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Original Article

Anaesthesia Section

# Platelet Rich Plasma Therapy for Knee Joint Pain in Diagnosed Cases of Rheumatoid Arthritis: A Prospective Observational Study

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## ABSTRACT

**Introduction:** Rheumatoid Arthritis (RA) is a chronic disease characterised by severe inflammation, leading to degradation of articular cartilage and bony erosions. Women are affected two to three times more frequently than men. Platelet-Rich Plasma (PRP), a regenerative medicine therapy, has prompted interest in its potential use in patients with RA.

**Aim:** To assess the effectiveness of PRP in modulating chronic RA in terms of pain relief, work capacity and overall satisfaction.

**Materials and Methods:** This prospective observational study was conducted at Pain Clinic of R.G.Kar Medical College and Hospital, Kolkata, West Bengal, India, in collaboration with the blood bank. The effectiveness of PRP therapy in relieving knee joint pain was studied among 30 diagnosed cases of RA. Pain relief was analysed using the Visual Analogue Scale (VAS), and functional improvement was assessed using the Knee injury and Osteoarthritis Outcome Score (KOOS) at baseline (0-week), 12$^{th}$ week, and 24$^{th}$ week. Blood samples were collected, and a centrifugation protocol was followed for PRP preparation. A total of 12 mL (6 mL per knee) of PRP was administered intra-articularly into the suprapatellar recess of both knee joints. Data on age, gender, VAS, and KOOS scores were recorded in an Excel sheet. Statistical analysis was performed, and a p-value <0.05 was considered significant.

**Results:** The mean age of participants was 43.70±8.96 years {mean±Standard Deviation (SD)}, with 26 (86.7%) females and 4 (13.3%) males (N=30). Age distribution was as follows: 31-40 years: 46.7%, 41-50 years: 30%, and 51-60 years: 23.3%. Paired sample descriptive statistics for VAS and KOOS scores at 0, 12, and 24 weeks showed statistically significant improvement (p<0.05).

**Conclusion:** The PRP significantly improved pain scores on the VAS and enhanced pain, symptoms, daily activities, sports function, and quality of life as measured by KOOS over 24 weeks. PRP administration was associated with high patient satisfaction and no reported adverse effects or complications.


**Keywords:** Intra-articular injections, Knee injury and osteoarthritis outcome score, Visual analogue scale

## INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic disease characterised by severe inflammation, leading to articular cartilage degradation and bony erosions. Its global prevalence ranges from 0.25 to 1% [1]. RA can affect individuals of any age, with increased incidence in people over 40 years. Women are affected two to three times more frequently than men [2].

The RA progresses through four stages namely Stage 1-synovitis, Stage 2-pannus formation, Stage 3-fibrous ankylosis, and Stage 4-bony ankylosis. Despite ongoing advancements in treatment, patients often experience significantly diminished quality of life due to functional limitations. Therapeutic approaches primarily include Disease-modifying Anti-rheumatic Drugs (DMARDs) immediately after diagnosis [3]. However, commonly prescribed DMARDs are often unsuitable for long-term management due to limited efficacy, toxicity, and high costs, leading to treatment discontinuation [4-6].

Adjuvant therapies, such as glucocorticoids and Non Steroidal Anti-Inflammatory Drugs (NSAIDs), offer symptomatic relief during flare-ups but provide limited improvement in slowing the progression of joint erosion and irreversible damage [3].

The PRP has been studied in limited trials for ligament tears, Achilles tendinopathy, epicondylitis, cartilage regeneration, arthroplasty bone healing, rotator cuff repair, and Osteoarthritis (OA). There is even more limited knowledge regarding its efficacy in RA patients with knee joint pain [7-11]. It is hypothesised that PRP, due to its high concentration of platelets and growth factors, may reduce inflammatory factors and accelerate neovascularisation in joints affected by RA [12]. PRP may improve joint homeostasis by limiting synovial hyperplasia and decreasing cytokine levels without disrupting native cartilage tissue, leading to clinical improvement and enhanced productivity [7,8,13].

The PRP has been primarily studied in primary OA, with limited data on its use in RA-associated knee pain [14]. The present study aimed to explore the effects of autologous PRP in patients with RA-related knee joint pain.

A 30 mL venous blood sample typically yields 3-5 mL of PRP, depending on the individual's baseline platelet count, the device used, and the technique employed. Blood is drawn into tubes containing an anticoagulant, acid citrate dextrose, to prevent platelet activation prior to use.

