in the treatment of KOA in terms of pain relief and self-reported function improvement at 3, 6, and 12 months follow-up compared with other injections, including saline placebo, HA, ozone and corticosteroids.

This study confirms that PRP is superior to ozone in the treatment of KOA and is an encouraging treatment option. PRP injection alone was effective for achieving at least 3 months of pain-free daily activity. This work showed that PRP treatment is safe as no complications as infection or fever occurred.

Patel et al.[108] reported mild complications as nausea and dizziness which were of short duration and these complications were not reported in the current patients. A larger scale longitudinal study with a longer follow up is recommended to verify the reached results and combining PRP and ozone with rehabilitations programs may reveal the optimum associations of treatment lines for KOA. In conclusion, that study confirms that PRP is superior to ozone in the treatment of KOA and is an encouraging treatment option. PRP injection alone was effective for achieving at least 3 months of pain-free daily activity. Alberto Gobbi et al[109,T10] randomized study in which 93 patients (119 knees) were followed up for a minimum of 2 years. Fifty knees were randomly selected prior to the first injection, to receive a second cycle at the completion of 1 year. A cycle consisted of three injections, each given at a monthly interval. The outcome was assessed using Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), Tegner and Marx scoring systems, recorded prior to the first injection and then at 12, 18 and 24 months.There was a significant improvement in all scores over time compared to the pre-treatment value ($p < 0.001$). At 12 months, both groups showed similar and significant improvement. At 18 months, except for KOOS (Symptoms) and Tegner score, all other parameters showed a significant difference between the two groups in favour of the patients who had received the second cycle ($p < 0.001$). At 2 years, the scores declined in both groups but remained above the pre-treatment value with no significant difference between the groups despite the patients with two cycles showing higher mean values for all the scores. Intra-articular PRP injections into the knee for symptomatic early stages of OA are a valid treatment option. And he concluded that There is a significant reduction in pain and improvement in function after 12 months, which can be further improved at 18 months by annual repetition of the treatment. Although the beneficial effects are ill sustained at 2 years, the results are encouraging when compared to the pre-treatment function.A systematic review of the effects of platelet rich plasma on outcomes for patients with knee osteoarthritis and following total knee arthroplasty111A total of 2328 participants were analyzed across 17 included studies and pooled results showed a statistically significant reduction in pain in favor of PRP following TKA but not in non-surgical management of knee OA (P < 0.0001 and 0.13 respectively). No clinical benefit of PRP was found on quality of life and knee function (P = 0.07 and 0.05) following TKA, although a statistical improvement in knee function was demonstrated in patients with knee OA after PRP injection (P < 0.0001). There was no statistically significant clinical benefit of PRP on secondary outcomes including wound scores and length of hospital stay (p = 0.33 and 0.31, respectively). There was no statistically significant difference in respect to blood loss and overall symptoms in favor of PRP compared to control group following TKA (p = 0.37).This systematic review demonstrated no long-term statistically significant improvement in patient validated outcomes and secondary outcomes both in patients with knee OA or following TKA for OA[111]. However PRP has been shown to have short to medium-term benefits in pain control after TKA and activities of daily living in patients with OA Combined intra-articular injections (Hyaluronic acid, platelet-rich plasma, and corticosteroid) for osteoarthritis knee, an effective alternative treatment[112]Sanjay Kumar Rai, Vasudevan P Raman, Rohit Varma, Sunitkumar S Wani from Department of Orthopaedics, Indian Naval Hospital Ship Asvini, Mumbai, Maharashtra, India Department of Orthopaedics, Malla Reddy Institute of Medical Sciences, Hyderabad, Telangana, India in august 2018 concludedBy reviewing current literature and their own experience, they feel that IA injections of HA, PRP, and corticosteroids given together for knee OA are an effective nonoperative modality of treatment.In combination, they seem to have better efficacy than any of them given alone.These injections are clinically safe and have promising and very positive effects for patient satisfaction. When the heterogeneity of OA is considered, it is difficult to categorize which patients and what level of disease would be ideal indications for IA injections. Advanced or severe OA with significant deformity/radiological changes is less likely to benefit from this treatment stratagem. In our study, specific patient characteristics (parents of soldiers living in villages), symptoms and clinical findings (mild to moderately severe), and those reluctant or unwilling to undergo surgery may be indications for a practical/reasonable approach for IA injections, by which total knee replacement may be postponed or avoided.The addition of a steroid is reasonable in acute and persistent synovitis and gives faster relief in pain. Based on their study, they feel that a combination of IA injections (HA, PRP, and corticosteroid) for OA of the knee is an effective alternative treatment in patients with low-to-medium work demand and who are either unwilling or not yet candidates for total joint arthroplasty. ((Rai, Raman, Varma, & Wani, 2018)

