Original Article

Journal of Orthopedic Education
Volume 9 Number 1, January-April 2023
DOI: http://dx.doi.org/10.21088/joe.2454.7956.9123.6

A Clinical Study of Effectiveness of Intra Articular Platelet Rich Plasma as Initial Treament Modality of Early Osteoarthiritis of Knee

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How to cite this article:
Shaik Mohasin Kamal, M. Rohith Reddy/A Clinical Study of Effectiveness of Intra Articular Platelet Rich Plasma as Initial Treament Modality of Early Osteoarthiritis of Knee/J Orth. Edu. 2023;9(1):45–53.

Abstract

Osteoarthritis of the knee joint is the most common form of arthritis thatcause pain, stiffness and decreased function. It is one of leading cause of disability inIndian population. Many different methods are available to help the patients relieve their symptoms. Intra-articular steroid is one of them which is widely being used, but it has its own side effects. Further more, these treatments are generally intended to decrease pain, maintain or improve joint function and minimize disability but fail to regenerate the articular cartilage. Recent studies suggest intra-articular injection of autologous PRP as an effective and safe biological treatment method in the initial stages of knee osteoarthritis.

Keywords: Osteoarthritis; Platelet rich plasma; Intraarticular.

INTRODUCTION

Osteoarthritis (OA) of the knee is one of the main causes of musculoskeletal disability.[1] Osteoarthritis is a common, debilitating disease which is associated with a large societal and economic burden, in addition to the physical and psychological sequelae it often manifests in the affected individual.[2] Osteoarthritis is the fourth leading cause of 'years lived with disability' (YLD), accounting for 3.0% of total global YLD's. As per WHO by 2030, the demand for total knee arthroplasties will increase up to 670%. This condition places a staggering burden on our current economy, with billions of dollars of annual expenditure associated with pharmaceutical treatment for pain relief, rehabilitation, and joint replacements.[3]

Osteoarthritis is clinically heterogeneous, and the processes that cause deterioration are still poorly understood.[1] Current opinion is that the disease progression results from an imbalance between proinflammatory cytokines (including interleukin [IL]-1a, IL-1, and tumor necrosis factor-1 and anti-inflammatory cytokines (including IL-4, IL-10, and IL-1ra).This cytokine imbalance is thought to activate proteolytic enzymes, leading to the destruction of cartilage. The majority of recently

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Received on: 09.09.2022 **Accepted on:** 11.10.2022

proposed therapeutic modalities for osteoarthritis have a foundation in attempting to address this cytokine imbalance. In addition to cartilage loss, arthritis of the knee joint may adversely affect subchondral bone, synovium, ligaments, capsule, menisci, surrounding musculature, and perhaps the sensory nervoussystem.[3]

At present, there are few options for patients with mild to moderate arthritis. Most of the approaches are palliative and address the symptoms rather than influencing the biochemical environment of the joint or the disease process.[1] Weight loss and exercise are excellent treatment options for OA, yet are often associated with poor compliance.[3] Because of limitations in the effectiveness of conventional management options, alternative options such as biological and regenerative methods are coming into vogue. Current research efforts are focused on the identification of key biochemical pathways that can be targeted therapeutically through biological intervention and the testing of protein biotherapeutics for restoring the metabolic balance within the joint. In particular, the most recent knowledge regarding tissue biology highlights the potential use of specific growth factors as therapeutic proteins for cartilage repair, and this is now being widely investigated in vitro and in vivo. Some of the experimental ortho biological treatments include platelet-rich plasma (PRP) injection graft therapy, high concentrate PRP (HcPRP), autologous bone marrow aspirate concentration and adipose cells, IL-1 receptor antagonist, nerve growth factor inhibitor, and osteogenic protein-1 among others.[4] Autologous platelet rich plasma (PRP), which contains a pool of growth factors, appears to offer an easy solution for delivering multiple growth factors needed for tissue repair.[1]

Autologous PRP is a volume of plasma having a platelet concentration above normative baseline values.[4] Platelets are source of high concentrations of cytokines well documented to regulate a number of regeneration.[5,6] PRP therapy provides delivery of a highly concentrated cocktail of growth factors to accelerate healing.