The first centrifugation step is performed at constant acceleration to separate Red Blood Cells (RBCs) from the remaining whole blood. After this step, the blood separates into three layers:

- An upper layer containing mostly platelets and White Blood Cells (WBCs),
- A thin intermediate layer known as the buffy coat, which is rich in WBCs, and
- A bottom layer consisting mostly of RBCs.

For the production of Pure PRP (P-PRP), the upper layer and the superficial buffy coat are transferred to an empty sterile tube. For

Leucocyte-rich PRP (L-PRP), the entire buffy coat layer along with a small portion of RBCs is transferred. The second centrifugation step is then performed, with a relative centrifugal force ('g') sufficient to form soft pellets (erythrocyte-platelet) at the bottom of the tube. The upper portion, composed mostly of Platelet-poor Plasma (PPP), is removed, and the pellet is homogenised in the lower one-third of plasma (approximately 5 mL) to prepare PRP.

Centrifugation parameters, as per Indian Association of Dermatologists, Venereologists, and Leprologists (IADVL) Task force recommendations, are:

First spin: 100-300 g for 5-10 minutes

Second spin: 400-700 g for 10-17 minutes [15,16]

It is important to assess the functional capacity of patients with knee joint pain due to RA after PRP therapy using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and to evaluate pain relief using the Visual Analogue Scale (VAS) [16]. The present study aimed to assess the effectiveness of PRP in modulating chronic RA in terms of pain relief, work capacity, and overall patient satisfaction.

Therefore the primary objective of the present study was to assess pain relief using VAS before and after the procedure, and to assess functional improvement using KOOS before and after the procedure and the secondary objective was to assess patient satisfaction post-procedure, and to evaluate any complications associated with PRP injection.

## MATERIALS AND METHODS

This prospective observational study was conducted between August 2023 and July 2024 at the Pain Clinic of R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India, after obtaining approval from the Institutional Ethical Committee (Memo No. RKC/848, Dated: 08.06.2023). Informed consent was obtained from all participants. A total of 30 patients diagnosed with RA and presenting with knee joint pain (any stage) at the Pain Clinic Outpatient Department (OPD) were enrolled in the study.

**Sample size calculation [17]:** It was calculated using the formula:

$$n=\frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2\times(S_1^2+s_2^2/r)}{d^2}$$

n= sample size, Z1-$\alpha$/2= the Z-score for the confidence level (1.96 for 95%)

Z1-$\beta$= the Z-score for the desired power (0.84 for 80%)

$S_1$ and $S_2$ = the Standard deviations for each group

r= the ratio of group sizes (e.g., 1 for equal groups)

d=the difference in means want to detect

Considering Pain relief in KOOS between baseline and five weeks (p=0.0295 i.e., <0.05)

Using the above formula, the sample size was 10.

Considering 10% missing, the sample size (n) was 12;

As the sample size (n) was small, to make statistically significant authors have taken 30.

**Inclusion criteria:** Patients diagnosed with RA (any stage) according to the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) RA Classification Criteria 2010 and the 2022 ACR/EULAR Diagnostic Criteria [18,19], with knee joint pain (secondary OA), aged between 18 and 70 years, of either gender, were included in present study.

**Exclusion criteria:** Patients with abnormal hemogram results (e.g., low hemoglobin, low platelet count) or abnormal blood sugar levels, patients with primary OA of the knee (any grade), severe co-morbidities, or those unwilling to provide informed consent or attend follow-up visits were excluded from the study.

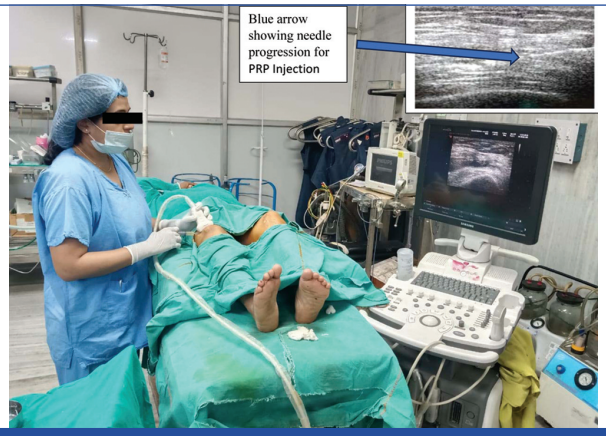
### Study Procedure

The present study was conducted to evaluate the effectiveness of PRP therapy in relieving knee joint pain in 30 diagnosed RA patients. Pain relief was assessed using the Visual Analogue Scale (VAS), and functional improvement was evaluated using the KOOS score at baseline (0-week), 12th week, and 24th week.

