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Effectiveness of Platelet Rich Plasma Injection in Comparison with Dextrose Prolotherapy on Improving Pain and Function in Osteoarthritis of Knee: A Randomized Controlled Trial

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ABSTRACT

Background: Osteoarthritis is a common and disabling condition that represents a substantial and increasing health burden with notable implications for the individuals affected, health-care systems, and wider socioeconomic costs. Despite significant advances in science and medicine, there is no cure for osteoarthritis. Numerous treatment options have been used for management of osteoarthritis including pharmacological and invasive techniques. Regenerative therapy like Platelet rich plasma and Prolotherapy are being extensively studied due to their ability to regenerate and repair damaged tissues.

Objectives: To evaluate the effectiveness of platelet rich plasma injection in comparison with dextrose prolotherapy on improving pain and function in patients with osteoarthritis of the knee.

Study Design: Randomized controlled trial

Methods: A single blind randomized controlled clinical trial was carried out in the Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal between September 2022 to February 2024. A total of 92 patients were recruited and block of four randomization was done for allotment of the study participants. The outcome measures were visual analog scale (VAS) and Western Ontario Mac Master Osteoarthritis Index (WOMAC) score. For descriptive statistics mean, standard deviation and frequency were used. Student's t-test and Chi square tests were used for analysis of different variables. A p-value <0.05 was taken as significant.

Results: The 2 groups were homogeneous in terms of baseline characteristics like age, sex, side of affection and duration of symptoms (Table 1). The outcome variables of VAS and WOMAC score at baseline were not significant (Table 2). The mean age of the participants was 63.18 ± 5.15 in years. The

mean duration of symptoms was 10.16 ± 1.22 in months. Between the groups comparison at the end of 4 weeks showed that there was no statistically significant reduction in the mean difference of outcome measures from baseline. However, at the end of 12 weeks and 24 weeks ($p<0.05$), there was statistically significant reduction in mean difference of outcome measures from baseline in both the groups but this was more in the Platelet rich plasma group.

Conclusion: Platelet rich plasma injection was more effective in comparison to dextrose prolotherapy injections on improving pain and function in patients with osteoarthritis of knee at 24 weeks.

Key words: Osteoarthritis; Knee; platelet-rich plasma; prolotherapy;

INTRODUCTION

Osteoarthritis is a common and disabling condition that represents a substantial and increasing health burden with notable implications for the individuals affected, health-care systems, and wider socioeconomic costs.[1,2] With the combined effects of ageing and increasing obesity in the global population, along with increasing numbers of joint injuries, this already burden-some syndrome is becoming more prevalent, with world-wide estimates suggesting that 250 million people are currently affected.[3] Knee osteoarthritis (OA), also known as degenerative joint disease, is typically the result of wear and tear and progressive loss of articular cartilage. It is most common in the elderly. Knee osteoarthritis can be divided into two types, primary and secondary. Primary osteoarthritis is articular degeneration without any apparent underlying reason. Secondary osteoarthritis is the consequence of either an abnormal concentration of force across the joint as with post-traumatic causes or abnormal articular cartilage, such as rheumatoid arthritis (RA).[4]

Articular cartilage is composed primarily of type II collagen, proteoglycans, chondrocytes, and water. Healthy articular cartilage constantly maintains an equilibrium between each of the components so that any degradation of cartilage is matched by synthesis. Healthy articular cartilage is thus maintained. In the process of osteoarthritis, matrix metalloproteases (MMPs), or degradative enzymes, are overexpressed, disrupting the equilibrium and resulting in an overall loss of collagen and proteoglycans. The loss in equilibrium results in a decreased amount of proteoglycans despite increased synthesis, increased water content, the disorganized pattern of collagen, and ultimately loss of articular cartilage elasticity. Macroscopically these changes result in cracking and fissuring of the cartilage and ultimately erosion of the articular surface.[5]