Currently, most studies on PRP therapy are anecdotal, non randomized, or involve insufficient sample sizes and are underpowered.[7] However, at present, there are limited studies documenting the safety and efficacy of a non-surgical PRP injectable for intra-articular use in knee Osteoarthritis.[8,9] PRP is being portrayed as a "wonder drug", without sufficient evidence to support its application inalmost all the areas in which it is used. No specific guidelines per dosage regimen.

Keeping in view these grey areas in our knowledge, this prospective clinical trial was designed to evaluate the role of PRP in the early stages of knee OA. In this study PRP from the patient's own blood i.e. autologous PRP has been immediately infiltrated into their knee joints with early osteoarthritis and the results of injection of PRP have been observed over a period of time.

OBJECTIVES

To study the effects of injection of platelet rich plasma (autologous) in the management of early osetoarthritic of knee joints.

To assess the functional outcomeafterinjecting autologous platelet rich plasma in osteoarthritic knee joints.

To assess the complications associated with PRP infiltration into the osteoarthritic knee joints.

MATERIALS AND METHODS

This study was conducted in PES Hospital, Kuppam, Andhra Pradesh from July 2016 to July 2017.

Inclusion criteria:

1 Patients with grade 1,2 primary osteoarthitic knee according to kellgren- lawrence gradingscale.

2. Patient age group ranged from 40 to 65 years, having stable knees without deformity or patellarmaltracking.

3. All patients were prospectively evaluated by WOMAC score & Koss Score for functional outcome and VAS score for pain. The score was recorded on initial presentation pre treatment and post treatment follow-up visit at 1st month, 3rd month and 6th month .

Exclusion criteria:

1. Patients with significant joint swelling or clinical signs ofacute inflammation (possible inflammation or infection).

2. Patients with secondary arthritis.

TECHNIQUE

Platelet Rich Plasma Preparation

Blood Collection

In the preparation of P-PRP, Blood withdrawn from

cubital vein (Fig. 2) with help of BD vacutainer eclipse (Fig. 1) in three BD vacutainer tubes. BD vacutainer is a 2.7 ml tube that contained 0.35 ml of 3.2% sodium citrate, an anticoagulant and volume of approximate 2.35 ml for whole blood (Fig. 3).

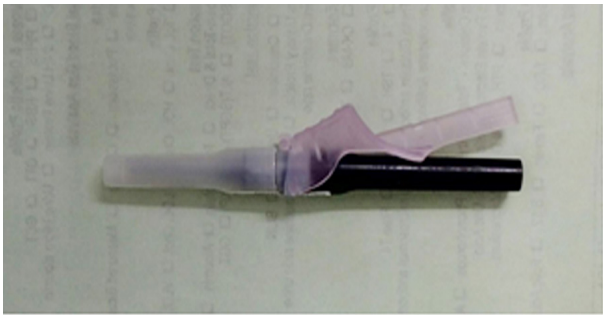


Fig. 1: Showing BD vacutainer eclipse, it is a blood collection needle used to withdraw blood from cubital vein.

Fig. 3: Showing BD vacutainer, is a 2.7 ml tube that contained 0.35 mL of 3.2% sodium citrate.

The objective of the anticoagulant is to bind calcium which stops the clotting cascade by preventing the conversion of prothrombin to thrombin (Arnoczky et al., 2011).

P- PRP PREPARATION

First Spin:

For the first spin, Three BD vacutainers with whole blood was centrifuged at 1200 rpm for 10 min in a Routine 380 R centrifuge model (Hettich, Zentrifugen). After the formation of three layers (Fig. 4) (a bottom layer composed of RBC; an upper layer composed of plasma, platelets and some WBCs; and an intermediate layer, or buffy coat, composed mostly of WBCs), the upper layer just above Buffy coat was collected with a 10 ml syringe (Fig. 5). This collection was performed carefully to avoid disturbing the bottom layer of RBC and the buffy coat layer. Depending on the centrifugal force of the spin, the collected volume ranged from 0.75ml to 1.25 ml in each BDvacutainer.