Blood was collected by trained blood bank personnel from each patient. Centrifugation was performed at 3500 revolutions per minute for eight minutes to concentrate platelets within the tube. The processing allows a visible gel separator within the tube to isolate PRP above the red blood cells and granulocytes for easy extraction. A total of 12 mL of PRP (6 mL per knee) was injected intra-articularly into the knee joint or suprapatellar recess [Table/Fig-1-4].

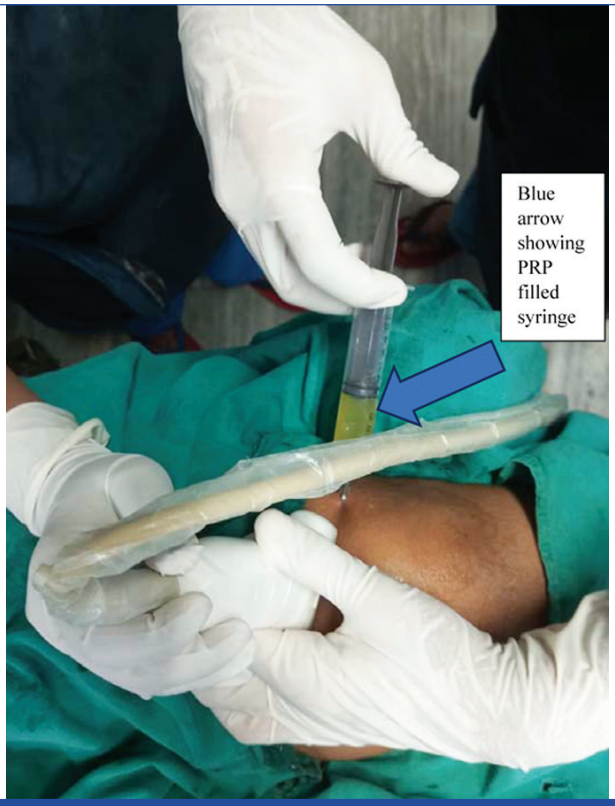
**[Table/Fig-1]:** Blood collected for PRP preparation.

**[Table/Fig-2]:** The PRP prepared ready for injection.




**[Table/Fig-3]:** The PRP injection under Ultrasonography (USG) guidance.

Baseline investigations included a complete haemogram, fasting and postprandial blood sugar levels, and X-rays of the bilateral knees (anteroposterior and lateral views in standing position) [20-23]. X-rays were performed to diagnose OA and to exclude any abnormalities that would prevent participation.




**[Table/Fig-4]:** The PRP injection given intra-articularly (blue arrow).

On arrival at the operating theatre, standard monitors such as non invasive blood pressure, pulse oximetry, and heart rate monitors were attached, and peripheral intravenous cannulation was performed. Injection Ceftriaxone 1 g was administered after proper skin test. Patients were positioned supine with the knee flexed and supported by a pillow. Under aseptic precautions and with ultrasonography guidance, 6 mL of PRP was injected into each knee joint (total 12 mL). After the procedure, the needle sites were dressed with antiseptic band-aids.

**Parameters assessed:** The effectiveness of PRP therapy in RA patients with knee joint pain was assessed using VAS for pain relief and KOOS for functional improvement at 0, 12, and 24 weeks.

The KOOS is a widely used patient-reported outcome measure for assessing treatment effects in knee OA. It is valid, reliable, and responsive, with improved validity compared to WOMAC. The KOOS consists of five subscales:

1. Pain – assesses knee pain,
2. Symptoms – assesses stiffness and other symptoms,
3. Activities of Daily Living (ADL) – measures functional limitations in daily activities,
4. Sport/Recreation – assesses ability to perform sports and recreational activities,
5. Quality of Life (QoL) – examines the impact of knee problems on overall quality of life.

The KOOS score ranges from 0 to 100, where 100 indicates no problems or difficulty, and 0 indicates extreme problems or difficulty [24].

The VAS is a unidimensional measure of pain intensity, first used in 1921 by Hayes MHS and Patterson DG [25]. It records patient-reported pain progression or compares pain severity between patients with similar conditions. VAS scores range from 0 to 100 mm along a 10-cm line, with higher scores indicating greater pain intensity [26]. Cut-off points for postoperative pain are: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm) [27].

Post-procedure patient satisfaction was also recorded as excellent, good, or fair [28-30].

