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Original Research Article

Intra-articular autologous conditioned plasma reduces pain in early osteoarthritis and improves stiffness in advanced osteoarthritis knee: a prospective observation

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ABSTRACT

Background: In this study, we aimed to investigate the effects of single-dose intra-articular autologous conditioned plasma injection as the treatment for early and advanced osteoarthritis knee.
Methods: A single centre-based prospective observational analysis was conducted among patients who opt for conservative management by intra-articular autologous conditioned plasma Injection between July 2022 to June 2023. Total 46 patients were included and analysed in study on 1, 3, and 6 months' follow-up after ACP injection. The WOMAC score and its sub scores were analysed and compared pre-procedure and on subsequent follow ups.
Results: A total of 46 patients were analysed in the study, with male predominance of 56.5% with mean BMI of 27.37±5.35. On KL grading, 34.8% patients had KL grade II Osteoarthritis, 52.2% had grade III and 13.0% had grade IV. On comparison of WOMAC score and its sub-scales, all the values were found to be statically significant while comparing before injection (p value <0.0001) and one month follow up and before injection and six months' follow-up (p value <0.0001).
Conclusions: Six months following intra-articular autologous conditioned plasma injection, there was a noteworthy decrease in pain in early stages of osteoarthritis and improvement in knee stiffness in advanced stages of osteoarthritis as compared to the pre-treatment state.

Keywords: Osteoarthritis, Intra-articular, Autologous conditioned plasma, WOMAC score, Outcome analysis

INTRODUCTION

Knee osteoarthritis (OA) is a degenerative disease marked by pain, stiffness, weakness, and deformity in the affected areas.[1] OA is the primary cause of disability worldwide. Because of medical advances, OA has become more common over time as people live longer.[2] For patients with advanced arthritic knees, total knee arthroplasty (TKA) is still the preferred procedure.[3] However, managing OA requires significant resources from health systems, including outstanding TKA and any revisions or difficulties brought on by external factors.[4] Furthermore, patients in developing countries choose conservative care until a severe deformity appears. Conservative therapies should avoid or at least delay surgery related to osteoarthritis in order to ease pressure on hospitals and healthcare systems.[2] Satisfactory conservative management would reduce the frequency of TKAs, second

interventions for complications, and surgical revisions of operated patients.[5]

In recent years, biological therapies, such as Autologous Conditioned Plasma (ACP) or platelet-rich plasma (PRP) or cell therapies, have developed in regenerative medicine.[6] These therapies aim to modify or interfere with the mechanisms causing degeneration of the joints. IL-1 receptor antagonists (IL-1ra) and anti-inflammatory cytokines like IL-4, IL-10, and IL-13 are involved in ACP. Randomised controlled clinical trials have demonstrated the potential benefits of ACP therapy for improving the course and symptoms of osteoarthritis.[7] Platelets become activated and release proliferative and morphogenic proteins outside the circulation, which is how platelet-derived growth factor work with PRP.[8] PRP promotes angiogenesis, cellular migration, extracellular matrix synthesis, and cell proliferation.[9] Current trends involve using ACP instead of PRP since recent research comparing the efficacy and superiority of long-term ACP and PRP treatments revealed that ACP treatment was more successful than PRP treatment.[10] Sufficient discussion of the use of ACP in osteoarthritis can be found in the literature currently available. Patients' satisfaction and the outcome data, however, require improvement. Our objective in this research was to examine the impact of an intra-articular single-dose autologous conditioned plasma injection on the course of treating both early-stage and advanced osteoarthritis of the knee.

METHODS

A single centre-based prospective observational analysis was conducted among patients of osteoarthritis who underwent autologous conditioned plasma injection from July 2022 to June 2023. An ethical clearance was taken from the institutional ethical clearance committee. Written and informed consent was taken from all patients included in the study.

