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COMPARISON BETWEEN INTRA-ARTICULAR PLATELET RICH PLASMA VERSUS CORTICOSTEROIDS IN THE TREATMENT OF PATIENTS WITH GRADE II AND III KNEE OSTEOARTHRITIS

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ABSTRACT

Introduction: Knee osteoarthritis is the most prevalent type of arthritis, a common disease in aged adults. Osteoarthritis of knee is the most common worldwide degenerative joint disease and is a common condition associated with pain and morbidity which significantly impacts the patient's mobility and quality of life. Pharmacological treatment for knee osteoarthritis, such as intra-articular platelet-rich plasma is a promising treatment option. It accelerates the process of healing, ligament repair, cartilage regeneration, and bone formation when given in supra physiological doses. Corticosteroids produce an immediate reduction of the patient's pain as well as an improvement in the patient's mobility and quality of life, but with a limited long-term efficacy.

Aim And Objectives: To evaluate and compare the clinical benefits of intra-articular platelet rich plasma and commonly used corticosteroid in the treatment of patients with grade II and III knee osteoarthritis.

Materials and Methods: This prospective study was conducted in the department of Orthopedics,Apollo Hospital Navi Mumbai. In this randomized study 30 patients, radiologically and symptomatically confirmed knee osteoarthritis (Kellgren-Lawrence grade II and III) were enrolled. The enrolled patients were evaluated from out-patient department. The enrolled patients fulfill all inclusion criteria. The selected patients were randomly distributed in two groups A and B with equal number of patients. Group A patients were given 6ml intra-articular platelet-rich plasma and Group B patients were given methyl prednisolone 80 mg plus lignocaine 5ml of 2%. The pain and function of the target knee were evaluated by the VAS, IKDC, and KSS scales at the baseline, 1 week, 5 weeks, 15 weeks, 30 week, and 1 year after treatment.

Results: Both groups shows significant relief in pain and improvement in the knee function in very short term follow-up of one week. Up to the follow-up of 6 weeks a high improvement was observed for both groups with no significant differences for the VAS, IKDC or KSS. Group A showed significant improvements in all scores as compared to group B after the follow-up of 18 weeks. The patients in group A showed better outcomes than group B patients in a longer follow-up up to 48 weeks.

Conclusion: Intra articular platelet rich plasma produce superior outcomes when compared with corticosteroid for symptomatic management in the treatment of patients with knee osteoarthritis grade II and III, including improved pain management, less joint stiffness and better participation in daily activity.

KEYWORDS

Meta-analysis, Knee, Osteoarthritis, Platelet-rich plasma, Corticosteroids, Intra-articular

INTRODUCTION

Knee osteoarthritis (OA) is a slowly progressive chronic disease characterized by pain, loss of function, and deformity of the affected joints. In the past, OA was considered a normal sign of aging and it was described as a degenerative disorder that mainly causes cartilage loss [1]. However, more recent studies have shown that OA occurs and evolves due to the interaction of multiple risk factors affecting the whole joint including the cartilage, subchondral bone, synovium, ligaments, and menisci [2]. Adding to this, the burden of knee OA continues to grow [3], estimated to affect between 10 and 25% of patients over 60 [4], alongside a population that is increasingly co-morbid and obese [3, 5].Knee osteoarthritis is a common condition associated with pain and morbidity [6]. It is also the second leading cause of disability and a heavy economic and social burden [7].

Knee osteoarthritis is divided into five grades (Kellgren-Lawrence (KL) grading) as normal (Grade 0), minor (Grade 1), mild (Grade 2), moderate (Grade 3) and severe (Grade 4). Grade 2 OA of the knee is considered a mild stage of the condition. This stage will reveal greater bone spur growth but the cartilage is usually still at a healthy size. However this is the stage where people may first begin experiencing symptoms such as pain after a long day of walking or running, greater stiffness in the joint when it is not used for several hours and tenderness when kneeling or bending. Grade 3 OA is classified as moderate OA. In this stage cartilage between bones shows obvious damage and the space between bones begins to narrow. People with grade 3 OA of knee are likely to experience frequent pain, while walking, running, bending and kneeling.

