Randomized Controlled Study

Safety and Efficacy of Platelet Rich Plasma for Treatment of Lumbar Discogenic Pain: A Prospective, Multicenter, Randomized, Double-blind Study

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Background: Interventions for chronic discogenic spine pain are currently insufficient in lowering individual patient suffering and global disease burden. A 2016 study of platelet rich plasma (PRP) for chronic discogenic pain previously demonstrated clinically significant response among active group patients compared with controls.

Objectives: To replicate the previous research to move this intervention forward as a viable option for patient care.

Study Design: A double-blind, randomized, placebo-controlled study.

Setting: Multicenter private practices.

Methods: Twenty-six (12 men, 14 women) human patients, ages 25 to 71 with a diagnosis of chronic lumbar discogenic pain, were randomly assigned to active (PRP) or control (saline) groups in a ratio of 2 active to 1 control. Baseline and follow-up Oswestry Disability Index and Numeric Pain Rating Scale questionnaires were obtained to track patient outcomes at 8 weeks postoperatively.

Results: Within group assessment showed clinically significant improvement in 17% of PRP patients and clinically significant decline in 5% (1 patient) of the active group. Clinically significant improvement was seen in 13% of placebo group patients and no placebo patients had clinically significant decline secondary to the procedure.

Limitations: Possible explanations may include a range of factors including differences in patient demographics, outcome-measure sensitivity, or misalignment of statistical analyses.

Conclusions: These findings are markedly different than the highly promising results of the 2016 PRP study. This study posits necessary caution for researchers who wish to administer PRP for therapeutic benefit and may ultimately point to necessary redirection of interventional research for discogenic pain populations.

Key words: Degenerative, disc, growth factors, lumbar, pain, platelet, plasma, PRP, regenerative, spine

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Given the high prevalence of discogenic back pain and consequent socioeconomic burden, there is a great need to develop cost-effective interventions (1,2). The use of platelet rich plasma (PRP) was considered for such a purpose based on applying autologous regenerative factors (3-10). Preclinical studies of blood plasma substrates demonstrate relevant concentrations of biomolecular materials, including growth factors that have been implicated in cellular growth and repair (1,9,11-14). The process of centrifuge and filtration has also demonstrated an ability to yield highly concentrated solutions of this viable biological material for injection in the patients from which it is derived (4,15). Theoretically, the injection of PRP could multiply the availability of growth factors and cytokines in augmenting healing, collagen synthesis, and cell proliferation, enhancing the body's own regenerative mechanisms in these regions (16). Ideally, for treatment of degenerative disc disease (DDD), this enhancement could include the proliferation and deployment of stem cells in discs and possibly counteract the degenerative process (9,17). This theoretical concept has spurred on recent undertakings to employ PRP in the clinical domain (2-3,18,19). An array of clinical investigations of PRP for treatment of varying orthopedic complaints has demonstrated inconsistent results between positive and negative response to treatment (20,21). In 2016, highly promising results were published by Tuakli-Wosornu et al (16) from a study of PRP for lumbar discogenic pain. This study employed a single-institution, randomized study design. Study inclusion and exclusion criteria were rigorous so that more than half of the patients assessed were excluded. Exclusion criteria included a marked reduction in disc height (Pfirrmann Grade V). Since the initial conceptualization of this study, a 2018 meta-analysis (22) detailing the findings of other uncontrolled single-site studies has again supported the use of PRP as a potentially effective and viable intervention for discogenic pain. In an attempt to evaluate with a more rigorous experimental design, the present study is a multi-institutional, randomized, double-blind, controlled trial of PRP for treatment of lumbar DDD.