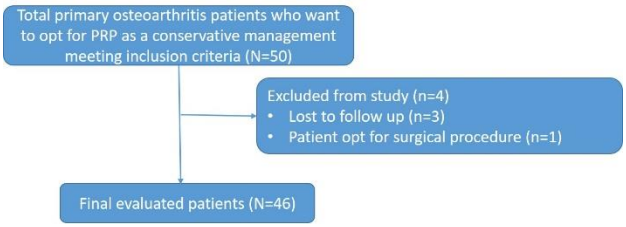

Figure 1: Study and inclusion of cases.

The study included patients with primary osteoarthritis who preferred conservative therapy. Excluded from the analysis were patients who had undergone high tibial osteotomy, knee replacement surgery, prior history of surgical intervention in the knee, prior history of knee joint infection, and prior history of knee ligament reconstruction or repair. Fifty patients meeting the aforementioned criteria were enrolled in the trial for the whole period; three patients were lost to follow-up at six months of the final follow-up, and one patient chose to have a total knee replacement during the first six months of the study. Hence, 46 patients were analysed for outcome analysis (Figure 1).

Protocol of ACP administration

We began injecting autologous conditioned plasma intra-articularly for all of our patients, choosing a conservative approach and being willing to continue injecting ACP after July 2022. Individuals who chose to get an intra-articular ACP injection were chosen based on acceptance criteria. Patients having bilateral knee osteoarthritis were offered ACP injections on the most affected side only. The standard protocol for ACP preparation on the Arthrex ACP® Double-Syringe System was adhered to. Both the inner and outer syringes were primed by pulling the plungers all the way back and forth. Using the suggested 19-gauge butterfly needle, the patient's 15 mL of venous blood was gently extracted, and the syringe was closed with a cap.

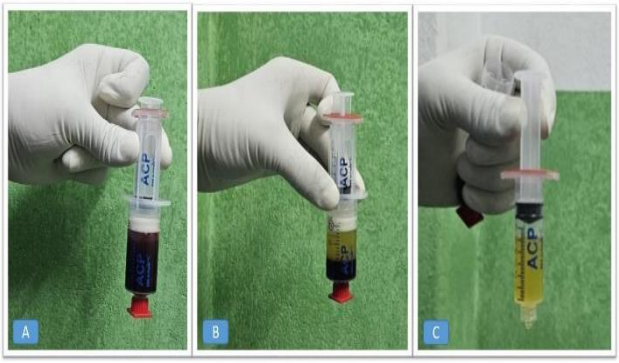

Figure 2: Preparation of ACP: (A) extracted patients' blood in double loaded syringe; (B) plasma and sediment RBCs after centrifugation; (C) platelet rich plasma ready for injection.

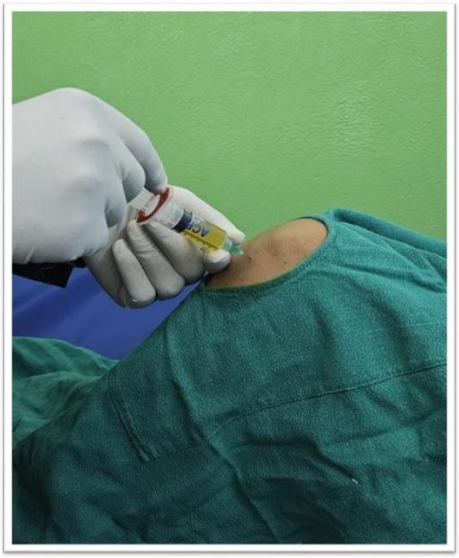

Figure 3: Injection of intra-articular ACP using standard protocol under aseptic precautions.

The centrifuge was operated for five minutes at 1500 rpm with the syringe and a suitable-sized counterweight in the opposite bucket. The syringe was carefully taken out of the way so that red blood cells and plasma wouldn't mix. 4-6 mL of ACP were transferred from the larger outer syringe into the smaller inner syringe by slowly pushing down on the red wings of the syringe. The tiny inner syringe was then removed by unscrewing it (Figure 2). The prepared ACP was then injected into the patient's knee using the standard surgical technique under aseptic precaution (Figure 3).

