

Effectiveness of Platelet-Rich Plasma in the Treatment of Moderate Knee Osteoarthritis.

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ABSTRACT

Background: To assess the effects of platelet-rich plasma (PRP) applications on pain and physical function in grade 3 knee osteoarthritis (OA). **Methods:** A total of 120 patients with grade 3 knee OA were randomly divided into three groups: Group 1 received a single injection of PRP, Group 2 received two injections of PRP two weeks apart, Group 3 received three injections of PRP at 2-weeks intervals. All patients were evaluated with a visual analog scale (VAS), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Timed-Up and Go test (TUG) before the treatment and at 1, 3 and 6 months after the treatment. **Results:** The mean ages of the patients were 55.8±5.1, 54.6±5.4, 55.3±5.7 years in Group 1, Group 2, and Group 3, respectively. Statistically significant improvements were noted in VAS score, TUG Score, WOMAC total as well as subgroup scores. Best scores were found at the 1st month after treatment. The scores deteriorated over time but even at 6 months follow up the final scores were significantly better than pre-injection scores. The mean differences of Group 1-Group 2, Group 1-Group 3, and Group 2-Group 3 in VAS and TUG scores were found to be significant. 3 injection therapy gives far more superior results than the single injection therapy with significantly better score. **Conclusion:** PRP is an effective treatment for functional status and pain in moderate knee osteoarthritis and a minimum of two to three injections is appropriate.

Keywords: Platelet-rich plasma effectiveness, Moderate, Knee osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease of synovial joints resulting from the combination of mechanical stress and biochemical cellular changes which ultimately cause pain and impair joint function. Osteoarthritis is the eighth leading non-fatal burden of disease worldwide and a major cause of disability.^[1] Increased longevity coupled with epidemic of obesity and the resultant motivation to exercise, often through sports, the burden and prevalence of OA is expected to grow further.^[2,3]

Conservative treatments have been reported to increase the quality of life of patients particularly in the early phases, when the pathophysiology of the disease doesn't change.^[4]

Non-surgical interventions, such as corticosteroid injections, have a short duration, require repeat administration, and have potential for local and systemic side effects.^[5,6] Therefore, there is a need for a noninvasive but effective treatment for knee OA.

There is a growing body of literature on the role of regenerative injectable therapies in the treatment of refractory knee pain.^[7-11]

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Platelet-rich plasma (PRP) is an autologous concentration of a high number of platelets in a small volume of plasma, and it is prepared by centrifugation of blood. Platelets contain significant amounts of cytokines and growth factors which are capable of stimulating cellular growth, vascularization, proliferation, tissue regeneration, and collagen synthesis. Platelet-rich plasma (PRP) is a regenerative therapy that is thought to promote healing by augmenting and accelerating the natural healing cascade.^[12-15]

The healing process is schematically divided in three stages: inflammation, proliferation, and remodeling. Healing begins with the release of inflammatory mediators, followed by extracellular matrix rearrangement, and finally collagen

production and matrix maturation.^[16] Platelet alpha granules contain growth factors (platelet derived growth factor, insulin like growth factor, vascular endothelial growth factor, and transforming growth factor β) that are involved in each stage of the healing cascade. The injection of autologous PRP into the joint space and surrounding painful soft tissues delivers a concentrated dose of these growth factors, which enhance the healing process and reduce pain.^[8] Several studies have shown that PRP injections in osteoarthritis patients is effective in controlling pain and improving mobility however,^[17-19] there is no consensus on eligible patient selection, the number and frequency of injections, the preparation technique, or the appropriate platelet concentration.^[4]

In the present study the effects of PRP administration to control the disease activity of grade 3 knee OA either with one injection, two injections two weeks apart, or three injections separated by 2-week intervals on the patients' pain, quality of life and physical activity levels were investigated.

MATERIALS AND METHODS

A total of 120 patients with grade 3 osteoarthritis of single knee (according to Kellgren- Lawrence20 grading system) in the age range 40-70 years who visited our outpatient department during the period of April 2016-september 2016, were studied. The exclusion criteria were bilateral symptomatic knee OA; age older than 70 years; intra-articular steroid, hyaluronic acid or PRP injections in the last 6 months; active infection, inflammation or tumor existence around the knee; history of diabetes mellitus, coagulopathies, malignant, immunosuppressive, collagen vascular or autoimmune disorders; genu varum or valgus greater than 5 degrees.

