



International Journal of Orthopaedics Sciences

E-ISSN: 2395-1958
P-ISSN: 2706-6630
IJOS 2020; 6(4): 08-13
© 2020 IJOS
www.orthopaper.com
Received: 03-08-2020
Accepted: 07-09-2020

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Effectiveness of platelet-rich plasma (PRP) in the treatment of mild to moderate knee osteoarthritis

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DOI: <https://doi.org/10.22271/ortho.2020.v6.i4a.2310>

Abstract

Aim: To assess the functional outcome of treatment of osteoarthritis knee joint by intra articular injection of platelet rich plasma.

Methods: A total of 50 patients with grade 0 to grade 3 osteoarthritis knee joint were randomly selected and 2 doses of intraarticular injection of platelet rich plasma were given at interval of 1 month and the outcome was evaluated with visual analog scale (VAS) and the western Ontario and mcmaster universities arthritis index (WOMAC) at preinjection, 1,3 and 6 months interval.

Results: The mean age of patients were 55.5. There were better improvements noted in VAS and WOMAC scale. Best scores were noted in 2 months interval. The scores got deteriorated over 6 months interval but the final scores were better than the pre injection scores. Two injection therapy gives better result than single injection therapy.

Conclusion: Platelet rich plasma injection is effective in the treatment of osteoarthritis knee with minimum of two injections is appropriate therapies in treatment of osteoarthritis knee joint.

Keywords: platelet rich plasma, osteoarthritis

Introduction

Osteoarthritis of knee is progressive degenerative synovial joint disease resulting due to mechanical stress and biochemical cellular changes resulting in pain and joint impairment. It is the common cause of pain, loss of function and walking related disability among older adults. Moreover increased epidemic of obesity and the resultant motivation to exercise also has increased the prevalence of osteoarthritis knee [1].

TKR is the treatment for severe OA knee to get rid of pain and to increase function. Due to the limited lifespan of joint replacement owing to implant wear conservative treatment modalities are becoming the central focus of management. Moreover oral NSAIDs and intra articular corticosteroid injections have short duration and require repeat administration and are potential for local and systemic side effects [2, 3]. Recently now there is a growing literature of regenerative injectable therapies for OA knee [4, 5].

Platelet-rich plasma (PRP) is an autologous blood containing a high concentration of platelets in and is obtained by centrifugation of blood. It contains growth factors, chemokines and cytokines which are shown to promote vascularization, tissue regeneration, cellular growth, proliferation and collagen synthesis and is a regenerative therapy that aids in promoting healing by augmenting and accelerating the natural healing cascade.

It thereby promotes chondrocyte proliferation, chondrocyte cartilaginous matrix secretion and decreases the catabolic effects by pro inflammatory cytokines. Platelet alpha granules contain growth factors such as insulin like growth factor (IGF-1), vascular endothelial growth factor (VEGF), and transforming growth factor β (TGF- β), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), bone morphogenics protein (BMP) 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. TGF- β induces chondrocyte proliferation and differentiation and decreases the catabolic effects of IL-1 [6, 7, 8]. IGF-1 promotes chondrocytes mitosis and extracellular matrix synthesis. BMP helps in migration of chondrocytes. FGF aids in cartilage repair [9].

PDGF helps in cartilage regeneration by chondrocytes proliferation. VEGF increases the nutrient flow to the cartilage [10, 11].

This study evaluate the effects of PRP from grade 0 to 3 knee OA with two injections at 1 month intervals apart and the patients pain, quality of life and physical activity levels were investigated.

Materials and Methods

A total of 50 patients with grade 0 to grade 3 osteoarthritis of knee (according to Kellgren- Lawrence grading system) in the age between 40-70 years who visited our outpatient department during the period of september 2018-september 2020, were studied.

Exclusion criteria

Patients with

- Immunosuppressed patients
- Secondary osteoarthritis
- Connective tissue disorders,
- Inflammatory disorders of joint,
- Who had received hyaluronic acid, steroid injections within past 8 months
- Haemoglobin less than 10 mg%
- Tumours.

After complete medical history and examination, Subjects' age, gender, height and weight were recorded and their BMI was calculated. Basic routine investigations were done on

Case -1



Pre-Injection range of movements



outpatient basis. The participants were given 2 doses of injection PRP at 1 month of intervals

PRP Preparation

20-30 cc of venous blood was collected from antecubital vein in a sodium citrated sterile tube. It was centrifugated twice first at 1,800 rpm for 30 minutes to separate erythrocytes; then at 3,500 rpm for 30 minutes to concentrate platelets. The final product was 10 cc of PRP-containing leukocytes. Then the PRP of about 5 cc was extracted using sterile needle.

PRP was injected in a sterile condition in operation theatre using classic supero lateral approach or by para patellar approach by a 22G needle. No local anaesthetic was used. Post injections immediately patients were asked to actively extend and flex their knees to allow the PRP to distribute uniformly throughout the joint.

Patients after taking 30 minutes of rest were discharged with advice to take rest and to use cold packs 4-5 times a day for 5 minutes for 2-3 days. Patients were advised to take paracetamol if only necessary for pain. The patients were instructed to not take them in the 48 hours before an assessment. Patients were inhibited from using other NSAIDS, steroids, opioids. Physical exercise was not allowed to eliminate synergistic effects.