Outcomes measurements

An independent observer noted all outcomes prior to the procedure and on subsequent visits. Patient's age, sex, side involved, height, weight, Body mass index (BMI), co-comorbid condition, and Osteoarthritis grade on weight-bearing plain radiograph anteroposterior view by Kellgren-Lawrence (KL) grade was done.[11] The Western Ontario and McMaster University Arthritis Index (WOMAC) score was computed prior to injection, one month after the procedure, three months after the procedure, and at the conclusion of six months.[12] Each subscale (pain, stiffness, and physical function) on the WOMAC score was scored individually. On a 4-point scale, which is equivalent to None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4), the test questions are scored. Pain is rated on a 5-point scale from 0 to 4, with a maximum score of 20. Pain is evaluated in relation to walking, using stairs, sleeping, sitting or lying down, and standing up straight. The two factors that make up the stiffness scale are stiffness upon first awakening and later in the day. The scale runs from 0 to 4, with a maximum score of 10. The Physical Function test consists of 17 items that are graded from 0 to 4, with a maximum score of 68. The items are related to difficulties using stairs, getting in and out of a car, shopping, putting on and taking off socks, rising from bed, lying in bed, getting in and out of the bath, sitting, getting on and off the toilet, heavy and light domestic duties, and rising from sitting to standing.

Statistical Analysis

A Microsoft Excel spreadsheet was used to initially gather and tabulate the data. The continuous data were presented as means, standard deviations (SD), and percentages for the categorical variables. The results of the Shapiro-Wilk Test, which examined every parameter for normality, showed that they were all regularly distributed. The student T-test was used to compare continuous parametric variables for both groups. The current study employed two-sided statistical tests for all analyses, with a five percent significant threshold. When the P value was less than 0.05, the results were deemed statistically significant. The SPSS programme, version 25.0 for MAC, was used to analyse all test outcomes (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 46 patients were analysed in the study. Of them, 26 (56.5%) were males and 20 (43.5%) were females. ACP was injected in the right knee in 19 (41.30%) and the left knee in 27 (58.69%). The mean age of the patients included was 52.11±10.023 years, and the mean BMI was 27.37±5.35. In the co-morbid condition, 7 (15.2%) had diabetes, 5 (10.90%) had hypertension, and 2 (4.3%) had a thyroid disorder. On the weight-bearing plane radiograph, 16 (34.8%) patients had KL grade II Osteoarthritis, 24 (52.2%) had grade III and 6 (13.0%) had grade IV (Table 1 and Table 2).

The mean stiffness scale was 5.58±1.11, the mean pain scale was 13±2.171 out of 20, the mean function scale was 38.02±5.55 out of 68, and the final mean WOMAC scale was 56.60±7.84 prior to ACP injection. The mean pain scale out of 20 was 11.06±2.17, the mean stiffness scale out of 8 was 3.47±1.098, the mean function scale out of 68 was 34.02±5.45, and the final mean WOMAC scale was 48.56±7.99 during the month that followed the ACP injection. The mean pain scale out of 20 was 9.17±2.33 over the three months after the ACP injection, the mean stiffness scale out of 8 was 2.28±0.92, and the mean function scale out of 68 was 29.45±5.22. 40.91±7.56 was the final mean WOMAC scale. The mean pain scale out of 20 was 9.04±30.4, the mean stiffness scale out of 8 was 2.02±0.82, the mean function scale out of 68 was 27.60±6.05, and the final mean WOMAC scale was 38.67±9.43 throughout the six months after the ACP injection. Every value on the sub-scales was found to be statistically significant when comparing the results before the injection and the one-month follow-up and the results before the injection and the six-month follow-up (p value <0.0001) (Table 3).

Table 1: Baseline characteristic of study.

Characteristic		Total (N=46) N (%)
Gender	Male	26 (56.5)
	Female	20 (43.5)
Side	Right	19 (41.30)
	Left	27 (58.69)
KL grading	I	0 (0)
	II	16 (34.8)
	III	24 (52.2)
	IV	6 (13.0)
Co-morbidities	Diabetes	7 (15.2)
	Hypertension	5 (10.90)
	Hypothyroidism	2 (4.3)

Table 2: Baseline characteristic of study.