Osteoarthritis is typically a progressive disease that may eventually lead to disability. The intensity of the clinical symptoms may vary for each individual. However, they typically become more severe, more frequent, and more debilitating over time. The rate of progression also varies for each individual. Common clinical symptoms include knee pain that is gradual in onset and worse with activity, knee stiffness and swelling, pain after prolonged sitting or resting, and pain that worsens over time.[4] Osteoarthritis is primarily a clinical diagnosis. However, plain radiography can be helpful in confirming the diagnosis and ruling out other pathology.[3,4] MRI and computed tomography are rarely needed. There are certain plain radiographic findings characteristic of OA. OA often demonstrates joint space narrowing, osteophyte formation, subchondral sclerosis, and cysts.[6]

There is no current cure for OA. Treatment can be broadly classified into reduction of modifiable risk factors, NSAIDS, intraarticular therapy, physical modalities, alternative therapies, and surgical treatments.

There is also emerging evidence for several novel treatments.[6,7,8] Regenerative therapy has been one the latest rapidly growing strategies to treat OA. Platelet-rich plasma, which is harvested from a patient's blood with the theory that it will provide important growth factors, has been investigated. A systematic review found that platelet-rich plasma resulted in clinical improvement up to 12 months following injection.[9] PRP injections are used increasingly to manage osteoarthritis. It has a plasma concentration of 5 to 8 times the normal platelet levels. It regulates the articulatory surroundings due to the release of growth factors, enhancing an anti inflammatory, anabolic and analgesic effect.[9]

Prolotherapy is one of the methods which can raise growth factor levels or increases growth factor efficiency to stimulate tissue regeneration.10 Hackett first described this method in 1950, and various clinical studies have performed this method on humans and animals.[11,12,13,14] In dextrose prolotherapy, increased extracellular glucose has been revealed to increase the amount of numerous polypeptide growth factors in a diversity of human cells.[15,16,17,18,19] Additionally, contact of various human cells to a hypertonic dextrose solution may lead to an increase in levels of growth factors.[20,21] It is believed that prolotherapy may increase the levels of of growth factors in target injected tissue. it improves the condition of vital cells in the joint like chondrocytes, fibroblasts, and osteocytes. So far, various studies have been done on dextrose prolotherapy; however, its therapeutic effects remain unclear. In one study, prolotherapy injection with 10% dextrose resulted in clinically and statistically significant improvements in knee osteoarthritis.[22]

This randomized controlled trial was conducted with the objective to determine the effectiveness of platelet rich plasma injection in comparison with dextrose prolotherapy injection on improving pain and function among patients with osteoarthritis of the knee.

MATERIALS AND METHODS

This study was a single blind randomized controlled clinical trial carried out in the Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal between September 2022 to February 2024 after it was approved by the Ethics Committee of the institute. The inclusion criteria for recruitment of participants included patients in the age range of 40-70 years, duration of symptoms more than 3 months, stage 1 or 2 OA (based on the Kellgren– Lawrence scale of the Radiological Society of America); and the willingness to comply with treatment and follow up. Participants were excluded if they had history of local injection within 6 months, thrombocytopenia (<1.8 lakhs/cumm), rheumatoid arthritis or hemophilia, previous history of knee surgery, drug or alcohol addiction, uncontrolled systemic illness, use of anticoagulant or nonsteroidal anti-inflammatory drugs (NSAIDs) in the previous 4 weeks.

The sample size was determined based on data from a study conducted by Pishgahi A et al.[23] Considering confidence interval of 95%, study power of 90% and 10% possible follow up loss, the final sample size was determined to be 92 (dextrose prolotherapy =46; PRP=46).

Those participants fulfilling the inclusion and exclusion criteria were recruited and informed written consent was obtained.