## STATISTICAL ANALYSIS

Data were entered into an Excel sheet and analysed using Statistical Packages of Social Sciences (SPSS) (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism. Numerical variables were summarised using means and standard deviations, while categorical variables were described using counts and percentages. Paired t-tests were used to account for correlations in paired data. A p-value≤0.05 was considered statistically significant.

## RESULTS

In present study, the mean age of participants was 43.70±8.96 years. Of the 30 participants, 26 (86.7%) were females and 4 (13.3%) were males. Age distribution was as follows: 31-40 years, 46.7%; 41-50 years, 30%; and 51-60 years, 23.3% [Table/Fig-5].

| Parameters | n (%) |
|---|---|
| **Age range (in years)** | |
| 31-40 | 14 (46.7%) |
| 41-50 | 9 (30%) |
| 51-60 | 7 (23.3%) |
| Total | 30 (100%) |
| **Gender** | |
| Female | 26 (86.7%) |
| Male | 4 (13.3%) |
| Total | 30 (100%) |

**[Table/Fig-5]:** Age and gender distribution of participants (N=100).

**VAS score:** At baseline (0-week), the mean VAS score was 76.33±8.899; SE=1.625. At 12 weeks, the mean VAS score decreased to 49.00±9.229; SE=1.685, and at 24 weeks, it further reduced to 31.33±7.761; SE=1.417. This indicates a gradual reduction in pain among study participants [Table/Fig-6].

| Parameters | | Mean±Std. deviation | Std. error mean |
|---|---|---|---|
| Pair 1 | VAS (at 0 week) | 76.33±8.899 | 1.625 |
| | VAS (at 12$^{th}$ week) | 49.00±9.229 | 1.685 |
| Pair 2 | VAS (at 0 week) | 76.33±8.899 | 1.625 |
| | VAS (at 24$^{th}$ week) | 31.33±7.761 | 1.417 |
| Pair 3 | VAS (at 12$^{th}$ week) | 49.00±9.229 | 1.685 |
| | VAS (at 24$^{th}$ week) | 31.33±7.761 | 1.417 |

**[Table/Fig-6]:** Paired samples descriptive statistics for VAS Scores at different time points (0, 12, and 24 weeks).

Paired comparisons were performed as follows:

Pair 1: VAS at 0-week vs. VAS at 12-week

Pair 2: VAS at 0-week vs. VAS at 24-week

Pair 3: VAS at 12-week vs. VAS at 24-week

All three comparisons showed statistically significant improvement (Sig. 2-tailed <0.0001), indicating significant pain reduction over time [Table/Fig-7].

**KOOS score:** At baseline, the mean KOOS score was 65.17±7.769; SE=1.418. At 12 weeks, the mean KOOS score decreased to 44.53±6.824; SE=1.249, and at 24 weeks, it further improved to 35.27±6.669; SE=1.218, demonstrating progressive functional improvement [Table/Fig-8].

Paired comparisons were performed as follows:

Pair 1: KOOS at 0-week vs. KOOS at 12-week

Pair 2: KOOS at 0-week vs. KOOS at 24-week

Pair 3: KOOS at 12-week vs. KOOS at 24-week

All three comparisons showed statistically significant improvement (Sig. 2-tailed <0.0001), indicating significant improvement in pain, symptoms, daily activities, sports function, and quality of life over the study period [Table/Fig-9].

| Paired samples test | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Parameters | | Paired differences | | | | t | df | Sig. (2-tailed) |
| | | Mean±Std. deviation | Std. error mean | 95% confidence interval of the difference | | | | |
| | | | | Lower | Upper | | | |
| Pair 1 | VAS (at 0 week) - VAS (at 12th week) | 27.333±6.915 | 1.262 | 24.751 | 29.915 | 21.650 | 29 | <0.0001 |
| Pair 2 | VAS (at 0 week) - VAS (at 24th week) | 45.000±6.823 | 1.246 | 42.452 | 47.548 | 36.125 | 29 | <0.0001 |
| Pair 3 | VAS (at 12th week) - VAS (at 24th week) | 17.667±6.789 | 1.240 | 15.132 | 20.202 | 14.253 | 29 | <0.0001 |

**[Table/Fig-7]:** Paired samples samples test showing mean differences in Visual Analogue Scale (VAS) scores between baseline, 12 weeks, and 24 weeks.