	Minimum	Maximum	Mean	Std. Deviation	Variance
Age (years)	32	73	52.11	10.023	100.455
Weight (kg)	50	98	71.28	12.261	150.341
Height (cm)	148	182	162.46	8.671	75.187
BMI	18	44	27.37	5.358	28.704

Table 3: Outcome analysis of WOMAC score.

	Pain (20) Mean±SD	Stiffness (8) Mean±SD	Function (68) Mean±SD	WOMAC Mean±SD
Before injection	13±2.171	5.58±1.11	38.02±5.55	56.60±7.84
1 month follow-up	11.06±2.17	3.47±1.098	34.02±5.45	48.56±7.99
3 months follow-up	9.17±2.33	2.28±0.92	29.45±5.22	40.91±7.56
6 months follow-up	9.04±30.4	2.02±0.82	27.60±6.05	38.67±9.43
P-value (before injection Vs. 1 month follow-up)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
P-value (1 month follow-up Vs. 3 months follow-up)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
P-value (3 months follow-up Vs. 6 months follow-up)	0.6714*	0.0216*	0.0009*	0.0077*
P-value (before injection Vs. 6 months follow-up)	<0.0001*	<0.0001*	<0.0001*	<0.0001*

*Paired student t-test.

Table 4: Outcome analysis on WOMAC score according to KL grades.

		Pain (20) Mean±SD	Stiffness (8) Mean±SD	Function (68) Mean±SD	WOMAC Mean±SD
KL grade II (N=16)	Before Injection	11.27±1.26	4.62±0.599	32.56±3.63	48.56±5.04
	1 month follow-up	9±1.54	2.81±0.634	28.62±3.38	40.43±4.384
	3 months follow-up	7.18±2.37	1.62±0.59	24.81±3.97	33.62±6.37
	6 months follow-up	6.25±2.91	1.375±0.59	21.87±4.31	29.5±6.53
	Difference between before injection and 6 months follow-up	5.12±1.86	3.25±0.75	10.68±4.10	19.06±5.59
KL grade III (N=26)	Before injection	13.66±1.24	5.83±0.84	40.04±3.63	59.54±4.81
	1 month follow-up	12.04±1.67	3.54±0.86	36±3.43	51.58±4.82
	3 months follow-up	10.33±1.43	2.5±0.64	31.70±3.80	44.54±4.35
	6 months follow-up	10.33±2.22	2.29±0,73	30.20±4.01	42.83±6.36
	Difference between before injection and 6 months follow-up	3.33±2.32	3.54±0.95	9.83±4.64	16.70±7.155
KL grade IV (N=6)	Before injection	14.66±0.74	7.16±0.68	44.5±3.25	66.33±3.03
	1 month follow-up	12.66±0.94	5.00±1.29	40.5±3.81	58.16±5.42
	3 months follow-up	9.83±1.46	3.16±1.34	32.83±4.52	45.83±5.95
	6 months follow-up	11.33±2.42	2.66±0.74	32.50±5.12	46.50±7.22
	Difference between before injection and 6 months follow-up	3.33±2.62	4.50±0.50	12.00±2.76	19.83±5.04

Based on the KL grade analysis, the mean differences in pain, stiffness, function, and WOMAC score were 5.12±1.86, 3.25±0.75, 10.68±4.10, and 19.06±5.59 between the pre-injection and 6-month follow-up periods for KL grade II. For KL grade III, the mean difference in pain from pre-injection to the 6-month follow-up was 3.33±2.32, for stiffness it was 3.54±0.95, for function it was 9.83±4.64, and for WOMAC score it was 16.70±7.155. The KL grade IV mean difference in pain between pre-injection and 6-month follow-up was 3.33±2.62, for stiffness it was 4.50±0.50, for function it was 12.00±2.76, and for the final WOMAC score, it was 19.83±5.04 (Table 4).