Management is directed to reduce pain, improve function and limit disease progression [8]. Currently, no disease-modifying treatment has been approved. Non-pharmacological treatments include patient education, exercises, weight reduction, walking supports, bracing, acupuncture, and electromagnetic therapy [9, 10]. Pharmacological treatments include topical and oral NSAID [11], intra-articular (IA) injections of corticosteroids, visco-supplements, and blood-derived products, including platelet-rich-plasma [12]. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have suboptimal effectiveness. Surgical treatment can reduce pain and improve joint mobility and function; however, it is associated with significant cost and potential morbidity [13, 14]. Corticosteroids and hyaluronic acid injections provide short-term reduction in pain of OA [15]. Recently, placebo-controlled studies have shown that intra articular platelet-rich plasma can relieve pain, improving knee function and quality of life [16, 17]. Despite numerous studies and metaanalyses, the efficacy of intra articular platelet rich plasma in patients with knee OA remains debated and uncertain worldwide [18-20].

In this study we have used corticosteroids and intra articular platelet rich plasma for the treatment of patients with knee osteoarthritis of grade II and III. Corticosteroids produce an immediate reduction of the patient's pain as well as an improvement in the patient's mobility and quality of life, but with a limited long-term efficacy. Iintra-articular platelet-rich plasma is a promising treatment option. It accelerates the process of healing, ligament repair, cartilage regeneration, and bone formation when given in supra physiological doses. The objective of this study was to evaluate the clinical benefits of platelet rich plasma when injected into the intra-articular space compared to a corticosteroid (methyl prednisolone 80 mg plus lignocaine 2%) in the treatment of patients with knee osteoarthritis grade II and III.

MATERIALS AND METHODS

This prospective and randomized study was conducted in the department of Orthopedics, Apollo Hospital Navi Mumbai from March 2020 to February 2021. In this randomized study we compare intra articular platelet rich plasma versus methylprednisolone 80 mg in patients with grade II and III knee osteoarthritis. The severity of OA was defined by Kellgren-Lawrence (KL) grading [21].

Inclusion Criteria

- Patients with clinical and radiological diagnosis of knee OA either KL Grades 2 and 3 without knee deformity.
- Symptomatic for at least 6 months with pain of >40 mm on a 100 mm as per VAS pain despite. treatment.

- Above the age of 50 years
- Swelling or reduced range of motion in the knee joint.

Exclusion Criteria

- KL Grade 4
- Severe mechanical deformity or received IA injection of HA in the past 6 months.
- Patients who had received either oral, injectable steroid during the 3 months before the study.
- Uncontrolled diabetes mellitus
- Secondary knee osteoarthritis
- Post-traumatic knee osteoarthritis
- Pregnancy, breastfeeding, oncological diseases, endocrine diseases, rheumatoid arthritis.

Patients who met the inclusion criteria were included. In this study we enrolled 30 patients, radiologically and symptomatically confirmed knee osteoarthritis (Kellgren-Lawrence grade II and III). Demographic variables such as age, sex and the degree of radiological involvement were collected. The selected patients were randomly distributed in two groups A and B with equal number of patients. Group A patients were treated with 6ml of intra-articular platelet-rich plasma and group B patients were treated with methylprednisolone 80 mg plus lignocaine 5ml of 2% at baseline, which was repeated at 12 weeks. The use of analgesics, physiotherapy was not restricted during the study period for both groups. The pain and function of the target knee were evaluated by the VAS, KSS and IKDC scales at the baseline, 1 week, 6 weeks, 12 weeks, 18 weeks, 24 weeks and 48 weeks after treatment. Because of the heterogeneity of outcome measures, a best-evidence synthesis [22] was used instead of a meta-analysis. The results of the quality assessments of the individual studies were used to classify the level of evidence [23]. This qualitative analysis was performed with 5 levels of evidence based on the quality and results of the included studies [24]. In addition, study methodological quality was analyzed using the Modified.

Coleman Methodology Score (MCMS) [25]. Descriptive statistics were calculated using the mean standard deviation for quantitative continuous data and frequencies with percentages for qualitative categorical data. Comparisons in outcome scores at pre and post-injection time points and between PRP and CS groups were made using the 2-proportion z-test calculator using alpha 0.05 because of the difference in sample sizes between compared groups.