| Paired samples descriptive statistics | | | |
|---|---|---|---|
| | | Mean±Std. Deviation | Std. error mean |
| Pair 1 | KOOS (at 0 week) | 65.17±7.769 | 1.418 |
| | KOOS (at 12th week) | 44.53±6.842 | 1.249 |
| Pair 2 | KOOS (at 0 week) | 65.17±7.769 | 1.418 |
| | KOOS (at 24th week) | 35.27±6.669 | 1.218 |
| Pair 3 | KOOS (at 12th week) | 44.53±6.842 | 1.249 |
| | KOOS (at 24th week) | 35.27±6.669 | 1.218 |

**[Table/Fig-8]:** Paired samples descriptive statistics for KOOS at different time points (0, 12, and 24 weeks).

In the present study, there was a gradual reduction in pain as measured by VAS and gradual improvement in functional outcomes and quality of life as measured by KOOS [Table/Fig-6,8]. Comparisons between 0 vs. 12 weeks, 0 vs. 24 weeks, and 12 vs. 24 weeks all showed statistically significant improvements for both VAS and KOOS. Similarly, Khuba S et al., reported significant reductions ($p<0.05$) in VAS and OKS scores at 0, 4, and 24 weeks, with no adverse effects [31].

Joshi Jubert N et al., in a prospective, randomised, double-blinded clinical trial, considered changes in VAS scores at one month as the primary outcome, with secondary variables including VAS, KOOS,

| Paired samples test | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Parameters | | Paired differences | | | | t | df | Sig. (2-tailed) |
| | | Mean±Std. deviation | Std. error mean | 95% confidence interval of the difference | | | | |
| | | | | Lower | Upper | | | |
| Pair 1 | KOOS (at 0 week) - KOOS (at 12th week) | 20.633±4.803 | 0.877 | 18.840 | 22.427 | 23.530 | 29 | <0.0001 |
| Pair 2 | KOOS (at 0 week) - KOOS (at 24th week) | 29.900±7.068 | 1.290 | 27.261 | 32.539 | 23.171 | 29 | <0.0001 |
| Pair 3 | KOOS (at 12th week) - KOOS (at 24th week) | 9.267±4.425 | .808 | 7.614 | 10.919 | 11.470 | 29 | <0.0001 |

**[Table/Fig-9]:** Paired samples t-test results for KOOS scores at different time points between baseline, 12 weeks, and 24 weeks.
t-test

**Patient satisfaction:** Post-procedure, patient satisfaction was reported as excellent in 24 patients (80%), good in 4 patients (13.33%), and fair in 2 patients (6.67%) (N=30, 100%).

No adverse effects or complications were reported in any of the participants following PRP injection.

## DISCUSSION

In present study, there were 30 participants, of whom 26 were females and 4 were males, with ages ranging from 31 to 60 years. The mean age of participants was 43.70±8.96 years. Khuba S et al., in their retrospective study, evaluated 31 patients (20 females, 11 males) who received PRP therapy for OA, with a mean age of 53.9 years (range: 42-79 years) and a follow-up of 5.53±2.35 years [31].

In present study, a single intra-articular PRP injection was administered, and outcome parameters were assessed using VAS and KOOS at baseline, 12 weeks, and 24 weeks. Khuba S et al., suggested that a single intra-articular PRP injection may be safe and effective for pain relief and functional improvement for up to six months in patients with early-stage OA, assessed using VAS and Oxford Knee Score (OKS) at 0, 4, and 24 weeks [31].

Similarly, Sun SF et al., studied 41 patients with knee OA (Kellgren-Lawrence grade 1-2) who received a single PRP injection. Assessments at 0, 4, 12, and 24 weeks showed that a single PRP injection improved pain and function for six months, supporting the use of a one-injection regimen in clinical practice [32].

Parmanantham M et al., compared the functional outcomes of single versus multiple intra-articular PRP injections in early knee OA [33]. They concluded that, in terms of VAS, single PRP injections (S-PRP group) provided lower pain scores than multiple injections (M-PRP group) upto 12 weeks. However, at 24 weeks, single PRP injections were no more effective than multiple injections, while the M-PRP group showed greater pain reduction on follow-up. There was no statistically significant difference between groups on the WOMAC score [33].

and quality of life assessed using Short Form (SF)-36 at 1, 3, and 6 months post-treatment [34]. A systematic review and meta-analysis by Xiong Y et al., including 24 Randomised Controlled Trails (RCTs) with 1,344 patients, concluded that PRP injections effectively improve functional activity and provide analgesic effects in patients with OA [35]. Another meta-analysis by Dong Y et al., demonstrated that intra-articular PRP injections produce better outcomes in knee OA in terms of pain reduction and functional improvement [36].