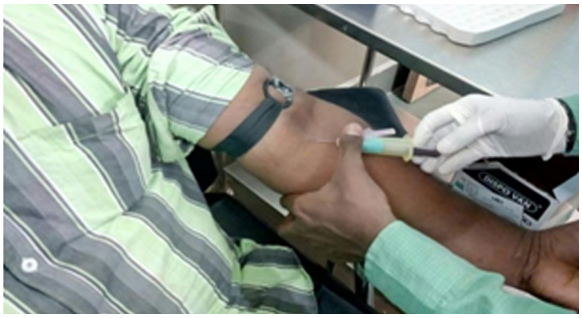


Fig. 2: Showing collection of blood from cubital vein with BD vacutainer eclipse

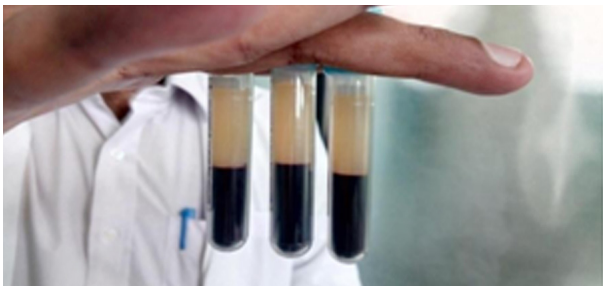


Fig. 4: After 1ststpin, each BDvacutainer showing three layers

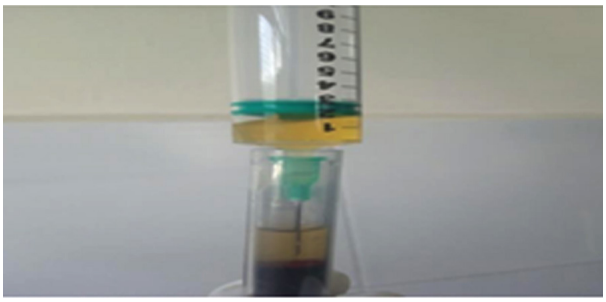


Fig. 5: Test tube showing platelet rich plasma

Second Spin

Approximately 1ml of the upper layer of the sample that underwent the first spin step was collected and transferred to one empty tube approximate is 3 ml. The tube centrifuged again for 10 min at speed of 2400 rpm. The upper half of the plasma volume, platelet poor plasma (PPP), was removed. The remaining volume of PPRP (Fig. 6) was used for injection.

Fig. 6: Test tube showing platelet rich plasma

Platelet count estimated by pathologist, The PRP is randomly checked for no. of platelets by Neubauer's chamber or auto analyser. Most of the samples have platelet count more then 1,000,000/ ul in 5 ml volume that is 5 times the baseline. After this the PRP is shaken by just turning the tube 2 to 3 times to mix the platelets.

Prp Injection Technique:

The procedure is explained to the patient, consent is obtained. Patient in supine position, involved KNEE is identified. Knee was scrubbed, painted and draped with sterile towels. With the patients knee in 30-40 flexion so that joint is opened for injection through lateral parapatellar approach. Under aseptic conditions, 4 ml platelet concentrate was injected into the knee jointwithoutlocal anesthetic. After the procedure, Jone's compression bandage was applied and the knees were immobilized for 10 minutes. Patients were observed for 30 minutes for any possible side effects like dizziness, sweating. During the follow-up period, non-steroidal anti-inflammatory drugs were not allowed, and tramadol (dosage, 50 mg bd) was prescribed in case of discomfort.

