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Original Research Article

Intradiscal Platelet-Rich Plasma Injection for Discogenic Low Back Pain and Correlation with Platelet Concentration: A Prospective Clinical Trial

Dhruv Jain, MD, Titiksha Goyal, MD, Nimisha Verma, MD, Anil Kumar Paswan, MD, and Rajeev Kumar Dubey, MD

Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Correspondence to: Nimisha Verma, MD, Department of Anaesthesiology, IMS, BHU, Varanasi, Uttar Pradesh 221005, India. Tel: +915422369003; E-mail: verma.nimisha@gmail.com.

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Abstract

Objective. Discogenic pain is common cause of low back ache and may result in significant morbidity. Platelet-rich plasma (PRP) is an upcoming regenerative therapy that has treatment potential for this condition. The objective of this study was to correlate platelet concentration in intradiscal PRP injection with improvement in low back pain and functional status at three and six months. **Design**. Prospective single-arm interventional study. **Setting**. Outpatient pain clinic and operation theater. **Subjects**. Twenty-five patients with discogenic pain diagnosed by clinical means and imaging with confirmation by provocative discography were recruited. **Methods**. The patients received PRP injection at a single or multiple disc levels. Preprocedure numerical rating scale (NRS) pain scores and Oswestry Disability Index (ODI) scores were calculated. Platelet counts of patients and PRP samples were measured. At three and six months postprocedure, NRS and ODI scores were measured, and improvement in these scores was correlated with platelet concentrations in the PRP sample. **Results**. Twenty patients completed the study. The improvement in NRS and ODI scores positively correlated with platelet concentrations in the PRP sample. We determined the correlation coefficient (r) of platelet concentrations with a reduction in NRS at three months ($r=0.65$) and six months ($r=0.73$) and in ODI score at three months ($r=0.72$) and six months ($r=0.7$). **Conclusions**. This study supports the use of intradiscal PRP for treatment of discogenic pain with preferably higher platelet counts to elicit a favorable response.

Key Words: Platelet-Rich Plasma; Discogenic; Chronic Pain; Low Back; Platelet Concentration; Intradiscal

Introduction

Low back ache is a common cause of pain in the general population and can lead to varying disability and high socioeconomic burden. There are many pain generators in low back ache, and intervertebral discs account for nearly 40% of these cases [1]. Disc degeneration results in morphologic and cellular changes, causing loss of proteoglycans, collagen fibers, and increased enzymatic activity [2]. In the natural process of healing of annular tears, granulated tissue formation along with growth of abnormal nerve fibers may occur in annulus fibrosus and nucleus pulposus. These changes result in inflammation, leading to discogenic pain [3].

Various treatments have been proposed for managing discogenic pain, including medications, physical therapy,

epidural steroids, and radiofrequency ablation [4], but they do not regenerate the structure of the disc. Surgical procedures like disc replacement and lumbar fusion surgeries have variable success rates and may result in serious complications [5].

As the intervertebral disc is an avascular structure with minimal regenerative capacity, there has been renewed interest in platelet-rich plasma (PRP) injections that release growth factors; these have found application in many degenerative conditions. The growth factors released by platelets include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor (TGF) β-1, and platelet-derived growth factor (PDGF); this process results in cellular and tissue proliferation [6]. PRP is prepared by centrifugation of autologous blood to prepare a concentrated solution of platelets. Various studies have shown promising results in degenerative disc disease [7,8].

Higher platelet concentration in PRP results in secretion of increased growth factors and cytokines [9]. This has not been proven clinically in degenerative conditions. Therefore, we hypothesized that platelet concentration would affect the regenerative properties of PRP, with higher concentrations resulting in better results. According to the literature, intradiscal PRP therapy is not associated with any major complications [7]. Intradiscal procedures carry a rare but serious complication of discitis, which may be decreased by strict aseptic technique and prophylactic antibiotics [10].

The primary objective of the study was to correlate platelet concentration in intradiscal PRP injection with improvement in low back pain and functional status at three and six months.

Methods

Study Design

Prospective single-arm interventional study.