PRP CONCENTRATE COMPARISION

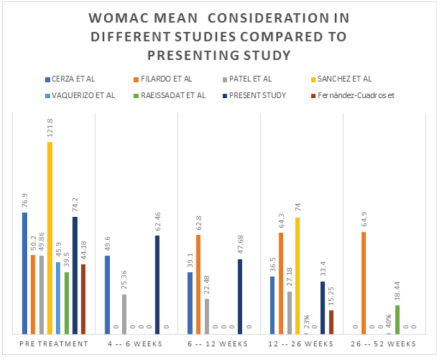
AUTHOR	SPIN1	SPIN2	TIME 1ST SPIN	TIME FOR 2ND SPIN	AMOUNT OF WHOLE BLOOD	PRP OBTIANED
PRESENT STUDY	1700	3700	10 MIN	20	10 ML PER 0.5 ML TIRSODIUM CITRATE CONTAINERS	10TIMES INCREASE
KHAN ET AL	3731	0	4 MIN	0	478 ML	3.2 TIMES CONC
SLICHTER & HALKER ET AL	1000	3000	9 MIN	0	250—450	3.27
NAHITA SYSTEM	1500	0	7 MIN	0	3.5 ML CITRATE TUBES WITH 0.5 ML TRI SODIUM CITRATE	2.27 TIMES
Mazzocca et al	1500	6300	7 MIN	20 MIN	25 ML	17 TIMES



WOMAC MEAN CONSIDERATION IN DIFFERENT STUDIES COMPARED TO PRESENTING STUDY

articles	pretreatment	4-6 weeks	6-12 weeks	12-26 weeks	26-52 weeks
Cerza et al.27	ACP: WOMAC 76.9 9.5 HA: WOMAC 75.4 10.7	ACP: WOMAC 49.6 17.7 HA: WOMAC 55.2 12.3 (P < .001) between groups	ACP: WOMAC 39.1 17.8 HA: WOMAC 57 11.7 (P < .001) between groups	ACP: WOMAC 36.5 17.9 HA: WOMAC 65.1 10.6 (P < .001) between groups	DNC
Filardo et al.28	PRP: IKDC score 50.2 15.7 Tegner score 2.9 1.4 HA: IKDC score 47.4 15.7 Tegner score 2.6 1.2	DNC	PRP: IKDC score 62.8 17.6 HA: IKDC score 61.4 16.2	PRP: IKDC score 64.3 16.4 HA: IKDC score 61.0 18.2	PRP: IKDC score 64.9 16.8 Tegner score 3.8 1.3 HA: IKDC score 61.7 19.0 Tegner score 3.4 1.6 P values not recorded
Patel et al.29	PRP1: WOMAC 49.86 17.83 VAS 4.56 0.61 PRP2: WOMAC 53.20 16.18 VAS 4.64 0.56 Saline: WOMAC 45.54 17.29 VAS 4.57 0.62	PRP1: WOMAC 25.36 PRP2: WOMAC 24.96 Saline: WOMAC 46.78	PRP1: WOMAC 22.48 PRP2: WOMAC 25.70 Saline: WOMAC 50.70	PRP1: WOMAC 27.18 VAS 2.16 1.543 PRP2: WOMAC 30.48 VAS 2.54 1.717 Saline: WOMAC 53.09 VAS 4.61 0.745 WOMAC:	DNC
Sanchez et al	PRGF: WOMAC 121.8 44.4 Lequesne 9.5 3.0 HA: WOMAC 115.6 45.1 Lequesne 9.1 3.2	DNR	DNR	PRGF: WOMAC 74.0 42.7 38.2% of patients had 50% decrease in WOMAC pain score 57.3% of patients had 20% decrease in WOMAC pain scoreLequesne 5.2 3.4 HA: WOMAC 78.3 48.1 24.1% of patients had 50% decrease in WOMAC pain score. 52.9% of patients had 20% decrease in WOMAC pain score. Lequesne 5.4 3.3 Differences between PRGF and HA for 50% decrease in WOMAC pain score (P ¼ .044), for 20% decrease (P ¼ .555), for total WOMAC score (P ¼ .561), and for Lequesne score (P ¼ .714)	DNC
Vaquerizo et al.	PRGF: WOMAC 45.9 12.7 Lequesne 12.8 3.8 HA: WOMAC 50.8 18.4 Lequesne 13.1 38	DNC	DNC	For patients with 30% decrease in: WOMAC summed score: rate of response of PRGF was 66, 43, and 23 percentage points higher than that of HA for pain, physical function and stiffness, respectively (P < .001, P < .001, P ¼ .02, respectively). Lequesne score: PRGF group is 56 percentage points higher than HA group (P < .001) For patients with 50% decrease in: WOMAC summed score: rate of response of	For patients with 30% decrease in: WOMAC summed score: rate of response of PRGF was 46, 37, and 40 percentage points higher than that of HA for pain, physical function and stiffness, respectively (P < .001, P < .001, P < .001, respectively). Lequesne score: PRGF group 46 percentage points higher than HA group (P < .001) For patients with 50% decrease in: WOMAC
				For patients with 30% decrease in: WOMAC summed score: rate of response of PRGF was 66, 43, and 23 percentage points higher than that of HA for pain, physical function and stiffness, respectively (P < .001, P < .001, P ¼ .02, respectively). Lequesne score: PRGF group is 56 percentage	For patients with 30% decrease in: WOMAC summed score: rate of response of PRGF was 46, 37, and 40 percentage points higher than that of HA for pain, physical function and stiffness, respectively (P < .001, P < .001, P < .001, respectively). Lequesne score:

				points higher than HA group (P < .001) For patients with 50% decrease in: WOMAC summed score: rate of response of	PRGF group 46 percentage points higher than HA group (P < .001) For patients with 50% decrease in: WOMAC
Raeissadat et al	PRP: WOMAC 39.5 17.06 SF-36 (PCS) 178.14 81.0 SF-36 (MCS) 229.22 95.62 HA: WOMAC 28.69 16.69 SF-36 (PCS) 180.4 68.52 SF-36 (MCS) 226.43 97.39	DNC	DNC	DNC	PRP: WOMAC 18.44 14.35 (P < .001)SF-36 (PCS) 255.96 77.59 (P < .001)SF-36 (MCS) 269.92 91.48 (P < .001) HA: WOMAC 27.46 16.36 (P ¼ .009)SF-36 (PCS) 189.39 103.73 (P ¼ .37) SF-36 (MCS) 216.91 100.9 (P ¼ .74)
Fernández-Cuadros et al112	44.18	DNC	DNC	15.25	DNC



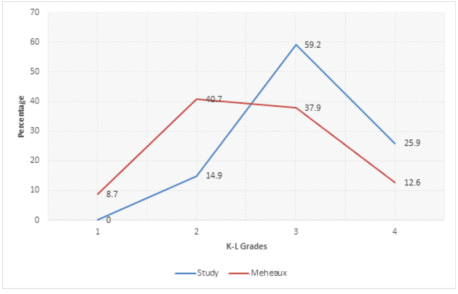


Table showing the studies considered for treatment

	Kanchatanawan	Dais' meta analysis	Gomelis'andSanchez'
K-Lgrades considered for Rx	1 and 2	1 to 3	4

CONCLUSION

Our study relied on injecting a highly concentrated mix of platelets into joint cavity and observing the patients for reduction in symptoms of pain, stiffness and improvement in physical function .our study has revealed a consistent reduction in pain and stiffness and a clear improvement in lifestyle of the patients.

Our study has thrown up an interesting choice of treatment modality using Platelet Rich Plasma in the treatment of Knee Osteoarthritis and it has proved efficacious in the observation period of six months.

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