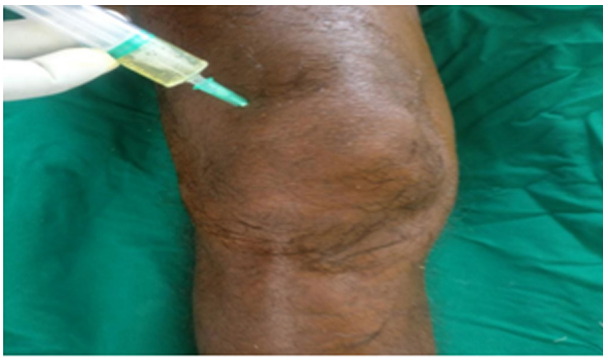


Fig. 7: Platelet-rich plasma is injected into knee

POST INJECTION CARE

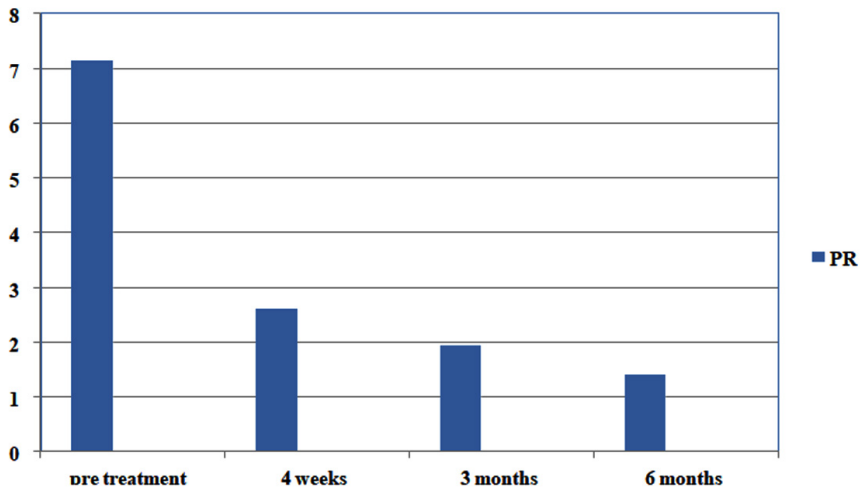
Post injection, patients are rested for 10 mins and then allowed to walk. As PRP effectively induces an inflammatory response, some patients experienced minimal to moderate discomfort following the injection which may last for up to 1 week. They were instructed to ice the injected area if needed for pain control and modify activity as tolerated. We recommended acetaminophen as the optimal analgesic, and avoided use of NSAID's.

RESULTS

1. ***Gender Distribution:*** In the study it was observed that PRP group (n = 60) contain 56.66% of females, and 43.33 % of male.
2. ***Age Distribution:*** In the study the Mean age of the subjects in PRP group was 47.27 ± 6.430 years .
3. ***Number of Right, Left and Bilateral Knees Affected Instudy Group:*** In the study it was observed that among PRP group right knee involved in 55%, Left knee involved in 38.33 % and bilateral knee involved is6.7%.
4. ***Visualanalogue Score:***

Table 1: Showing mean VAS score in PRP group

Variables	Prp Group (n = 60)	S.D
Pre Treatment	6.930	1.01
4 Weeks	2.62	0.82
3 Months	1.83	0.76
6 Months	1.13	0.62



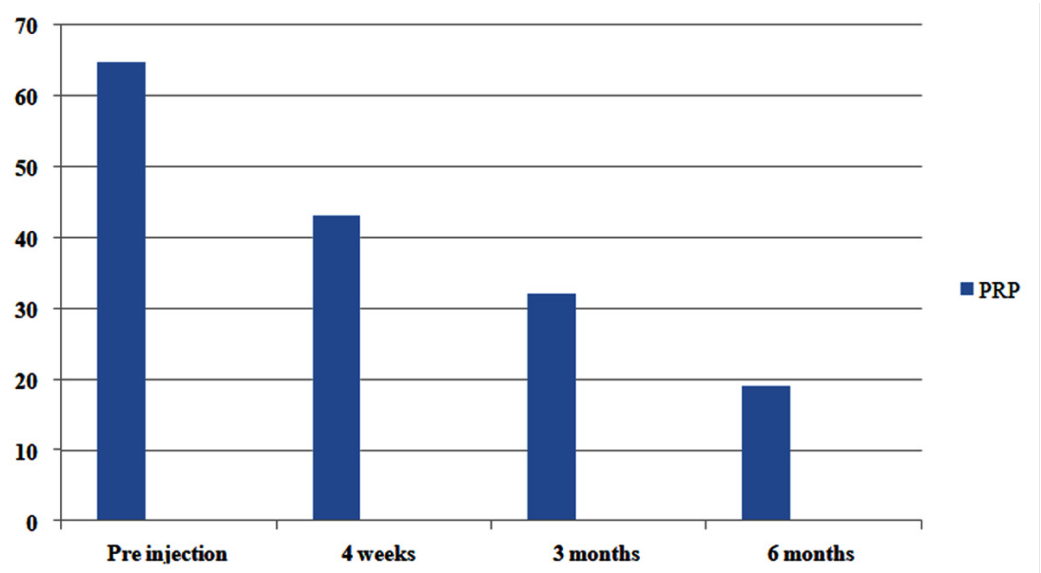
Clustered column 1: VAS at various intervals in PRP group

In this study the PRP group at the initial visit had VAS of 6.93. On injection of PRP In the group, 4 weeks evaluation of VAS showed a significant decrease in PRP group (2.62). At the end of 3 months, the VAS further decreased in PRP group (1.83). At the end of 6 months, the PRP group (1.12) showed significant reduction in VAS. This shows that PRP is more effective for long term relief

5. *Womac (Western Ontario and McMaster Universities Osteoarthritis Index)*

Table 2: Showing mean WOMAC at various intervals in PRP groups.