When comparing the difference in outcome between KL grade II and KL grade III before injection and 6 months afterward, it was discovered that there was a significant difference in pain (p value=0.016), but not in stiffness (p value=0.323), function (p value=0.564), or WOMAC score (p value=0.286). When the KL grade III and KL

grade IV outcomes from before the injection were compared to the 6-month follow-up, it was discovered that there was a significant difference in function (p value=0.029), but not in pain (p value=1.000), function (p value=0.298), or WOMAC score (p value=0.338). On comparison of difference of outcome between before injection and 6 month follow up KL grade II and KL grade IV, it was found to be significant difference in terms of function (p value=0.0017), however no significant difference in terms of pain (p value=1.004), function (p value=0.479) and WOMAC score (p value=0.781) (Table 5).

Table 5: Comparison of outcome scale according to KL grade.

		Pain (20) Mean±SD	Stiffness (8) Mean±SD	Function (68) Mean±SD	WOMAC Mean±SD
KL grade II vs KL grade III	Before injection	<0.0001+	<0.0001+	<0.0001+	<0.0001+
	1 month follow-up	<0.0001+	0.007596+	<0.0001+	<0.0001+
	3 months follow-up	<0.0001+	0.00015+	<0.0001+	<0.0001+
	6 months follow-up	<0.0001+	0.000121+	<0.0001+	<0.0001+
	Difference between before injection and 6 months follow-up	0.016239+	0.323058+	0.564251+	0.286478+
KL grade III Vs KL grade IV	Before injection	0.079787+	0.001832+	0.013093+	0.003541+
	1 month follow-up	0.40134+	0.003427+	0.011446+	0.008813+
	3 months follow-up	0.468346+	0.101501+	0.552197+	0.567195+
	6 months follow-up	0.359211+	0.290637+	0.264092+	0.245629+
	Difference between before injection and 6 months follow-up	1.000000+	0.029509+	0.298964+	0.338102+
KL grade II vs KL grade IV	Before injection	<0.0001+	<0.0001+	<0.0001+	<0.0001+
	1 month follow-up	<0.0001+	<0.0001+	<0.0001+	<0.0001+
	3 months follow-up	0.024521+	0.002071+	0.000958+	0.000924+
	6 months follow-up	0.000229+	0.000202+	0.000181+	<0.0001+
	Difference between before injection and 6 months follow-up	0.104874+	0.001773+	0.497896+	0.781117+

Systemic problems were not reported by any of the participants in our research sample. Two patients complained local site pain, which was treated with analgesics. After two months after ACP injection, one patient decided to have a total knee replacement. A patient who co-morbidly had diabetes mellitus reported having a superficial infection over the injection site; this infection was treated with systemic and local antibiotics and resulted in a negative knee aspirate. During their six-month follow-up, the remaining patients received treatment without incident.

DISCUSSION

This experiment specifically studied the impact of intra-articular ACP injections on the treatment of early-stage osteoarthritis in the knee. The number of surgeries necessary for OA therapy may be decreased by employing ACP as a conservative therapeutic method. It has been shown that by functioning as an anti-inflammatory and analgesic and promoting angiogenesis, cell proliferation, and collagen production, it can treat avascular wounded tissues with low self-healing potential, such as tendons, ligaments, and cartilage.[13] Numerous studies have indicated that various growth factors and inflammatory cells may be involved in how PRP treats OA.[14–16] However, the precise mechanism is yet unknown. Numerous plasma proteins in PRP activate fibrinogen to form fibrin scaffolds, induce chondrocyte proliferation and differentiation, and facilitate cartilage injury recovery.[17–19]

