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Efficacy and safety of platelet rich plasma in primary osteoarthritis of the knee joint

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Abstract
Osteoarthritis (OA) is the most prevalent form of arthritis and a major cause of disability in people aged 50years and older. It is the clinical and pathologic outcome of a range of disorders that results in structural and functional failure of synovial joints. At first, articular cartilage may be the primary injury site but eventually all structures, synovium, muscle, capsule, ligaments and meniscal cartilage are involved. This prospective study was conducted in 60 patients of age 35-70years with grade1-2 osteoarthritis attending orthopedics OPD in a tertiary care centre. Having diagnosed by American College Of Rheumatology Criteria and staged as per Ahlback's radiological grading along with detailed history of secondary causes and pathological factors inducing osteoarthritis were ruled out.The age of the patients in our study ranged from 35-70 years with the mean age of 53.75 years. Female predominance was noted with females 40 (66.7%) and males constituting 33.3% (20 cases) in our study. In our study majority cases (n=46) presented with grade 2 while rest of the patients presented with grade 1 disease. VAS score depicted decrease in mean of 6.45 at baseline to 3.76 after six months. The improvement was statistically significant with p value (0.002). Total WOMAC score was noted at the end of six months and depicted by p value of (0.000). No complications related to PRP injection were reported. Platelet rich plasma has a role in the treatment of osteoarthritis which in our study is supported by the improvement seen in VAS and WOMAC scores. This improvement is possibly due to the anti inflammatory properties or due to release of various growth factors. PRP may also influence the overall joint homeostasis by reducing hyperplasia of the synovial membrane and modulating cytokines level.

Keywords: PRP, Osteoarthritis, VAS, WOMAC

1. Introduction
Osteoarthritis (OA) is the most prevalent form of arthritis and a major cause of disability in people aged 50 and older [1]. At first, articular cartilage may be the primary injury site but eventually all joint structures- bone, synovium, muscle, capsule, ligaments and meniscal cartilage become involved [2]. Researches seek to identify key biochemical pathways that can be targeted therapeutically through biological intervention like the use of inhibitors of interleukin-1 (IL-1) that reverse cartilage destruction [3]. Efforts towards the testing of protein bio-therapeutics for restoring the metabolic balance within the capsular joint are in progress. Potential use of specific growth factors as therapeutic proteins for cartilage repair is also examined [4]. Bioactive growth factors and autologous platelet rich plasma (PRP) are recently being considered as therapeutic possibilities to enhance healing of chondral injuries and modify early degenerative arthritis [5]. The concept that application of PRP would improve cartilage repair is based on the physiological role of platelets in wound healing. In response to tissue injury, clots rich in platelets and fibrin form, which consolidate and adhere to form a scaffold for subsequent healing. Growth factors stored in platel*et al*pha granules that are known to play important role in the normal healing response, including PDGF, VEGF, TGF-beta, FGF, and EGF. Through modulation of the inflammatory response, promotion of local angiogenesis, attraction of fibroblasts and local stem cells to the site of injury and an induction of autocrine growth factor production by uninjured adjacent cells, platelets and their products are instrumental in normal tissue repair and regeneration [5]. The clinical use of PRP therapy in the practical setting of orthopedic fields is increasing partly because of the accessibility of

devices that are used in outpatient preparation and delivery. [6] PRP derived from centrifugation of autologous whole blood contain a platelet concentration four to five times higher than that of normal blood. The administration in the form of platelet gel provides an adhesive support that can confine secretion to a chosen site [7].

2. Material and Methods

The study was conducted on patients attending Orthopaedics outpatient Department, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana who had early osteoarthritis knee diagnosed by American College of Rheumatology Criteria and staged as per Ahlback's radiological grading. The sample size studied was 60 patients, out of which 7 patients presented with bilateral knee involvement therefore making the final figure of 67 knees. The patients selected were having Grade 1 and Grade 2 OA knee with age group of 35-70 years excluding osteoarthritis secondary to inflammatory diseases, metabolic diseases. All the patients were evaluated at first visit before giving first injection using Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and thereafter at subsequent follow ups at three weeks, three months and six months post injection.

2.1 Platelet Rich Plasma Preparation

The platelet rich plasma required for injection was prepared and provided by The Department of Transfusion Medicine, Mullana. About 100ml of whole blood was drawn under aseptic precautions from the antecubital vein atraumatically in efforts of avoiding irritation and trauma to the platelets which are in resting. The blood is collected in 100ml bag with CPD-A1 (Citrate Phosphate Dextrose and Adenine) as anticoagulant. The whole blood was transferred from the blood bag into sterile tubes (50ml) using a blood transfusion set. The tubes were then centrifuged for 15 minutes at 1500 rpm on a table top centrifuge. The blood was then separated into platelet rich plasma (PRP) and residual RBC's with the buffy coat. The PRP was extracted through a pipette and transferred to a test tube. PRP ready to be injected was supplied in a syringe in a quantity of 8 ml meant for injection into one knee.