Variables	Prp Group	
	Mean	S.D
Pre-treatment	64.75	8.92
4 Weeeks	43.20	11.62
3rd month	32.18	9.67
6th month	19.03	3.366



Clustered column 2: Representation of womac

The PRP injection group at the initial visit had WOMAC of 64.75 ± 8.92. On injection of PRP, 4 weeks evaluation of WOMAC Score showed decrease in group (43.2±11.6). At the end of 3 months, the WOMAC Score further decreased in group (32.18±9.67). At the end of 6 months, the group (19.03±3.36) showed significant decrease in WOMAC Score. This shows PRP is more effective for long term relief.

6. *Grade of Osteoarthritis (Kellegren and Lawrence)*:

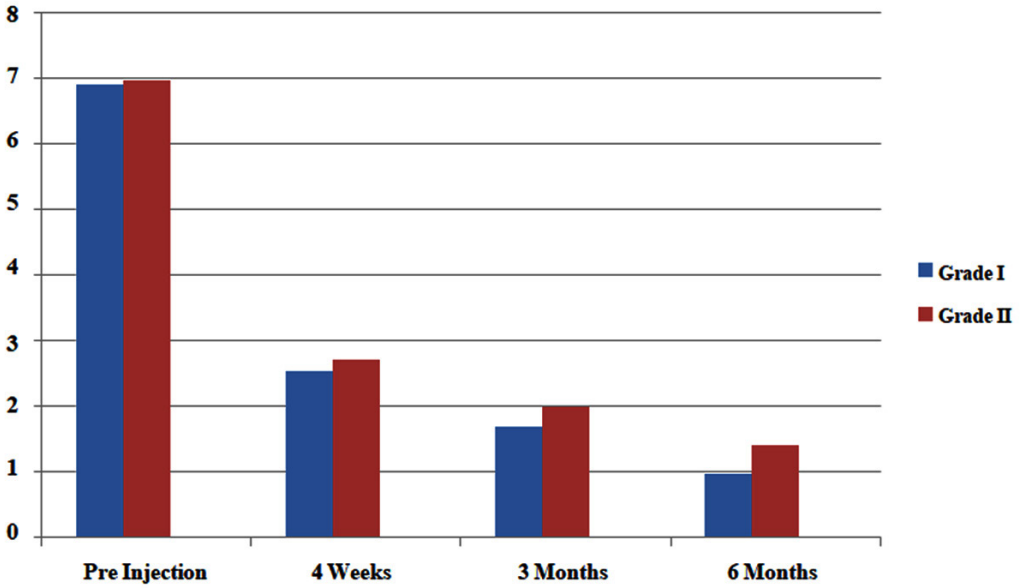
Table 3: Representation of Frequency & percentage in Grade I & II in group.

Variables	Frequency	Percentage
Grade I	35	58.33
Grade II	25	41.66

7. *Vas Score:*

Table 4: Showing mean VAS score & p value in Grade I & Grade II.

VAS	Grade I OA Knee (n= 35)	Grade II OA Knee (n= 25)	P Value
Pre-treatment	6.91	6.96	0.4320
4 Weeks	2.54	2.72	0.1893
3 Months	1.68	2.0	0.0268
6 Months	0.98	1.4	0.0119



Clustered column 3: MeanVAS at various intervals in Grade I & Grade II.

Table 5: Showing mean womac score & p value in Grade I & Grade II.

WOMAC	Grade I(n=35)	Grade II (n=25)	P Value
Pre treatment	61.2	69.72	0.0001
4 Weeks	40.42	47.08	0.013
3 Months	28.11	37.88	0.01
6Months	13.65	26.56	0.01

DISCUSSION

Articular cartilage lesions and degeneration are difficult to treat and present a challenge for orthopaedic surgeons because of the distinctive structure and function of hyaline cartilage and its inherent low healing potential. For therapeutic intervention, laboratory investigations are focusing on the possibility of preserving normal homeostasis or blocking or at least delay the need for more invasive surgical procedures. Current pharmacologic interventions may only temporarily reduce chronic pain, but for the time being, no proven disease modifying therapy is available.[10]