The diagnosis was made on the basis of clinical presentation and radiographic examination. Routine baseline investigations were performed before the interventions. Recruited patients were randomized to 2 groups (A and B) and block of four randomization was done. Group A study participants received a single injection of PRP (4 ml) given intraarticularly using supralateral approach. PRP was freshly prepared using the

Double spin centrifuged method under aseptic condition. Group B study participants received 4 ml of Dextrose prolotherapy (2ml of 25 % dextrose and 2 ml of 2% lidocaine) injection intraarticularly using a supralateral approach while taking all aseptic precautions. In both the groups only paracetamol (650 mg) tablets were allowed as rescue medication. Following the interventions the patients were called for follow up assessment at 4 weeks, 12 weeks and 24 weeks post intervention. All the participants, irrespective of the group underwent a rehabilitation program that focussed on strengthening exercises of quadriceps, hamstrings, hip extensors, abductors and flexors.

OUTCOME MEASURES

Pain intensity: This was assessed using the Visual Analog Scale (VAS), a subjective assessment scale of perceived pain. VAS uses a numerical scale ranging from 0 to 10, where 0 indicates no pain and 10 indicates maximum possible pain. Assessment was done at 4 weeks, 12 weeks and 24 weeks post intervention.

Functional outcome: Functional outcome was measured using the Western Ontario Mac Master Osteoarthritis Index (WOMAC) score. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitations (score range 0–68). Thus, the possible WOMAC score is between 0 and 96. Assessment was done at 4 weeks, 12 weeks and 24 weeks post intervention.

Single blinding was done where assessors were blinded. Patients of both the groups underwent rehabilitation programs that focused on strengthening exercises of hamstrings, quadriceps, hip extensors and hip abductors.

STATISTICAL ANALYSIS

Collected data were checked for completeness and consistency. Statistical analysis was done using IBM-Statistical Package for the Social Sciences (IBM-SPSS) Version 21. For descriptive statistics mean, standard deviation and frequency were used. Continuous variables (age, duration of symptoms, VAS, WOMAC) were analysed by student's t-test. Categorical variables (gender, side of affection) were analysed using Chi-square test. Within the group comparison (baseline and follow up data of each group) was done by repeated measures ANOVA test. Between the group comparison (intervention group and control group) was analysed using student's t-test. A p value of <0.05 was taken as significant.

RESULTS

Demographics and baseline characteristics

A total of 92 patients were recruited and equally divided into study and control groups. No patients were lost to follow-up or had undergone a surgical intervention during the follow-up period. The 2 groups were homogeneous in terms of baseline characteristics like age, sex, side of affection and duration of symptoms (Table 1). The outcome variables of VAS and WOMAC score at baseline were not significant (Table 2). The mean age of the participants was 63.18 ± 5.15 in years. The mean duration of symptoms was 10.16 ± 1.22 in months.

Visual Analog Scale (VAS)

Within the group comparison showed no significant reduction in VAS at 4 weeks, but significant improvement was found at 12 weeks and 24 weeks follow up in both the groups ($p < 0.05$) (Table III). Between the groups comparison at the end of 4 weeks showed that there was no statistically significant reduction in the mean difference of VAS from baseline. However, at the end of 12 weeks and 24 weeks ($p=0.04$) ($p=0.03$), there was statistically significant reduction in mean difference of VAS from baseline in both the groups but this was more in the Platelet

rich plasma group (Table IV).

WOMAC SCORE

Within the group comparison showed no significant reduction in WOMAC score at 4 weeks, but significant improvement was found at 12 weeks and 24 weeks follow up in both the groups (p <0.05) (Table III). Between the group comparison showed statistically significant reduction in WOMAC scores in both the groups but it was significantly more in the Platelet rich plasma group at 12 weeks and 24 weeks (p=0.00) (p=0.03) (Table IV).