Interventional Procedure

The patient was placed in the supine position with the knee in full extension. Under aseptic conditions, in group A intra articular platelet rich plasma 6 ml and in group B corticosteroid 2ml (80mg) with 5ml of 2% lignocaine mixed in a single syringe was injected to knee joint. The intra-articular knee injection was performed under sterile conditions, without any local or general anesthesia, with 18G needle using an anterolateral approach. Echographic control allowed the correct needle positioning by direct visualization. 0.5 ml of CaCl2 (M/40) was injected for every 6 ml of PRP to activate platelets. The knees were immobilized for 10 min after injection. After this manipulation, an aseptic cool bandage was applied for 15 minutes for local compression. The patients were observed for half an hour for some common complaints as dizziness or sweating and were discharged. During the follow-up period, patients carried on their ordinary lives without any specific treatments or restrictions.

RESULTS

The study population consisted of 30 patients with grade II and III knee osteoarthritis. Kellgren and Lawrence grade of knee OA, 19 (63.33 %) of patients had grade 3 osteoarthritis and 11(36.37 %) patients had grade 2 OA, as shown in Table 1. In group A (PRP) the mean age of the patients was 59.23 years (range 40-70 years). The majority of patients 7 (46.80 %) belonged to age group of 51–60 years. Out of 15 patients, 11 (73.33 %) were males and 4 (26.67%) were females. The mean change in VAS pain from baseline to 24 weeks was 5.0± 1.3 statistically significant. In group B (CS) the mean age of the patients was 61.40 years (range 40-70 years). The majority of patients 9 (60 %) belonged to age group of 51–60 years. Out of 15 patients, 9 (60 %) were males and 6 (40%) were females. The mean change in VAS pain from baseline to 24 weeks was 2.9n± 1.7.

Both groups showed effective reduction in pain, and they improved the knee function after the first week of treatment. A significant reduction of pain from baseline for both groups was found 1 week after treatment (mean VAS change— Group A− 2.9 ± 2.1 and Group B − 3.5 ± 1.4, $p < 0.0001$). Similarly, significant function improvements from baseline were obtained in the first week for both groups (mean IKDC change in Group A 24.8 ± 15.7 and in Group B 37.1 ± 11.3 and mean KSS Change in Group A is 23.5 ± 12.6, Group B is29.7 ± 11.8). The highest change in the VAS score from the baseline was at 24 weeks for Group A patients (mean – 5.0 ± 1.3) and at 6 weeks in the group B patients (− 3.7 ± 1.7). The pharmacological effect of CS seemed to disappear 18 weeks after receiving treatment as all scores tended to worsen after this period. For instance, pain in Group B patients improved rapidly but, in general, worsened after 18 weeks of treatment, and the pain steadily increased in each follow-up visit. At the same time, in group A patients, a sustained improvement in pain relief up to 30 weeks, showing a small increase in pain in the 1-year evaluation follow-up. VAS score changes at 1 year showed a higher mean change from baseline in group A than the group B. Interestingly, the pain reduction and the knee functional improvement was not significant between both groups in the very short-term follow-up of 6 weeks. For all other outcome scores, there were significant differences between pretreatment and post-treatment results at any time, evaluated up to the follow-up 48 weeks. Knee function improvement was observed in both groups up to 18 weeks with no significant differences between groups ($p > 0.05$). At the follow up of 24 weeks group A presented a better significant improvement in the IKDC and KSS scores compared to the group B, which decreased in effectiveness up to 1 year. Maximum functional improvement and better patient expectation, satisfaction, and activity levels were observed after 15 weeks for the group A (mean change from baseline of 44.3 ± 12.9 and 28.2 ± 11.7 for IKDC) and after 6 weeks for the group B (mean change from baseline of 36.5 ± 13.5 and 26.1 ± 12.8 for KSS).

Table 1: Baseline Characteristics Of The Study Groups

		Group A	Group B
Mean age in years		59.23±6.70	61.40±7.20
Sex	Male	11 (73.33%)	9 (60%)
	Female	4 (26.67%)	6 (40%)
Body mass index (Kg/M2)		29.23± 3.60	27.90± 2.90
Mean duration of OA in years		6.7± 1.30	7.9±1.60
Kellgren and Lawrence grade of knee OA	Grade 0	0	0
	Grade 1	0	0
	Grade 2	3	4
	Grade 3	12	11
	Grade 4	0	0
VAS Baseline mean		6.8 ± 1.4	6.5 ± 1.6
KSS Baseline mean		62.8 ± 6.9	58.8 ± 7.9
IKDC Baseline mean		39.1 ± 11.2	31.2 ± 8.6

Table 2 Primary Outcome And Secondary Outcomes In Per-protocol Population During The Follow-up Of The Study