Patient Selection

The study was undertaken by the Pain Division, Department of Anesthesiology, Institute of Medical Sciences, BHU. The trial was registered with Clinical Trial Registry of India (CTRI no. CTRI/2019/05/019434). After obtaining departmental and institutional ethics committee approval, the study was carried out in 25 patients with discogenic pain who were recruited in the period of May 2019 to September 2019. Discogenic pain was diagnosed clinically, correlated on imaging, and confirmed by provocative discography. On magnetic resonance imaging (MRI), diagnosis was aided by visualizing features suggestive of discogenic pain (high-intensity zone, decreased signal intensity in discs on T2 imaging, disc protrusion, loss of disc height, and end plate changes). Diagnosis was confirmed by performing provocative discography with a 22-G needle on suspected discs with <2 mL of iohexol dye in a 3-mL syringe. A positive test was confirmed if patient complained of concordant back pain at one or more levels with a pain intensity ≥6 on the numeric rating scale (NRS). Control discs were not used, keeping in mind that puncture of a healthy disc might lead to early degeneration [11]. A pressure manometer was not used, but no excessive pressure was applied with the thumb while injecting the dye. Intravenous prophylactic antibiotic was given during the procedure. Patients with a positive test were recruited for intradiscal PRP injection after meeting the following inclusion and exclusion criteria.

Inclusion criteria:

1. Age 18 years and above with more than six months of low back ache
2. Not responding to conservative management (medications, physical therapy, steroid injections)
3. Concordant pain on discography

Exclusion criteria:

1. Radicular pain more than back pain
2. Spinal canal stenosis
3. Spondylosis and spondylolisthesis
4. Other causes of low back pain like facet arthropathy and sacroiliac joint pain
5. Leakage of dye on discography
6. Disc height <50%
7. Coagulation disorders or patient on anticoagulants
8. Pregnancy
9. Extruded or sequestered disc
10. Previous spinal surgery
11. Skin infection
12. Psychiatric illness
13. History of substance abuse

After meeting the inclusion criteria, written informed consent was taken from the patients explaining about intradiscal PRP. Preprocedure NRS was noted (0–10). Oswestry Disability Index (ODI) score for functional status was calculated by filling out the questionnaire. If the patient was on any nonsteroidal anti-inflammatory drug therapy, it was stopped. Patients were called after two weeks for the procedure. The level of the disc for PRP injection for intervention was decided based on provocative discography findings, with only the positive discs being injected. Blood samples from the patients were sent for manual platelet count.

PRP Preparation and Procedure

PRP was made by a two-spin technique using the DrPRP kit (Dr PRP USA LLC) in a PRP centrifuge machine (PRP plus, Remi Healthcare, Mumbai, Maharashtra, India). Eighteen milliliters of blood was taken from the patient with all aseptic precautions and mixed with 2 mL of citrate-dextrose-phosphate-adenine (CDPA) anticoagulant in the PRP kit. The machine was initially precooled to avoid a rise in temperature during centrifugation, thereby preserving the integrity of platelets. The first spin

was performed at 2,000 RPM for 12 minutes, followed by 2,400 RPM for six minutes. Five milliliters of PRP concentrate was prepared, out of which 1 mL of the sample was sent for manual platelet count. The kits we used were unable to produce leucocyte-poor PRP without leucocyte reduction filter. As the filter was not used and we included the buffy coat in our sample, our concentrate was assumed to be leucocyte-rich PRP.

Injection Technique

In the operation theater, routine monitors were attached to the patient—spo2, ECG, noninvasive blood pressure. Intravenous access was secured. The patient was placed in the prone position with a pillow under the abdomen to minimize lumbar lordosis. A fluoroscope was used to visualize the landmarks for needle insertion in the oblique view. After proper cleaning and draping and all aseptic precautions, a 22-G, 15-cm-long spinal needle was introduced into the desired disc. The end point of needle insertion was the center of the disc, confirmed on anteroposterior and lateral fluoroscopic views. The PRP prepared was mixed with 0.1 mL of 10% calcium chloride and injected into the diseased disk at a dose of 1–2 mL per disk. All patients received antibiotic prophylaxis with a 300-mg intravenous dose of clindamycin 60 minutes before the procedure. After the procedure, patients were taken to a recovery area for monitoring. After 12 hours of observation, patients were discharged and sent home. Patients were instructed to not take NSAIDS for at least two weeks and not receive steroids by any route. Physical therapy was started after four weeks in all the patients, and strenuous physical activity was discouraged during this period. All procedures were carried out with a strict aseptic technique.