Table I: Comparisons of background and baseline characteristics between the between PRP group (study) and Dextrose Prolotherapy group (Control)

Characteristics	Groups		p-value
	Intervention Group (PRP)	Control group (DP)	
Mean Age (years)	62.44 ± 5.64	63.38 ± 6.10	0.442*
Mean duration of symptoms (months)	9.65 ± 1.73	10.11 ± 1.64	0.210*
Gender			
Male	14	11	0.770**
Female	32	35	
Side of Affection			
Right	32	27	0.558**
Left	14	19	

***Independent t test, **Chi-square test, p value <0.05 taken as significant**

Table II: Comparisons of baseline dependent variables between the between PRP group (study) and Dextrose Prolotherapy group (Control)

Characteristics	Groups		p-value*
	Intervention Group (PRP) (Mean ± SD)	Control group (DP) (Mean ± SD)	
VAS	7.38 ± 0.98	7.12 ± 1.01	0.96
WOMAC	66.36 ± 8.32	64.47 ± 7.35	0.69

***Independent t test, p value <0.05 taken as significant**

Table III: Within the group comparison of outcome measures in both groups

Outcome measures	Study groups	Baseline	4 weeks	12 weeks	24 weeks
VAS	Intervention (PRP)	7.78 ± 0.98	5.51 ± 0.799	4.15 ± 0.612	2.53 ± 0.857
	p value*		0.45	0.01	0.00
	Control (DP)	7.12 ± 1.01	4.99 ± 0.780	4.24 ± 0.689	3.16 ± 0.884
	p value*		0.26	0.02	0.01
WOMAC	Intervention (PRP)	66.36 ± 8.32	51.14 ± 6.81	37.14 ± 5.40	24.12 ± 3.50
	p value*		0.19	0.00	0.00
	Control (DP)	64.47 ± 7.35	49.97 ± 6.76	39.17 ± 6.61	31.42 ± 7.87
	p value*		0.41	0.00	0.00

***Repeated measures ANOVA, p-value < 0.05 is taken as significant**

Table IV: Comparisons of mean difference changes from baseline in outcome measures between PRP group (study) and Dextrose Prolotherapy group (Control)

Outcome measure	Follow up	Intervention Group (Mean ± SD)	Control group (Mean ± SD)	p- value*
VAS Score	4 weeks	2.27 ± 0.82	2.13 ± 1.33	0.10
	12 weeks	3.63 ± 1.92	2.88 ± 1.31	0.04
	24 weeks	5.25 ± 1.17	3.96 ± 1.15	0.03
WOMAC	4 weeks	15.22 ± 3.85	14.50 ± 4.41	0.16
	12 weeks	29.22 ± 7.66	25.32 ± 6.14	0.00
	24 weeks	42.24 ± 10.07	33.05 ± 9.55	0.03

***Independent t test, p value <0.05 taken as significant**

DISCUSSION

Osteoarthritis (OA) is a typical progressive, chronic disorder of the articular cartilage associated with pain, disability, and eventually deformity of the affected joint.[24,25] Various studies have shown that the prevalence of Knee OA is high in the elderly, more commonly affected women than men, and can be significantly disabling hampering the quality of life.[25,26,27] Musculoskeletal pain and movement restriction are symptoms associated with OA, resulting in a reduction in daily performance.[28,29] According to Kurtz et al.[30] the percentage of knee OA is expected to increase over the next 10 years due to the growing rate of obesity and of the population's average age. Numerous treatment methods including both noninvasive and invasive methods have been used for the treatment of knee osteoarthritis. Treatment choices fall into four main categories: non pharmacologic, pharmacologic, complementary, and surgical. [31]

PRP is an autologous blood product containing a high percentage of various growth factors (GFs), such as fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, transforming growth factor-β and platelet-derived growth factor.[29] A recent study suggested that these GFs and cytokines, released by platelets after being damaged by an injury or pathology, might be involved in modulating the inflammatory processes contributing to the tissue structures preservation or regeneration.[32] Various meta-analyses investigated the effectiveness of the Platelet-rich plasma (PRP) by comparing it with other procedures, the results highlighted a better pain relief and functional improvement observed at different times after injection. [33]