2.2 Interventional Procedure

The subject was placed in supine position with knee in full extension and under full aseptic precautions 8 ml of platelet concentrate was injected by lateral approach by 18-20 Gauge needle. After 30 minutes of observation patients were discharged. Any patient who complained of complications was observed for at least 2-3 hours and was discharged when fully recovered. Patients were given a total of three injections at four week interval.

2.3 Follow Up

The patients were then followed up in the outpatient department using VAS and WOMAC score at three weeks, three months and six months.

3. Results

In the present study the majority cases belonged to the age group of 51-60 years. The youngest patient in the series was 35 years old and oldest was 70 years with a mean age group ± SD being 53.75±8.74 years. Out of 60 patients, females formed the majority 40 cases (66.7%) and males constituted the rest 20 cases (33.3%). Four females had bilateral and thirty six had unilateral involvement whereas three males showed bilateral and seventeen showed unilateral involvement. Total WOMAC score, individual parameters of WOMAC score (pain, stiffness and physical function) and VAS were analysed in all the patients at pre injection, and subsequent follow ups at three weeks, three months and six months post injection. After mean WOMAC score assessment, pair wise comparison of WOMAC parameters was done separately at each time frame which is as follows.

3.1 Pain Parameter

The pain parameter shows decreased mean values at each follow up from pre injection value and statistically significant change with p value of <0.05.

3.2 Stiffness Parameter

Same results were seen with mean stiffness score and stiffness value on pair wise comparison at each time frame with a significant p value of .032 from pre injection to first follow up and .000 at subsequent follow ups and decreased from a mean of 5.01 at pre injection to 2.03 at third follow up.

3.3 Physical Function Score

Similarly mean physical function score and pair wise comparison of physical function values was done at each time frame. There was no significant change from pre injection to first follow up seen as (p value= 1.000) and decrease from a mean of 36.52 to 35.03, however the difference was statistically significant from first follow up to third follow up with p values .000 and .008 respectively and decrease in mean 35.03 (first follow up) to 23.82 (second follow up) and 19.07 (third follow up).

Analysis of mean Total WOMAC score and pair wise comparison was done (Table 3.1 and 3.2) Even though the pain and stiffness values show statistical significance at first follow up, the Total WOMAC mean score decreased from 55.75 to 52.34 from pre injection to first follow up which was not significant (p=0.487). However significant difference was seen at second follow up and third follow up with decrease in mean score to 35.82 and 27.66 (p=.000)

Table 3.1: Mean Total WOMAC score at different time frame

Total WOMAC score	Mean ± SD
Pre injection	55.75±10.90
1st follow up	52.34±11.54
2nd follow up	35.82±9.92
3rd follow up	27.66±12.48

Table 3.2: Pair wise comparison of mean Total WOMAC score at pre injection and each follow up with one another

Total WOMAC (I)	Total WOMAC (J)	Mean difference (I-J)	P value
Pre injection	1st follow up	3.403	.487
	2nd follow up	19.925	.000
	3rd follow up	28.090	.000
1st follow up	Pre injection	-3.403	.487
	2nd follow up	16.522	.000
	3rd follow up	24.687	.000
2nd follow up	Pre injection	-19.925	.000
	1st follow up	-16.522	.000
	3rd follow up	8.164	.000
3rd follow up	Pre injection	-28.090	.000
	1st follow up	-24.687	.000
	2nd follow up	-8.164	.000

3.4 Visual Analog Scale (VAS) for Pain

The improvement was observed in VAS score from pre injection to second and third follow up. The p value calculated was 0.000. No improvement was observed at first follow up (p value=1.000). Table 3.3 and 3.4 shows the improvement observed in mean scores of VAS.

Table 3.3: Trend of VAS score means with time

VAS score	Mean ±SD
Pre injection	6.45±1.22
1st follow up	6.22±1.19
2nd follow up	4.54±1.11
3rd follow up	3.76±1.37

Table 3.4: Pair wise comparison of VAS score at pre injection and each follow up with one another

VAS (I)	VAS (J)	Mean difference (I-J)	P value
Pre injection	1st follow up	.224	1.000
	2nd follow up	1.910	.000
	3rd follow up	2.687	.000
1st follow up	Pre injection	-.224	1.000
	2nd follow up	1.687	.000
	3rd follow up	2.463	.000
2nd follow up	Pre injection	-1.910	.000
	1st follow up	-1.687	.000
	3rd follow up	.776	.002
3rd follow up	Pre injection	-2.687	.000
	1st follow up	-2.463	.000
	2nd follow up	-.776	.002

3.5 Complications of PRP

Forty three patients had no complications, Twenty one patients had mild pain and two patients had moderate pain which subsided in 2-3 days without any intervention. One patient experienced episode of sweating and tachycardia subsided in an hour.

3.6 Patient's Satisfaction

In the present study patients were analyzed based on the satisfaction at the third follow up. The response of the patients was graded as good, moderate, mild and no improvement. None of the patients reported worsening.