Regarding RA, Aletaha D and Smolen JS evaluated the progression of joint damage and remission in RA, concluding that scientific advances have improved therapies capable of preventing irreversible joint damage in up to 90% of patients, with a treat-to-target strategy aimed at preventing RA-related disability [3,4].

Badsha H et al., in a case series, reported the use of PRP for RA. While PRP may help reduce joint inflammation by modulating synovial cell proliferation and differentiation and inhibiting catabolic pathways, its use in RA remains limited. They administered PRP (2-4 mL) to four RA patients with inadequate response and persistent pain despite intra-articular steroids. All patients showed improvement in VAS and Disease Activity Score 28 (DAS28) at 4 and 8 weeks post-injection, with effects sustained for up to one year [6].

Studies suggest that the high concentration of platelets and growth factors in PRP may help reduce inflammatory factors, accelerate neovascularisation in joints, and improve joint homeostasis by limiting synovial hyperplasia and decreasing cytokine levels without disrupting native cartilage tissue, resulting in clinical improvement and increased functionality [8,13].

Anitua E et al., studied that autologous platelets act as a source of proteins for healing and tissue regeneration. Platelets also release substances that promote tissue repair and influence the reactivity of vascular and other blood cells in angiogenesis and inflammation. They contain storage pools of growth factors, including Platelet

Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF), as well as cytokines [5].

Frisbie DD et al., assessed the clinical, biochemical, and histologic effects of intra-articular administration of Autologous Conditioned Serum (ACS) in the treatment of experimentally induced OA in horses. Evaluations included clinical assessment of lameness and synovial fluid analysis (performed biweekly), as well as gross pathologic and histologic examinations of cartilage and synovial membrane samples at necropsy. No treatment-related adverse events were detected. ACS-treated horses demonstrated significant clinical improvement in lameness compared with placebo-treated horses. In OA-affected joints, ACS treatment significantly decreased synovial membrane hyperplasia compared with placebo-treated joints. Although not statistically significant, ACS-treated joints also appeared to have less gross cartilage fibrillation and synovial membrane hemorrhage. Additionally, synovial fluid concentrations of interleukin-1 receptor antagonist increased following ACS treatment. Overall, ACS treatment led to significant clinical and histologic improvement in OA-affected joints compared with placebo [13].

In the present study, no adverse effects or complications were observed in any participant following PRP injection. Similarly, Khuba S et al., reported no adverse effects in their study [31], Xiong Y et al., concluded that PRP injection therapy can be used safely [35], and Badsha H et al., observed no adverse effects in any patient [6]. These findings suggest that PRP may be a safe and effective therapy for patients with RA who fail to respond to established treatments.

Post-procedure patient satisfaction in present study was excellent in 80% of patients, good in 13.33%, and fair in 6.67%. Nair V et al., reported 37% "excellent," 30% "good," and 3% "poor" at nine months follow-up in terms of participant satisfaction, considering reductions in pain and improvements in knee range of motion [37]. Joshi Jubert N et al., in their study "PRP Injections for Advanced Knee OA: A Prospective, Randomised, Double-Blinded Clinical Trial," reported patient satisfaction as 52.94% "very good," 20.59% "good," 8.82% "regular" (fair), and 17.65% "poor" at six months [34].

Clinical implications: Autologous PRP can modify the anatomical and biochemical environment of the osteoarthritic knee, providing symptomatic relief (in terms of pain) and functional improvement. These findings corroborate the results of present study.

### Limitation(s)

Limitations of present study include the lack of access to past specific rheumatologic data for each patient, which restricted the ability to objectively quantify the severity of the initial disease and evaluate objective measures of healing. Objective radiological analysis would have provided stronger evidence.

## CONCLUSION(S)

The present study demonstrated statistically significant improvement in pain, functional activity, and quality of life following autologous PRP injection. Post-procedure patient satisfaction was excellent in most cases, and no adverse effects or complications were reported. Overall, the findings suggest that autologous PRP can be recommended to alleviate knee joint pain in patients with RA. A single intra-articular PRP injection was effective in reducing pain, improving activities of daily living, and enhancing quality of life without adverse effects. Multicentric randomised clinical trials with larger sample sizes using multiple autologous PRP intra-articular injections at regular intervals, along with objective indicators (biochemical, histopathological) and imaging assessments to evaluate OA progression or remission, are needed to further assess the efficacy of autologous PRP therapy in patients with different stages of knee OA and RA.

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