Dextrose prolotherapy is an alternative method that has been proposed for treatment of osteoarthritis, due to its ability to aid tissue regeneration, improve clinical manifestations, and repair damaged tissue structures, which are pathological conditions in osteoarthritis. [34] Prolotherapy is a non-surgical regenerative injection technique, in which small amounts of an irritant solution are applied to painful sites and degenerated tendon attachments (entheses), joints, ligaments, and adjacent joint spaces during multiple treatment sessions to promote the growth of normal cells and tissues.[35,36] The most commonly used prolotherapeutic agent is dextrose, in concentrations ranging from 12.5% to 25%.[37] The mechanism of action of prolotherapy is not fully understood. However, current theory suggests that the injected proliferant mimics the natural healing process of the body by initiating a local inflammatory cascade that triggers the release of growth factors and collagen deposits. This is achieved when induced cytokines mediate chemo modulation, which leads to the proliferation and strengthening of new connective tissue, joint stability, and reduction in pain and dysfunction.[35,36]

The results of our study found that PRP injection is more effective than Dextrose prolotherapy on improving pain and function in Knee osteoarthritis at 24 weeks. The mean reduction in VAS score from baseline at 24 weeks post intervention, was found to be 5.25 ± 1.17 in the PRP group compared to a reduction of 3.96 ± 1.15 in the dextrose prolotherapy group and this was statistically significant. (p = 0.03) WOMAC scores was used to assess the functional improvement as well as stiffness among the participants.

The baseline WOMAC score in the PRP group was 66.36 ± 8.32 which reduced to 24.12 ± 3.50 (p=0.00) while the reduction in WOMAC score in the prolotherapy group was from 64.47 ± 7.35 to 31.42 ± 7.87. (p = 0.00). These study findings, suggest that PRP injections can significantly decrease pain, functional limitations, and stiffness in patients with knee osteoarthritis.

In a study by Chang et al[7] that compared the effects of PRP and hyaluronic acid injection for knee pain, it was found that PRP injection was more effective for patients with damaged articular cartilage than was hyaluronic acid. Moreover, patients with mild OA responded better to PRP injection than those with severe OA. In another study by Gobbi et al[38] 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, it concluded that the PRP treatment showed positive effects in patients with knee OA. All patients showed significant improvement in all scores at 6 and 12 months (P < 0.01) and returned to previous activities.

The present study found that although there was a reduction in pain measured using VAS and functional improvement in symptoms assessed using WOMAC scores in both the Platelet rich plasma injection and dextrose prolotherapy group, this improvement was significantly more in the PRP group at 24 weeks follow up, thereby possibly suggesting PRP injections to be more effective in managing Osteoarthritis in the long run. Our findings are consistent with a study conducted by Rahimzadeh et al[39] which found a significant decrease in the overall WOMAC score of patients who undergo either PRP therapy or Prolotherapy injections. It concluded that PRP injection was more effective than PRL in treating knee OA.

Limitations:

Our study was a single blinded study where only the assessor was blinded. It was not possible to blind the patients to the injections due to the different colors as well as the viscosity of the two interventions. Another limitation was the follow up period of 6 months which could be considered short, considering osteoarthritis is a chronic and progressive disorder. Lastly, there was a lack of assessment of cartilage, soft tissue, and structures in and around the knee joint which could have been possibly carried out via ultrasonographic evaluation post interventions. Perhaps a future study, assessing the morphological changes in articular cartilage using ultrasound and a follow up of patients for a longer period could further enhance our belief that PRP injections are safe, easy to administer, and an effective treatment option in early osteoarthritis of the knee.

CONCLUSION

Platelet rich plasma injection is more effective in comparison to dextrose prolotherapy injections on improving pain and function in patients with osteoarthritis of knee at 24 weeks.

Declaration by Authors

Ethical Issues: Ethical clearance was obtained from the Institute's Ethical committee

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Conflicts Of Interest: None

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