After complete medical history and examination, Subjects' age, gender, height and weight were recorded and their body mass index (BMI) was calculated. Basic routine investigations were done on outpatient basis. The participants were randomized by block randomization into three groups: 40 participants in [Figure 1] received a single injection, 40 participants in [Figure 2] received two injections two weeks apart, and 40 participants in [Figure 3] received three injections of PRP separated by 2-weeks interval.

30-40 cc of venous blood sample from antecubital vein was collected in a sterile sodium citrated tube. It was centrifuged twice first at 1,800 rpm for 15 minutes to separate erythrocytes; then at 3,500 rpm for 5 minutes to concentrate platelets. The final product was 4-5 cc of PRP-containing leukocytes. Finally, 0.0425 mL of 10% calcium chloride per 1 mL of PRP was added to the final product to activate the platelets.

PRP was injected in a sterile condition using classic lateral approach and a 22G needle. No local anaesthetic was used. The second and third injections were administered under the same conditions as the first injection.

After the injections patients were told to actively flex and extend their knees a few times to allow the PRP to spread throughout the joint before gelling. Patients in each of the three groups were discharged to home after 30 minutes of rest with instructions to have rest, to limit weight bearing and to use cold packs 3-4 times a day for 10 minutes for 48- 72 hours. During the follow-up period, the patients were asked to take paracetamol only when necessary, or paracetamol with tramadol for persistent pain. The patients were instructed to not take them in the 48 hours before an assessment. Patients were prohibited from using other analgesics, NSAIDs, steroids or medications which might have influenced platelet count or function. Exercise or physical treatment was not allowed during the study period to eliminate synergistic effects.

Scores were taken for visual analog scale (VAS) for pain²¹, Western Ontario and McMaster Universities Arthritis Index (WOMAC)²², and Timed- Up and Go test (TUG) ²³ before the injection, 1 month , 3 months and 6 months after the treatment with injections. For blinding purposes scoring was done by a resident in the author's department. In our study, the patients' WOMAC sub-scores (pain, stiffness, function) and total WOMAC score were calculated. For TUG three measurements were taken and the best value was recorded and categorized as: < 10 seconds = freely mobile, 10-19 seconds = mostly independent, 20-29 seconds = variable mobility, >30 =impaired mobility.^[23]

The means of age and BMI of the groups were analyzed by one way ANOVA followed by the Bonferroni post-hoc test.

Scoring system Data were analyzed using repeated ANOVA and multiple comparisons (the Bonferroni test) test. The SPSS statistical program was used to perform statistical analyses and values of $p < 0.05$ were considered significant.

RESULTS

Table 1:

	Group I Mean \pm SD	Group II Mean \pm SD	Group III Mean \pm SD
Age (yrs)	55.8 \pm 5.1	54.6 \pm 5.4	55.3 \pm 5.7
BMI(kg/m ²)	23.8 \pm 2.1	24.1 \pm 1.7	24.3 \pm 1.9

The groups were homogenous in terms of age, gender and BMI; the results are presented in [Table 1].

VAS score, TUG score and WOMAC scores improved in all three groups with maximal improvement seen in group 3 and minimal in group

1. The best scores were noted 1 month after the completion of treatment.

VAS scores, TUG scores and WOMAC total and subscores were significantly better than preinjection scores in all of the three treatment groups at 6 months ($p < 0.05$) [Table 2]. The mean differences, the SEM of mean differences, p value and 95% confidence intervals of two groups were compared and the mean differences of Group 1- Group 2, Group 1- Group 3, and Group 2- Group 3 in VAS and TUG scores were found to be significant. No significant complications were observed other than transient increases in local pain

or swelling during the treatment and follow-up periods.

Our study suggests effectiveness of PRP in grade 3 osteoarthritis knee. With a single injection of PRP there is significant reduction in pain and significant improvement in functional scores. However 3 injection therapy gives far more superior results than the single injection therapy with significantly better scores. Best scores are noted at first follow up (one month) in VAS, WOMAC and TUG scores. These scores gradually deteriorate over time but even at 6 months follow up the final scores were significantly better than pre-injection scores.

Table 2: Mean and Standard error of Mean (SEM) of scores at each visit.