Weeks	VAS Mean		KSS Mean		IKDC Mean	
	Group A	Group B	Group A	Group B	Group A	Group B
Baseline	6.8 ± 1.4	6.5 ± 1.6	62.8 ± 6.9	58.8 ± 7.9	39. 1 ± 11.2	31.2 ± 8.6
1 Week	3.9 ± 2.2	3.0 v 1.7	86.3 ± 11.4	88.5 ± 9.2	63.9 v 13.7	68.3 ± 12.6
6 Weeks	3.0 ± 1.9	2.8 ± 1.5	90.7 ± 9.8	85.7 ± 10.4	71.5 ± 13.9	66.5 ± 13.9
12 Weeks	2.1 ± 1.3	3.6 ± 1.7	93.8 ± 7.9	78.3 ± 12.7	81.4 ± 14.3	60.6 ± 12.4
24 Weeks	1.8 ± 1.0	3.9 ± 1.9	94.9 ± 8.4	75.9 ± 11.9	86.1 ± 15.1	58.7 ± 14.6
48 Weeks	2.8 ± 1.4	4.5 ± 2.2	84.2 ± 11.8	62.6 ± 12.2	71.2 ± 15.8	42.2 ± 15.4

DISCUSSION

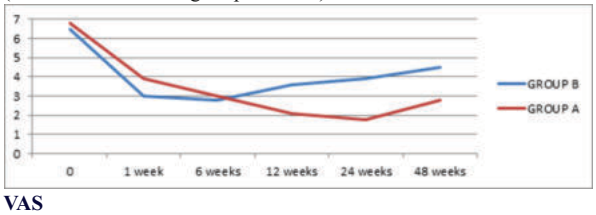
Treating OA non-operatively has been ongoing for several decades. Multiple studies have reported the use of PRP, and corticosteroids, among other agents in the non-operative treatment of knee osteoarthritis. In this prospective and randomized study we were comparing intra articular platelet rich plasma and corticosteroid injections for the symptomatic management of KL- grade II and III knee osteoarthritis and our meta-analysis shows that intra articular platelet rich plasma shows greater overall efficacy compared to corticosteroid injections over 12 months of follow-up. This effect

becomes statistically significant from 3 months onwards, and is most pronounced from 6 to 9 months, with the strongest evidence of benefit at 6 months post-injection. Mean changes in the scales and subscales between group A and group B from baseline to 24 weeks was statistically significant. Significant difference from baseline was seen as early as 6 weeks for all the outcome parameters in both groups. The decrease in pain for all scales and subscale scores was significantly greater for the group A. In group B, there was a decrease in efficacy at 12 weeks as compared to peak response at 6 weeks, which was statistically significant ($P < 0.05$), but significant decrease in efficacy at 24 weeks. With reference to CS injections, our results are in keeping with the literature, in that they appear equally efficacious to PRP injections at 1 month post-injection. A Cochrane review on the use of CS injections for knee OA conclude, that the effects of the injection decreases over time, with no evidence to suggest that an effect remains 6 months post-injection [26]. Similarly, both this review and another review of Level 1 studies found that the effect from CS injections were significant only at 1 week [26, 27], with a general consensus that there is little benefit from the injections after a period of 6 weeks [28]. Pain and stiffness scores in the PRP group continue to improve until 9 months post-injection, with statistical significance from three months onwards. This is supported by previous evidence by Shen et al. [29] and Filardo et al. [30], who suggested a sustained effect following PRP injections of up to 12 and even 24 months. The former study was a systematic review and meta-analysis investigating the temporal effect of PRP injections compared to control (including HA, CS, placebo and ozone) which reported superior treatment effects from PRP at 3, 6 and 12 months; the latter was a single arm study investigating whether beneficial effects from PRP persist. At 24 months, patient scores were still improved compared to baseline, but the median duration of effect was 9 months. Our study showed that 6–9 months was the time point when patients observed the greatest treatment effect from IA-PRP injections. In a review by Meheux et al. [31] comparing PRP to HA and placebo for knee OA, PRP was recommended to be reserved for patients with KL 1–3. This may be due to the ability of PRP to restore and protect cartilage [32, 33], as this may be more effective where there is more pre-existing joint cartilage. Gobbi et al. tried to determine the effectiveness of intra-articular PRP injections in active patients with knee OA and to evaluate clinical outcomes in patients with and without previous surgical treatment for cartilage lesions [34]. The PRP treatment showed positive effects in patients with knee OA. Operated and non-operated patients showed significant improvement by means of pain reduction and improved symptoms and quality of life. This recommendation is based on ranges used in the studies included in this review.