Follow-up

Patients were followed up at period of three and six months to see their improvement in pain. The patients were called into the pain clinic and asked about their postprocedure NRS scores, and ODI scores were also calculated. Any adverse events and complications were noted. The data were collected by the investigators involved in the PRP intervention. If no improvement was seen at the end of six months, the patients were advised on other procedures like epidural steroids and radiofrequency ablation.

Outcome Measures

1. NRS and ODI scores were documented before the procedure and at three and six months postprocedure.
2. Platelet counts of the patient and PRP sample were noted and correlated with improvement in back pain and functional status.

Statistical Analysis

With a correlation coefficient of $r = 0.6$ between platelet count and improvement in low back pain, 19 patients were to be included ($\alpha = 0.05$ and power of 0.8). We recruited 25 patients to compensate for loss to follow-up. The Kolmogorov-Smirnov test was applied for checking the normality of data. The Pearson coefficient (r) was assessed for correlation analysis. A P value of <0.05 was considered statistically significant.

Results

A total of 42 patients were screened for discogenic pain after other conditions of low back ache were ruled out. They underwent provocative discography, after which 31 patients had a positive test. A total of 25 patients were recruited after meeting the inclusion and exclusion criteria. Out of the 25 patients recruited, data were analyzed from 20 patients. Three patients were lost to follow-up, while two patients received epidural steroids at other centers. The patient characteristics are shown in Table 1.

The mean patient blood platelet concentration was $195.3 \pm 68.39 \times 10^3/\mu L$. The mean platelet concentration of the PRP samples prepared was $524.95 \pm 232 \times 103/\mu L$ (95% CI = 416.3707–633.5293). Thus, the platelets were concentrated by a mean factor of 2.69 times. The baseline NRS was 5.85 ± 1.14, and the baseline ODI score was 35.7 ± 7.74.

The subsequent NRS and ODI scores at three and six months are shown in Figure 1 and Figure 2. The reduction in mean NRS score was statistically significant at three months ($P = 0.0004$) and six months ($P = 0.00001$). The improvement in mean ODI scores was also significant at three months ($P = 0.0001$) and six months ($P = 0.00001$). The proportions of patients reporting >50% improvement in NRS and ODI scores are presented in Table 2. Four patients (20%) had no pain relief at the end of six months. Two patients had a decrease in pain and disability at three months, followed by an increase in scores at six months. However, these scores were lower than at baseline.

The Pearson correlation coefficients between platelet concentration (PRP) and reduction in NRS and ODI scores are presented in Table 3 and were found to positively correlate with $P < 0.05$. The scatter plot diagrams with regression equations for reduction in NRS and ODI at six months with platelet concentration (PRP) are shown in Figures 3 and 4, respectively. No adverse effects or complications like discitis, bleeding, or intravascular injection were observed in any patient.

Discussion

This prospective interventional trial shows promising results in the treatment of discogenic pain with regenerative therapy in the form of platelet-rich plasma. This study has shown a positive correlation of platelet count

Table 1. Patient characteristics and baseline NRS, ODI scores (SD)

S. No.	Variables	Value
1	Age, mean ± SD, y	34.75 ± 10.15
2	Weight, mean ± SD, kg	69.4 ± 8.52
3	Height, mean ± SD, cm	163.85 ± 7.44
4	Sex ratio (male/female)	12/8
5	No. of patients receiving intervention (1-disc level/2-disc level)	15/5
6	PRP volume per disc, mean ± SD, mL	1.69 ± 0.32
7	NRS—baseline, mean ± SD	5.85 ± 1.14
8	ODI score—baseline, mean ± SD	35.7 ± 7.74

NRS = numeric rating scale; ODI = Oswestry Disability Index; PRP = platelet-rich plasma.