Group		VAS Mean±SEM	W.total Mean±SEM	W.pain Mean±SEM	W.stiffness Mean±SEM	W.function Mean±SEM	TUG Mean±SEM
1	pretreatment	7.8±0.1	90.8±2.0	17.6±0.5	6.5±0.1	66.7±1.4	12.8±0.2
	1 month	5.8±0.2	80.2±2.1	14.8±0.5	5.3±0.1	60.1±1.6	12.3±0.2
	3month	6.3±0.2	84.1±3.5	15.8±0.6	5.9±0.2	62.4±1.4	12.4±0.2
	6 month	7.1±0.1	85.2±2.0	16.3±0.4	6.1±0.1	62.8±1.4	12.6±0.1
2	pretreatment	8.2±0.6	89.9±2.1	17.5±0.5	6.6±0.2	65.8±1.5	13.0±0.1
	1 month	4.1±0.2	73.2±2.0	12.9±0.4	4.7±0.1	55.6±1.4	12.1±0.3
	3month	4.9±0.4	76.8±2.0	14.1±0.6	5.1±0.1	57.6±1.6	12.3±0.1
	6 month	6.5±0.2	80.1±1.8	15.2±0.4	5.5±0.1	59.4±1.5	12.5±0.1
3	pretreatment	8.1±0.6	90.8±1.8	18.9±0.6	6.4±0.1	65.5±1.6	12.9±0.3
	1 month	3.8±0.2	66.2±1.6	11.2±0.5	3.9±0.2	51.1±1.7	11.5±0.1
	3month	4.5±0.2	69.6±1.6	12.6±0.4	4.1±0.1	52.9±1.3	11.8±0.1
	6 month	4.9±0.3	74.8±1.5	13.8±0.5	4.6±0.1	56.4±1.4	12.1±0.1

*VAS=visual analogue score, W=WOLMAC, TUG=timed up and go

DISCUSSION

Studies of in vivo application of PRP for knee OA report varying results, with only a few randomized controlled trials. Sampson et al reported a case series of 14 patients with primary or secondary knee osteoarthritis with each patient receiving three PRP injections at 4-week intervals. At 1-year follow-up, there was a significant reduction in pain at rest, with moving, and with the knee bent. There were no adverse outcomes and 8 of 13 patients felt they achieved their goal with the injection.^[17] Gobbi et al treated a group of 52 active patients with knee OA, and found a significant portion had reduced pain after two injections of PRP and returned to prior level of activity at 12 months follow-up^[18]. This same group found that at 2 years of follow-up and interval repeat injections, PRP treated patients continued to have improved pain control and mobility.^[19]

When compared to placebo (saline injection) PRP improved symptoms at up to 6 months.^[24] When compared to hyaluronic acid (HA), results have been favourable, with some studies showing PRP to be as effective as HA and other showing it to be more effective.^[25-27]

In 2012, Sanchez et al conducted the first multicenter,^[28] double-blind, randomized controlled trial comparing PRP to HA. The study of 176 patients with symptomatic knee OA found that 38 % of patients treated with PRP had greater than 50

% reduction in pain at 24 weeks compared to baseline. This was significantly higher than the pain reduction scores for patients treated with HA. Improvements in stiffness and physical activity were also higher in the PRP group but were not significant.

Age, severity of cartilage degeneration or knee osteoarthritis, duration of symptoms, prior therapeutic interventions, and patient activity level may all be relevant. When evaluating a patient for PRP, it is important to consider these variable, and advise patients accordingly, so as to set appropriate expectations for therapeutic benefit

Patient age impacts PRP outcomes, with younger individuals having greater benefits. In a subgroup analysis of 150 patients with cartilage degeneration or OA, Kon et al found that patients younger than age 50 had greater benefit from PRP at 6 months follow-up than patients over age 50 and that younger patients had a better response to PRP than HA.^[27] In patients over age 50, HA and PRP had similar results. Hypotheses for age related efficacy include a less robust response of aging chondrocytes to growth factors and a limited propensity for healing and regeneration in elderly patients.^[29]

Patients with cartilage defects and mild to moderate OA show greater improvement after PRP treatment than those with severe OA and significant joint deformity.^[29-31]

Chang's meta-analysis showed that PRP effectiveness was higher at the degenerative

chondropathy stage, and the effect decreased at two or lower doses when degeneration was worse.^[4] Despite poorer results, patients with advanced OA still benefit from PRP. In a comparative study of PRP and hyaluronic acid (HA) in grade 1–3 knee OA, the PRP group showed significantly better results after 6 months and the worst results were observed in HA-treated subjects with grade 3 knee OA.^[33]