In this prospective study, patients were treated with intra articular PRP,VAS and WOMAC scores were evaluated pre-injection and post-injection period on first month, three months and sixth months. In Grade I, the mean WOMAC score of pain, stiffness and functionality is lower than the Grade II osteoarthritis knee joints. There was no control group in this study. The number of platelets used are more than 5 times the base line, as all the patients selected were having more than one lakh platelets, so every patient got more than 5 lakh platelets per ml, which is preparedby double spinning of the sample for 20 minutes with 1st spin at 1200 and 2nd spin at 2400 RPM (Rotations per minute) and leucofilters were not used. Kon et al in 2011, used double spinning with more than 5 times the base line platelets activated with CaCl2 and given more than three dosesof injection with 2 weeks gap 10.

Patel et al in 2013, used single spinning technique with leucofilters. They have given two injections of PRP activated with CaCl2.

Each 8 ml, with 3 weeks gap. Their platelet count is less than 5 times the base line.[1,10] In 2011, Filardo et al., used 5ml PRP with 5 times the platelet count prepared from double spinning technique and activated with CaCl2. They have infiltrated three injections of PRP with one week gap.[11] In 2012, they compared the single versus double spinning and found no significant difference in the results. All the patients who have received the PRP have shown decrease in the pain, stiffness and functionality 12. Cerza et al. in 2012 used 5ml of PRP not activated with CaCl2, platelet count less than the 5 times the baseline with single spinning and without leuco-filters. They have infiltrated four injection with each one week gap. The idea of using CaCl2 was to activates the platelets.[13]

Spakovaetal in 2012 did a similar study, PRP prepared after spinning it for three times and without using leuco-filters and they have used three injections with one week gap. They have stated that the leucocyte content did not seem to induce negative effects or to impair the potentially beneficial effects of PRP, even when used in joints. However, they cannot conclusively claim that increased white blood cells in PRP have positive effect on knee joint.[14,15] The preparation of PRP, number of platelets, amount of PRP infiltrated, and frequency of injections were not uniform.

Different researchers have used different methods of preparation, different amount of PRP and at different time periods (table 6). Thus we can conclude that the method of preparation of PRP; the platelet count to beachieved before infiltration; the usage of leucofilters; the number of injections for each knee joints; the duration between injections; all are varying and not standardized at present.

Table 6: Comparison of different studies of PRP in treating osteoarthritis of knee joints.

Table 6: Comparison of different studies of PRP in treating osteoarthritis of knee joints. VAS-Visual analogue score, IKDC-International Knee Documentation Committee

Study	Type of study	Sample size		No. of Injection	Time of inject ION in weeks	Volume of PRP in ml	Platelet concentration	WOMAC score improvement
		PRP	Control					
Vaquerizo et al[16](2013)	PRP vs HA	60	60	3	0-2-4	8	<5× baseline	+
Patel et al[1](2013)	PRP vs Placebo	54	50	2	0-3	8	<5× baseline	+
Filardo et al[11](2011)	PRP vs PRGF	54	55	3	0-1-2	5	5×baseline	VAS
Cerza et al[17] (2012)	PRP vs HA	60	60	4	0-1-2-3	5	>5×baseline	+
Spakova et al[14] (2012)	PRP vs HA	60	60	3	0-1-2	3	<5×baseline	+
Filardo[18] et al (2012)	Single vs Double Spinning	72	72	3	0-3-6	5	<5×baseline	VAS
Kon et al[19] (2011)	PRP vs HA	50	50	3	0-2-4	5	>5×baseline	VAS AND IKDC
This Study	PRP	60	NA	3	0-4-12	4	>5×baseline	+