Additionally, a wide variety of PRP injections are currently offered. Based on the leukocyte and fibrin content of PRP products, Dohan Ehrenfest et al. initially suggested classifying them into the following four groups.[20] There are four types of platelet-rich plasma: leukocyte-poor or pure platelet-rich plasma (LP-PRP) has high platelet concentrations but little to no leukocytes; leucocyte- and platelet-rich plasma (LR-PRP) has high platelet concentrations and a significant number of leukocytes; leucocyte-poor or pure platelet-rich fibrin (PPRF) has rich circulating fibrin and little to no leukocytes; and finally leucocyte- and platelet-rich fibrin (L-PRF) has both a significant number of leukocytes and rich circulating fibrin. For injectable osteoarthritis therapy, two low-density fibrin formulations- LR-PRP and LP-PRP- are frequently utilised.[20] In contrast, ACS/PRGF has stronger proof of its efficacy than either LP or LR PRP. Several writers propose that platelets' anti-inflammatory cytokines, such as IL-1ra, TGF-β, and IL-10, are what cause PRP's advantages, whereas leukocytes, which

contain pro-inflammatory cytokines and metalloproteases, cause cartilage degradation. In this study, we used a ACP double syringe system with leucocyte-poor or pure platelet-rich fibrin (PPRF) with rich circulating fibrin and little to no leukocytes.

Most of the most recent trials have used intraarticular injections, and some researchers have looked into the ideal injection dosage. Three injections spaced one month apart appear to generate superior outcomes in short-term clinical follow-up; 66 of the 191 knees in Huang et al's 2017 retrospective analysis even exhibited improved outcomes.[21] Most authors prefer to receive repeated injections once every three weeks, twice a week, or once a month in order to maximise its advantages. A few clinical studies showed that a single injection was useful in treating early-stage knee OA.[11] In a prospective cohort research conducted in 2013 by Jang et al. on 90 joints with knee OA, every patient showed improved results after six months.[22] According to a 2013 case report by Halpern et al., all 18 joints with KL grades 1-2 of knee OA showed statistically significant improvements in pain and function. The clinical outcome in this trial improved dramatically after we injected a single dosage of ACP, as observed over the six-month follow-up period.[23] Our research was unable to determine if a single dose produces more significant results than numerous injections.

There are also questions about the effectiveness of ACP and its duration of action. The study, according to Jang et al., showed a drop in the findings at 12 months compared with the six-month follow-up, even though they were still above the baseline, and the ACP effect was expected to endure for 8.8 months.[22] In contrast, the duration of ACP's efficacy has yet to be evaluated in our study. One patient chose to have surgery during the study period because they were dissatisfied with the outcome of ACP.

According to Annaniemi et al's research, patients with KOA who are classed KL 1 seem to improve the most from treatment, with ACP intra-articular injections having a decreasing effect as KOA progresses. However, significant improvements are still visible in KL 1-3 grades.[24] In our study, we found that there was significant decrease in pain in early stages of osteoarthritis and improvement in knee stiffness in advanced stages of osteoarthritis.

Most of the adverse effects of ACP, according to published studies, are modest and temporary symptoms including oedema and soreness at the injection site. Uncommon side effects can include syncope, lightheadedness, headache, nausea, gastritis, sweating, and tachycardia in addition to pain and rigidity.[13] The study found that mild joint pain at injection site and local site infection following injection were adverse outcomes. In one case, the pain disappeared with analgesics, however one patient with pain opt for total knee replacement.

Further investigation into different injection schedules for ACP therapy of OA knee is still necessary. This study highlights the potential significance of intra-articular ACP injection treatment in conservative management and provides significant insights into the effects of this therapeutic method on OA knee. The observed decreases in stiffness, discomfort, and physical function imply that further research is necessary to demonstrate the safety and effectiveness of the therapy technique in a wider range of patient populations, especially in the form of randomised controlled trials.

It is essential to highlight that the study has some limitations, including the observational character of the research and the lack of a control group that allows for direct comparison. The small sample size may limit the findings' potential for generalisation. Long-term follow-up research would also be beneficial in evaluating the long-term advantages and possible drawbacks of intra-articular ACP injections.

CONCLUSION

In short-term follow-up, ACP injection seems to be beneficial in early symptomatic OA knees. Six months following therapy, there was a noteworthy decrease in pain in early stages of osteoarthritis and improvement in knee stiffness in advanced stages of osteoarthritis as compared to the pre-treatment state.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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