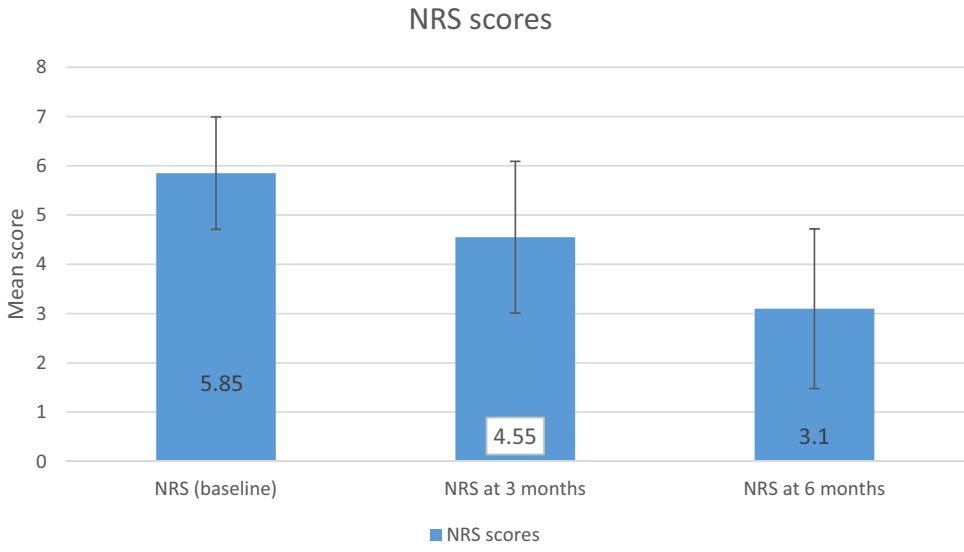

Figure 1. Mean numeric rating scale scores with standard deviation error bars (mean ± standard deviation).

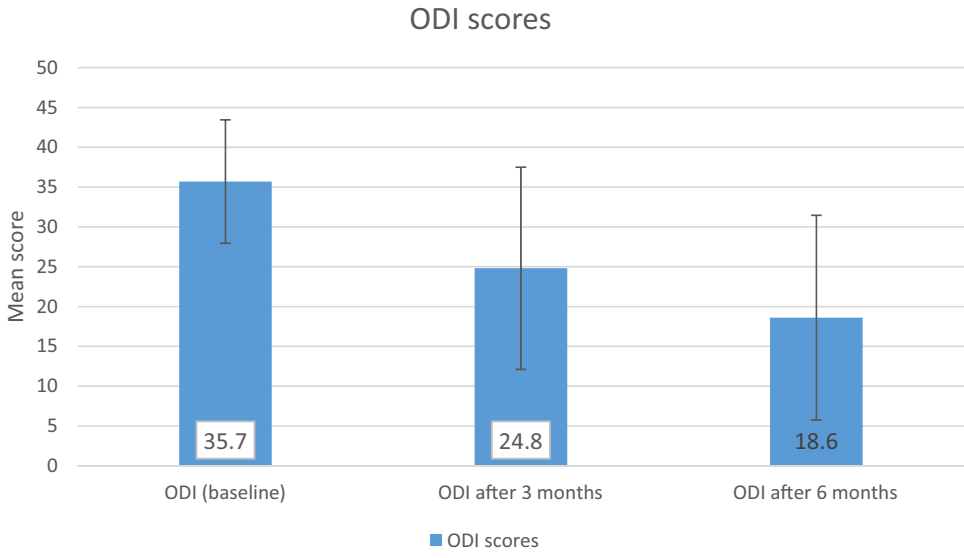

Figure 2. Mean Oswestry Disability Index scores with standard deviation error bars (mean ± standard deviation).

Table 2. Proportion of patients showing >50% reduction in NRS and ODI scores

S. No.	Variable	No. of Patients Reporting >50% Reduction in Scores	Proportion (95% Confidence Interval)
1	NRS at 3 mo	3/20	0.15 (0.0396–0.389)
2	NRS at 6 mo	11/20	0.55 (0.321–0.761)
3	ODI at 3 mo	6/20	0.30 (0.128–0.543)
4	ODI at 6 mo	13/20	0.65 (0.409–0.837)

NRS = numeric rating scale; ODI = Oswestry Disability Index.