4. Discussion

The age of the patients in our study ranged from 35-70 years with the mean age of 53.75 years. In a study by Sanchez *et al.* [8] mean age of the patients was 63.53 years whereas concordant results were seen in a study conducted by Filardo *et al.* [9] with mean age 54.5 years and Patel *et al.* [10] with mean age 52.8 years. Female predominance was noted with (66.7%) and males constituting 33.3% in our study. The results were similar to the studies done by Sanchez *et al.* and Patel *et al* whereas studies by Kon *et al.* [11] and Sampson *et al.* [12] showed male predominance.

In our study majority cases (n=46) presented with grade 2 while rest of the patients presented with grade 1 disease. When compared with other studies dissimilar results were seen. Sanchez *et al.* found equal proportion of patients in grade 1 and 2 whereas in a study by Patel *et al.* majority patients were from grade 1. Discordance in our study is attributed to the delay in seeking treatment on time as majority population belongs to low socioeconomic strata. Individual WOMAC mean score and total WOMAC score were analysed in each patient at pre injection and subsequent follow ups at three weeks and six months which at three weeks show improvement in pain and stiffness however, no improvement was seen in physical function with p value of 1.000 and 0.487 respectively. However statistically significant improvement in individual parameters as well as Total WOMAC score was noted thereafter at subsequent follow ups with p value of 0.000. In a study by Sanchez *et al.* [8] WOMAC score parameters Improvement was 33.3%, with (p value of 0.004). Similar changes were observed in the physical function and Total WOMAC score with statistically significant p value of 0.043 and 0.010 respectively. Patel *et al.* [10] (2013) in their study showed statistically significant improvement in all WOMAC parameters observed at 6 weeks and lasting until the final follow up at 6 months. Contrast to the above studies, our present study did not show improvement in Total WOMAC score at three weeks (first follow up), which could be due to platelet count of PRP and time taken by platelet rich plasma to show its beneficial effects completely. Relief of pain and stiffness, at first follow up can be explained on the basis of anti inflammatory properties of platelet rich plasma. VAS score showed statistically significant improvement from baseline to second and third follow ups with (p value of 0.000). Significant improvement in VAS score was seen in studies by Kon *et al.* [11] and Patel *et al.* [10] at six months with p values of <0.0005 and 0.001. In a study by Sampson *et al.* [12] final follow up was done at 52 weeks, with p values (<0.05). There was a definite correlation of Total WOMAC score and Ahlback's grading. Baseline Total WOMAC score at the time of pre injection (n=67) was less for grade 1 (45.52) in contrast to grade 2 (60.41). At third follow up only (n=58) patients underwent repeat X-ray. Kon *et al.* [11] (2010) concluded that younger patients with lower degree of degenerative chondropathy achieved better results in comparison to patients affected by early osteoarthritis, which in turn showed higher improvement in comparison to patients of advanced osteoarthritis. In our study majority of the patients (82.08%) received 8 ml of platelet rich plasma, however the quantity varied from 6-8 ml not more than that as injecting large amount of PRP can cause effusion in the joint. Sanchez *et al.* Sampson *et al.* and Patel *et al.* used same amount of PRP as in our study. Hence results of our study were corresponding to the other studies. Contrary to our study, Kon *et al.* used lesser amount (5ml) of PRP which could result in reduced number of platelets and growth factors released from the platelets with suboptimal treatment outcome. None of the previous studies in literature has mentioned any serious side effects on administration of platelet rich plasma. Same results were corroborated in our study apart from mild pain at the injection site. Sanchez *et al.* [8] (2008) reported mild pain and inflammation of short duration. Kon *et al.* [11] (2010) observed mild pain at injection site which persisted only for 2-3 days. Improvement as per patient version was asked at the end of six months post injection. Sixty patients comprising 89.55% showed improvement though the level varied from good improvement to mild improvement. Out of total, 10.45% of the patients did not experience any improvement but none reported worsening. Kon *et al.* [11] (2010) reported 80% satisfied patients, which showed close proximity when compared with our study.

5. Conclusion

With a detailed study we assume that platelet rich plasma does have a role in the treatment of osteoarthritis which in our study is supported by the improvement seen in VAS and WOMAC scores. The effect is possibly due to anti-

inflammatory action or release of various growth factors. PRP injection result in chondroprotective and chondroregenerative potential in knee joint cartilage and hence result in pain relief. It takes some time to induce the action and hence the onset of pain relief is slow but long lasting. The present state of knowledge holds promise for PRP for pain management in the early OA knee (grade 1 and 2, as per Ahlback's radiological grading system) without any complications. Nevertheless, a lot of grey areas remain in our understanding of PRP and OA, and many more focused clinical and in vitro studies are required. PRP along with other viscous supplementation seems to be an evolving future trend. PRP is definitely there to stay for OA therapy use in present and future.

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Nil.

Ethical statement
This study has been approved by the local ethical committee.

Conflicts of interest
No benefits in any form have been received or will be received from a commercial party-related directly or indirectly with regard to this article and there are no competing interests related to this article.

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