Scores were taken for visual analog scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), and before the injection, 1 month, 3 months and 6 months after the treatment with injections.

Post Injection range of movements



Case -2



Pre-Injection range of movements



Post Injection range of movements



In our study, the patients' WOMAC sub-scores (pain, stiffness, function) and total WOMAC score were calculated. The means of BMI and age of the groups were performed by one way ANOVA followed by Bonferroni post-hoc test. The SPSS statistical program was used to perform statistical analyses and values of $p < 0.05$ were considered significant.

Results

The best scores were noted 2 month after the completion of treatment. VAS and WOMAC total scores and sub scores compared to the pre injection scores was significantly better in all of the patients at 6 months ($p < 0.05$).

The mean differences, the SEM of mean differences, p value in VAS and WOMAC scores was 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 0 to 3 osteoarthritis knee. With a single injection of Platelet rich plasma there was significant reduction in pain and significant improvement in functional scores. However 2 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.

These scores gradually deteriorate over time but even at 6 months follow up the final scores was significantly better than pre-injection scores.

Table 1: Mean and Standard error of Mean (SEM) of scores at each visit

	VAS Mean±SEM	W.total Mean±SEM	W.pain Mean±SEM	W.stiffness Mean±SEM	W.function Mean±SEM
Pretreatment	7.8±0.1	90.8±2.0	17.6±0.5	6.5±0.1	66.7±1.4
1 month	5.8±0.2	80.2±2.1	14.8±0.5	5.3±0.1	60.1±1.6
3 month	6.3±0.2	84.1±3.5	15.8±0.6	5.9±0.2	62.4±1.4
6 month	7.1±0.1	85.2±2.0	16.3±0.4	6.1±0.1	62.8±1.4

*VAS=visual analogue score, W=WOMAC

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 knee osteoarthritis with each patient receiving three Platelet rich plasma injections at 4-week intervals. At 1-year follow-up, there was a 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 patients with active 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-up¹⁸.

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. When compared to placebo (saline injection) PRP improved symptoms at up to 6 months¹². On comparison to hyaluronic acid (HA), results have been favourable with studies showing PRP to be effective than hyaluronic acid¹³⁻¹⁵.

In 2012, Sanchez *et al.* conducted the first multicenter, 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 of 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 Platelet rich plasma 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. 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 limited propensity for healing and regeneration in elderly patients. Patients with mild to moderate Osteoarthritis knee show better improvement after Platelet rich plasma treatment than patients with severe Osteoarthritis knee and joint deformity^{16, 17}.

Chang's meta-analysis revealed that PRP effects were higher at the degenerative chondropathy stage, and were decreased when degeneration was Worse¹⁸. In spite of poorer results, patients with severe OA was still benefited from Platelet rich plasma.

Comparative study of platelet rich plasma (PRP) and hyaluronic acid (HA) in grade 0–3 knee OA, the PRP group showed better results after 6 months compared to results observed in HA-treated¹⁹. In severe stages of OA, platelet rich plasma (PRP) does not have a direct effect on chondrocyte anabolic process, but have an anti-inflammatory effect through regulation of the cytokine level¹⁷. However, contrary to this, Calis *et al.* opinion. showed that platelet rich plasma (PRP) given three times weekly intervals to the patients with grade 3 and grade 4 knee Osteoarthritis had improvements in quality of life, decreased levels of pain, and increased cartilage thickness measured by ultrasonography at 6-month follow up²⁰ patient selection parameters such as gender, BMI should be considered, with females, high BMI being presented with worse outcomes¹⁷. There is no evidence to quote 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.

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.

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 months²¹.

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 ^[11].

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. In those cases, patients should consider alternative treatment plans.

Attention should be given 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 ^[22]. The concentration of platelets is also important, and may vary depending upon centrifugation process. 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 ^[23].

In present study, 3 platelet rich plasma (PRP) injections at 2-week intervals each were found more effective for the improvement in pain and mobility than the 2 injections in Grade 3 OA patients; however, no differences was observed in the WOMAC values.

A significant effect were observed in early period after single injection of PRP, but the effect decreased in short time. Based on results, we recommend 2 or 3 injections of platelet rich plasma (PRP) for patients with mild to moderate knee OA, and decisions should be based upon various factors such as level of pain, activity, cost-effectiveness and BMI. This study had significant strength and limitations. Strength of the study was the prospective randomized design. Absence of control group and relatively small patient number was the limitation of the study.

Considering the evidence, the minimally invasive platelet rich plasma (PRP) injection procedure consider to be safe and effective, since platelet rich plasma (PRP) injections biologically realignment the articular cartilage. Hence they may be a noteworthy treatment option in mild to moderate knee osteoarthritis.

Conclusion

Platelet rich plasma injection represent a major advancement in the treatment of mild to moderate knee osteoarthritis when compared to intra-articular corticosteroid injections.

There is in vitro evidence to suggest that the tissue exposed to Platelet rich plasma has an intensity to undergo healing and self-repair. Clinical trials are being advancing to determine the role of Platelet rich plasma in clinical practice. Short-term studies showed that PRP is effective in reducing pain and increasing activity in patient 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 should be with mild to moderate symptomatic osteoarthritis. Attention should be needed more in 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 visco supplementation).

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