Table 3. Correlation coefficient between platelet concentration (PRP) and reduction in NRS, ODI at different time periods

S. No.	Parameters (% Age Reduction)	Pearson Coefficient (r)	P Value	R^2
1	NRS at 3 mo	0.65	0.002	0.43
2	NRS at 6 mo	0.73	0.0002	0.53
3	ODI at 3 mo	0.72	0.0003	0.51
4	ODI at 6 mo	0.7	0.0006	0.49

NRS = numeric rating scale; ODI = Oswestry Disability Index; PRP = platelet-rich plasma.

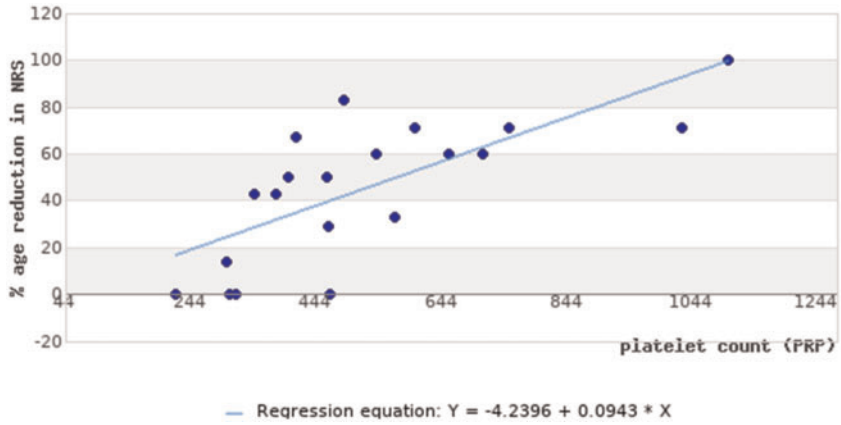

Figure 3. Scatter plot showing the correlation between reduction in numeric rating scale at six months and platelet concentration of platelet-rich plasma sample with regression equation.

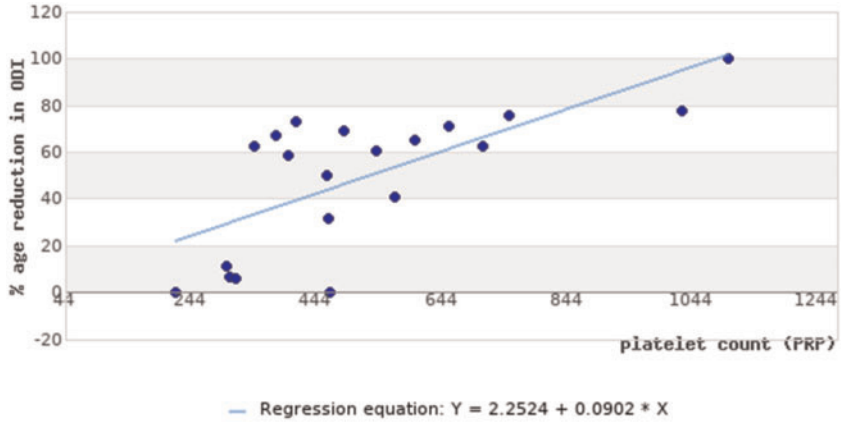

Figure 4. Scatter plot showing the correlation between reduction in Oswestry Disability Index score at six months and platelet concentration of platelet-rich plasma sample with regression equation.

in PRP with improvement in pain and physical functioning, corroborating our hypothesis. Growth factor or platelet concentration has been linked to improved clinical outcomes for degenerative conditions [12]. Concentration has not been evaluated with clinical improvement in degenerative disc disease, and this is probably the first study where platelet counts have been studied. Previous studies have shown mixed results when comparing growth factor concentrations with platelet counts in PRP samples. Growth factor (GF) concentration was not found to correlate with platelet count in two studies, with the authors concluding that GF levels might depend upon the method of separation of platelets and activation [13,14]. However, another study showed positive correlation of growth factors with platelet concentration [15]. In our study, growth factors were not measured, and therefore, we measured platelet count as a surrogate marker.