In the advanced stages of OA, PRP might not have a direct effect on the chondrocyte anabolic process, but an anti-inflammatory effect through the regulation of joint homeostasis and the cytokine level.^[29,34] However, contrary to this opinion, Calis et al. showed that PRP administered three times at weekly intervals to patients with grade 3 and 4 knee OA reported improvements in their quality of life, and reduced levels of pain, and had increased cartilage thickness as measured by ultrasonography at the 6-month follow up.^[35]

To a lesser extent patient selection parameters such as gender and BMI should be considered, with females and high BMI being associated with worse outcomes.^[29] Currently, there is no evidence to suggest that ethnicity, occupation, or muscle weakness (factors that contribute to OA) play a role in PRP efficacy.

There are no definitive guidelines on number or frequency of injections. Several clinical trials have found up to 12 months of improvement in knee pain with one injection.^[31,32]

In a randomized clinical trial, Sanchez et al administered PRP injections weekly for three consecutive weeks with greater than 50 % reduction in knee pain for 6 months.^[28] Other trials have followed a similar protocol, and found symptom improvement at up to 12 Months.^[25,26] Patel et al conducted a subgroup analysis of outcomes of one injection versus two injections 3 weeks apart and found no difference between the groups at 6 months.^[24] Gobbi followed 80 patients for 24 months. All patients received two injections 4 weeks apart. Two subgroups had repeat injections, one group at 6 and 12 months, and the other group at 12 and 18 months. Indications for repeat injections were to preserve outcomes and not for symptoms recurrence. Both groups had continued pain relief at 24 months.^[19]

The role of maintenance injections as compared to those for reoccurrence of symptoms has not been well studied. If patients fail to respond to a series of injections, there is currently no evidence to support the use of a second series of injections. In those cases, patients should consider alternative treatment plans.

Attention should be paid to the PRP preparation, including the presence of leukocytes, the platelet concentration, and means of platelet activation. Studies have used both leukocyte poor PRP (pure-

PRP) and leukocyte rich PRP in knee OA. In theory, leukocyte poor preparations may be favorable as in vitro studies of leukocytes in soft tissue injury show negative outcomes in wound healing and repair.^[36,37] The concentration of platelets is also important, and may vary depending on centrifugation process.^[38] An acceptable platelet concentration is considered at least 2–3 times baseline whole blood, ideally 6–7 times, while concentrations greater than 10 times baseline are considered to be excessive and potentially detrimental.^[39,40]

In the present study, 3 PRP injections separated by 2-week intervals were found to be more effective for the improvement of pain and mobility than 2 injections in Grade 3 OA patients; however, no significant differences were observed in the WOMAC values. A significant effect was observed in the early period after a single injection of PRP, but the effect decreased in a short time. Based on the present results, we recommend 2 or 3 injections of PRP for patients with moderate knee OA, and physicians' decisions should be based on various factors such as the level of pain, level of activity, cost-effectiveness, and BMI. This study had certain strengths and limitations. The strength of this study was the prospective randomized design. The absence of a control group and the relatively small patient numbers were the limitations of the study.

Considering the evidence, this minimally invasive injection procedure appears to be safe and effective, and since PRP injections biologically change the articular cartilage, they may be a worthwhile treatment option even in moderate knee osteoarthritis.

CONCLUSION

Platelet rich plasma and other regenerative injections represent a major paradigm shift and advancement in the treatment of knee osteoarthritis when compared to intra-articular corticosteroid injections. There is currently good in vitro evidence to suggest that tissue exposed to PRP has a propensity to undergo healing and self-repair. Clinical trials are advancing to determine the role of PRP in clinical practice. Short-term follow-up studies show that PRP to be effective in reducing pain and increasing activity in patients with knee OA. Long-term follow-up studies and randomized clinical trials are now underway to better characterize how to incorporate PRP into patient care. It is the responsibility of the clinician to select the appropriate

patient for this treatment. Ideal patients have mild to moderate symptomatic osteoarthritis. They lack

significant knee deformity and have not had complete failure of the knee joint. The method of PRP preparation may also contribute to its efficacy. Attention should be paid to the PRP preparation, including the presence of leukocytes, the platelet concentration, and means of platelet activation. There remains a need for strong, sufficiently powered, randomized controlled trials to validate its use over other traditional injection treatments (corticosteroid and viscosupplementation).

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