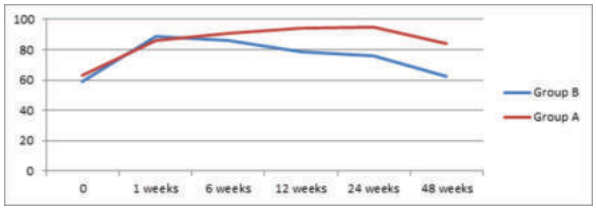
This study showed that a single intra-articular injection of PRP is more efficient than CS for treating moderate OA (Kellgren-Lawrence grades II–III). In this study, a single intra-articular injection of PRP resulted in significant pain relief for up to 12 months, with a maximum pain decrease after 3 months. This difference suggested that the number of PRP injections could be critical for the maintenance of the beneficial effect. In contrast to this, Patel et al. [35] did not find significant differences in WOMAC scores between single and double PRP injections for early OA at 6 weeks, 3 and 6 months.

Most of the studies of PRP commonly perform the first assessment of patients 1 month after treatment, making impossible the determination of the evolution in the first few days [36]. Based on this remark and on our personal experience that we have observed from this study, we evaluated the clinical outcome of the patients in the very short term (1 week). From our knowledge, this is the first PRP clinical study for early-stage knee OA that incorporated outcome assessment by means of this approach. We found that the analgesic effect of PRP in the very short term was comparable to CS, and the same was noticed for the knee function. The rapid reduction in pain observed upon treatment with PRP might be attributed to a combined effect, mainly due to the induction of endogenous cell endocannabinoids [37] together with the anti-inflammatory activity effect of PRP on chondrocytes [38, 39]. The variation in pain and knee function in the PRP group contributed to the sustained duration of the overall beneficial effects for up to 30 weeks, whereas in the CS group, a tendency to worsen after 5 weeks was registered. A recent metaanalysis reported the limitation of the beneficial effect of the CS 15 weeks after the end of treatment [40]. We hypothesized that the improvement of both parameters (pain and function) were mainly due to control of the inflammation of the knee rather than the trophic effect of PRP on cartilage. This rationale is due to the fact that it has not yet been demonstrated that the improvement of knee function after PRP treatment correlates with a volume increase of the articular cartilage [41-43].However, there is evidence that suggests that PRP has other effects on the joints other than the anti-inflammatory and this may probably explain why the group that received PRP had better results than the CS group. Even though the mechanism of action on improving cartilage repair remains unclear, it has been reported in the literature that PRP can induce tissue maturation characterized by increased cell proliferation and tissue stiffness [44]. These cells, in turn, produce more superficial zone protein that functions as a boundary lubricant that helps reduce friction and wear. Moreover, it has been reported that PRP can enhance HA secretion from synovial fibroblasts in arthritic patients, producing a lubricating effect that could reduce the shear stress of the joint [45].

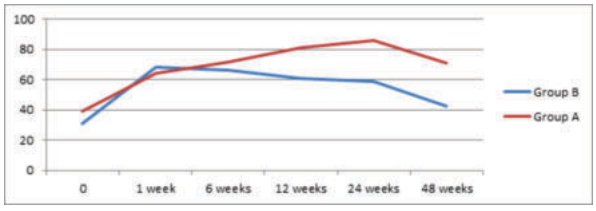
Administration of CS for treating OA has been controversial because these injections can reduce pain in the short term, but they may not be helpful in the treatment of the underlying arthritic lesion [46]. Intra-articular PRP infiltrations have been widely used for the treatment of knee OA with many beneficial results [35]. In this study, intra-articular PRP injections were well tolerated. The most common side effect being mild synovitis tended to resolve within the first week after treatment. Treatment with PRP injections can be considered safe since no severe adverse events or complications have been reported. We consider that the safety of PRP is mainly due to two factors: the administration of the PRP done through minimally invasive procedures and non-existent risk of transmission of infectious diseases (because it is an autologous procedure).



VAS



KSS



IKDC

CONCLUSION

Intra articular platelet rich plasma produce superior outcomes when compared with corticosteroid for symptomatic management in the treatment of patients with knee osteoarthritis grade II and III, including improved pain management, less joint stiffness and better participation in daily activity.

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