Correlation of platelet count with clinical and regenerative improvement has not been extensively studied. In a study conducted on rats with patellar tendinopathy, platelet counts of $1{,}000 \times 10^3/\mu L$ were associated with better outcomes compared with concentrations of $500 \times 10^3/\mu L$ [16]. An in vitro study showed optimal growth in fibroblast and osteoblast at a 2.5 times platelet concentration, with higher concentrations resulting in an inhibitory effect [17]. An in vivo study by Weibrich et al. demonstrated a beneficial effect on peri-implant bone regeneration with counts $900–1700 \times 10^3/\mu L$. Both higher and lower counts had a suboptimal effect. Our results showed a beneficial effect even at the highest platelet count ($1{,}100 \times 10^3/\mu L$, which is not in the very high range), which might lead to inhibitory effects.

It is to be noted that we obtained a mean platelet concentration of $525 \times 10^3/\mu L$, which is low compared with concentrations being obtained in other studies. However, we obtained a concentration factor of 2.7, which was satisfactory. This is explained by a low mean platelet count in our study population. Most of the patients who showed poor or no improvement in our study had platelet concentrations $<400 \times 10^3/\mu L$. Thus, obtaining a baseline platelet count becomes important, as a low count might result in an unfavorable outcome. This should be communicated to the patient so that an informed choice is made and expectations are kept accordingly. The treating physician may look for alternative treatments in such cases.

The clinical outcomes of our study are in accordance with previous studies by Levi et al. [18], where the authors used leucocyte-rich PRP, and Akeda et al. [19], who used PRP resealate. Our results closely match the study by Levi et al., where a successful outcome was seen in 32% patients at two months and 47% at six months. They did not use provocative discography for diagnosis of discogenic pain and used lignocaine in their PRP injectate. Thus their results might not be accurate and might explain the lower efficacy. Akeda et al. demonstrated success in 71% of patients within four weeks, which might be attributed to PRP resealate—a leucocyte-poor form of PRP. A randomized controlled study has shown favorable results for intradiscal PRP [20]. They followed the patients only up to eight weeks, with positive outcomes starting from four weeks postinjection. The analysis of content of PRP was not done in this study. The presence of neutrophils has been implicated for inflammation and increased pain due to release of catabolic cytokines. They might counter the anabolic cytokines released by the activated platelets [9]. Our PRP preparation was leucocyte-rich, which might have led to lower successful outcomes. This could also have led to a delayed effect in our study, as pro-inflammatory cytokines would have masked the beneficial effects of PRP. The choice of activation of platelets results in variability of release of growth factors. Though collagen results in activation and is present in the disc material, we added calcium chloride in our PRP sample for more reliable results [21].

We also reported failure of this intervention in four patients, and two patients had an increase in back pain after the initial decrease at three months. Multiple injections of PRP have been tried elsewhere, with mixed results [22], and intradiscal PRP should be limited to one injection until strong evidence favors it owing to serious adverse effects like discitis, which may be associated with disc procedures.

There were several limitations in our study. Follow-up was only for six months. For determining the true efficacy of single-shot PRP, follow-up should have been for one to two years. This would have estimated the duration of effects of single-shot PRP. Neutrophil count was not measured in our PRP samples. The effect of neutrophil count on pain scores and disability could have been evaluated. While performing provocative discography, the control disc was not taken to prevent degeneration. This could have led to a false-positive diagnosis of discogenic pain. However, strict inclusion criteria were kept to suspect discogenic pain by combining clinical and radiological findings. Other causes of localized back ache like facet arthropathy and sacroiliac joint pain were ruled out. Follow-up MRI was not done to observe the radiological improvement in disc degeneration. Various animal studies show regenerative potential in discs with increase in height and hydration [23]. Akeda et al. [19] showed no improvement in MRI after one year, but there was no further degeneration. A case report by Lutz et al. showed increased T2 signal intensity after one year of PRP injection [24].

Conclusions

This study shows a positive correlation between platelet concentration of PRP with improvement in pain and functional status in patients receiving intradiscal PRP for chronic discogenic low back pain. We recommend use of intradiscal PRP for treatment of discogenic pain with

preferably a higher platelet count to elicit a favorable response. Future studies are needed to compare leucocyte-poor PRP and measure growth factor concentration in the PRP sample for disc intervention. Ideally, patients should be followed up to one to two years, preferably with MRI analysis.

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