VAS- Visual analogue score, IKDC– International Knee Documentation Committee

In this study, all the patients have shown decrease in the WOMAC score. Their mean pain, stiffness and functionality scores have decreased. The decrease in WOMAC score continued upto six months. The improvement in our patients could be explained by the fact that injected platelets might have acted at different levels andwere stimulating the chondral anabolism or slowing the catabolicprocess.Though the mean pain scores have decreased in all the patients, the efficacy has been varied from patient to patient. The results have shown better in grade I osteoarthritis knee joints than grade II knee joints. In every patient, there is decrease in WOMAC score, but in no one it has reached. It means that PRP delays the osteoarthritic progression in the joints, but it has not curedosteo arthritis. To evaluate its duration of action long term follow up studies are required. Filardo et al. in 2012, have also shown similar results, better results are seen in early osteoarthritis knee joints than advanced arthritic knee joints in their comparative study done between PRP and hyaluronic acid treatment of osteoarthritis of knee joints 62, though they have not found significant improvement in PRP group when compared with hyaluronic acid. In their previous study in 2011, the final evaluation confirmed that female patients showed the poor results, which probably due to gender specific biological and biomechanical characteristics, which might influence the etio-pathogenesis, the effects of the growth factors and ultimately, the clinical response to treatment. Spakova et al. in 2012, in their study found statistically significant improvement in WOMAC score, VAS and pain relief when

compared to viscoelastic supplementation.[21]

Kon et al. in their study in 2011 had shown significant improvement in all parameters of the WOMAC score in the group of patients who were infiltrated with PRP upto 6 months follow up. But the condition of the patients were decreasedfrom 6 months to 12 months follow up, i.e the effect of PRP decreasing from 6 months onwards. Some influencing factors were detected, in particular it was observed that young male patients were the best responding group, especially in case of simple chondropathy without signs of oateoarthritis.[18] In a later study evaluating the same patients at 24 months of follow up confirmed this trend with a further decrease in the clinical outcome, thus concluding that intra articular therapy with PRP is time dependent with an average duration of 9 months and better and longer results are achieved in younger patients with lower levels of joint degeneration. They have also stated that PRP has no beneficial effect in advanced Osteoarthritis. Older and more degenerated joints present a low percentage of living and vital cells, therefore a low response potential to the growth factors. Extensive structural joint damage in severe osteoarthritis is hardly reversible. The biologic changes induced by PRP may only weakly influence older joints with higher degenration.[11] In this study the results have shown that the effect of PRP sustained for 6 months with continuous decrease in all parameters, i.e. pain,stiffness and functionality of the WOMAC score. Filardo et al. in 2012 found that there was worsening of the condition of the patients from the end of 9 months, implying that the duration of action of PRP was 9 months. But, the longevity of the benefits of PRP cannot be emphatically established by our study as the follow up is only short term, long term studies are necessary to study thisaspect.

Immediate post infiltration, some patients have complained of pain but no systemic and long term complications noted during the course of our study. Sandeep Patel et al, in 2013, in their study have documented some systemic adverse effects. Which were immediate and systemic rather than local and were of short duration not lasting more than 30 minutes. But they have not explained the characteristics of the adverse effects. They have attributed these adverse effects to the higher number ofplatelets in the infiltrating PRP sample and the possibility of CaCl2, which was used as an activating agent.[1] Kon et al. in 2010 and Sanchez et al. in 2007 have reported some injection pain, local inflammation of short duration and reaccumulation of effusion, but the exact numbers were not mentioned.[20,19]

All the patients have shown improvement at around fifteen days. Therapeutic benefit might not be because of chondrogenesis, because it would have taken moretime for the patients to perceive benefits. Filardoetalin 2012 have shown worsening of WOMAC score from nine months onwards[18], it implies that if the chondral remodelingwas the cause for the improvement of symptoms, the benefit would have started later and lasted for a longer duration.

Sandeeppatel et al. in 2013, through their study stated that the improvement in patients of osteoarthritis of knee joints is not because of the stimulation of the chondral anabolism or slowing the catabolic process.[1] PRP may influence the overall joint homeostasis, reducing synovial membrane hyperplasia and modulating the cytokine level, thusleading to an improvement in the clinical outcome, even if only temporarily and without affecting the cartilage tissue structure and joint degeneration progression.

This study has its limitations, the age, Body Mass Index (BMI) were not considered in selecting the patients. Cartilage mapping was not done because of its cost. Study follow up period was maximum for six months. It would have given more understanding on longevity if it was followed for longer periods

CONCLUSION

We can safely conclude that Autologous PRP infiltration in early Osteoarthritis gives relief from pain, stiffness and improves functionality without any major side effects and can be recommended as a viable modality oftreatment.

The PRP injection can be repeated with no adverse effects Immediate post injection, all patients complained of mild pain. 2 patients had knee effusion on the day of injection, but no systemic and long term complications were noted.

PRP is a biological option for early osteoarthiritis. Our study has shown that PRP injection is safe and effective treatment for relief of pain early OA and possibly delay progress of OA.

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