Methods

Patients

This study was Institutional Review Board approved and all patients provided written informed consent. The study was initially designed for patients to be randomized in a 2 to 1 ratio of treatment to control arms. This was a multi-institutional study with 5 research sites in the United States. Patients with suspected lumbar discogenic pain, who were already being considered for discography, were identified within the study clinics and given the opportunity to pursue inclusion in this study. No further recruitment was required. In addition to reviewing clinical history and individual patient rating scales, investigators screened patients who had at least 3 months of lumbar pain for inclusion using magnetic resonance imaging (MRI) and discography. Patients with any contraindication for discography or surgery were not able to participate in this study. Upon discography, at least 1 negative level and from 1 to 4 positive levels must be identified for inclusion. Eligible candidate for MRIs, which were required to be no more than 12 months old, were systematically evaluated using the Pfirrmann grading scale with inclusion criteria requiring grade changes of 4 or less at each treatment level. Only candidates with a history of nonresponsive conservative measures, including physical therapy and analgesics, were included in this study. Patients were excluded from this study if they had a history of unresolved lumbar pain from a previous surgery at any level, any indications of root or cord compression at treatment levels, or any diagnosis of a concurrent pain disorder or disability. Patients with active systemic infection or history of disc infection were not included in this study. Additional concerns regarding patient safety and data validity necessitated the exclusion of patients with daily opioid requirements greater than 180 grams of oral morphine equivalent per day, untreated disabling thought or mood disorders, or an inability to provide informed consent. Patients in socially compromised conditions, such as prisoners, were not able to enroll in this study.

Procedure

Active (PRP) and control (saline) groups were randomly assigned upon enrollment for all patients. Eligible candidates met with a study research coordinator for informed consent and administration of baseline questionnaires, at which point the process of blinding, follow-up, and all other study-related considerations were directly addressed. Baseline and follow-up questionnaires included the Oswestry Disability Scale (ODI) (23) and Numeric Pain Rating Scale (NPRS) (24), which served as primary outcome measures (25). Upon confirmation, screening and consent documents were

forwarded to the primary research coordinator, who identified a randomized treatment assignment (PRP or placebo). This was done according to a consecutive list created with an online randomization generator, which was for a ratio 2 active to 1 placebo assignment. Patients and all other study staff, including the treating physician, were blinded from the treatment assignment with the exception of one research staff member per study clinic. The unblinded coordinator for each site was confidentially informed of the active or placebo assignment in order to prepare the PRP or saline injection materials for the procedure without any identifying labels or indicators (see supplementary materials). The unblinded coordinator did not have any contact with patients during or after the study injection. The treatment procedure took place within 2 weeks of enrollment, and baseline measurements were completed within this 2-week window prior to the injection. Standardization of the procedure was clearly outlined for uniformity across all sites, and the product representative trained each study physician and relevant staff members on the procedure. Additional instructional materials, including video and written instructions, were also available to each study site to promote consistency (see supplementary materials). At the time of the procedure, patients were again briefed on the nature of the study and procedure including the process of blinding. Preoperative, intraoperative, and postoperative procedures were carried out in accordance with the standard of care and standard operating procedures of the surgical facility. All patients had blood drawn during the procedure. Those assigned to the active condition were injected with PRP at the symptomatic treatment levels, while saline was used for the control group injection. Enrolled patients were required to follow-up with a blinded investigator at 4 weeks and 8 weeks for data collection and safety monitoring. Eight-week data, including the NPRS and ODI questionnaires were collected for study data. At the 8-week follow-up visit, after completing all study-related questionnaires, research coordinators were permitted to reveal the patient's treatment assignment. Control patients were given the opportunity to crossover to receive the active placebo intervention after unblinding. If the decision to crossover was made, patients were again screened for eligibility. All patients were instructed to follow-up at 26 weeks post-procedure for continued safety monitoring. Those who underwent the crossover PRP procedure were instructed to follow-up 8 weeks and 26 weeks following this procedure.

Surgical Procedure and Materials

All patients had needles placed according to the standard discogram procedure. Twenty-five-gauge needles either with the single-needle or double-needle technique were aimed to the disc center on anterior, posterior, and lateral fluoroscope images. Only the unblinded nurse or technician was aware of the treatment condition at the time of the intervention and this individual had no further contact with the patient. All patients had 50 mL of blood drawn and this material was given to the unblinded nurse for further preparation. Further processing was done in a concealed manner. For placebo injections, saline was placed in centrifuges and run for the duration required for PRP preparation. Three mL of saline were then placed in 3 cc Merit Medallion syringes with opaque tape covering the barrel and connecting tubing to completely conceal the properties of the enclosed fluid. For PRP injections, the 53 mL of blood drawn were processed via centrifuge. The whole blood from the patient was mixed gently with a sodium citrate anticoagulant to prevent coagulation. Then, the anticoagulated whole blood was added to the concentration device through the needle-less port. Balance was ensured in the centrifuge using a counterbalance device with the same volume as the concentrating device placed directly opposite to each other in the centrifuge rotor buckets. A double-spin technique was used:

First Spin:

1. Platinum series centrifuge at PUREPRP SP SPIN 1
2. Executive series centrifuge at 3.8 x 1000 RPM (3800 RPM) for 1.5 minutes

Second Spin:

1. Platinum series centrifuge at PUREPRP SP SPIN 1
2. Executive series centrifuge at 3.8 x 1000 RPM (3800 RPM) for 5 minutes

After the double spin, the platelet concentrate, buffy coat separated at the bottom of the concentrating accessory. The platelet poor plasma was then aspirated leaving approximately 2 mL of plasma, which was attached to a 12 mL syringe and then swirled gently to re-suspend the platelet buffy coat into the plasma. The PurePRP was then extracted. This pure version of PRP removes 99% of the red blood cells and neutrophils, and is commonly referred to as leukocyte poor. The yield of EmCyte's high-yield PRP, the supernatant, except for a residual 2 mL, was drawn. The 25-30 mL of supernatant was then processed with the BioRich Medical ProPlaz Protein Plasma Concentrator filter by attachment of

the syringe to one end of the filter, priming for removal of air and subsequent attachment of another sterile syringe. Once primed for the removal of air for the target reduction of half the original volume, the prepared 4 mL of plasma concentrate were added to the PRP for a total of 6 mL. Again, the barrel was covered with opaque tape to conceal the fluid chamber. Following this preparation and directly before the procedure, the treating physician began provocative discography with contrast as is standard practice. Each disc tested, however, had its own contrast line to which the treatment or sham syringes (identical in appearance) could be attached for administration. After injection of ¼ to ½ cc of contrast, connection lines were clamped, and the contrast syringes were replaced with the study syringe. The amount of 1.5 mL of study materials were injected into each target lumbar disc so that each disc received approximately 2 mL. Total volume of materials, disc integrity, and patient pain response were noted along each step of this procedure.

Data Maintenance and Interpretation

The primary research coordinator oversaw all collection and distribution of relevant study and patient information. Patient information was maintained confidentially as is the ethical standard for medical practice and research. All private health information was transmitted confidentially and maintained in an anonymized, password-protected electronic database and in study binders kept under lock and key within the study facility. All study data were collected within one week of the defined schedule of events (i.e., 8-week data could be collected between 7 and 9 weeks following the procedure). Responsive outcomes for the given intervention was defined as a 30% improvement on both primary endpoints, ODI and NPRS, as is supported by investigations regarding the utility of these clinical measures (4). Clinically relevant declines of 30% or more were also noted.

Results

The study was initially designed to include 60 patients in total (2 to 1 ratio, power 80%, alpha .05). A planned futility analysis, however, prompted an early termination of the study. Eight control (saline) and 18 active (PRP) patients were randomly assigned for a total of 26 patients (men: n = 12, women: n = 14) enrolled across 5 research sites in the United States. Clinically significant pain relief defined as a 30% reduction on both measures at 8 weeks was seen in less than 30% of patients in both PRP and control patients (17% and 13% of patients in PRP and control groups, respectively). Clinically meaningful improvement was seen in just over 30% of patients in both PRP and control groups when considering ODI results in isolation (38% of PRP and 39% of control patients). Looking at the NPRS alone, a clinically significant improvement was seen in 38% of saline patients, but only 22% of PRP patients demonstrated this improvement. Considering the most liberal definition of efficacy (a relief in either 1 or both 2 outcome measures), 44% of the PRP group and 63% of the control group demonstrated a clinically meaningful improvement. Further interrogation demonstrated 16.8% prevalence of a clinically meaningful improvement of 50% or more on one or more of the outcomes. One patient (5%) in the PRP group demonstrated a clinically meaningful decline in condition, while no patients declined significantly in the control group secondary to treatment. Similarly, repeated measures analysis of variance did not reveal any significant differences in the ODI or Visual Analog Scale (VAS) (all P's > 0.1) between the PRP and control group. Post hoc analyses indicated that women tended to report greater improvement from baseline to follow-up than men ($F[1, 26] = 3.15$, $P = 0.08$). However, there was no significant difference in response to treatment between men and women ($P > 0.1$). Results did not change when co-varying for patient age. Similarly, patient age was not significantly correlated with baseline, follow-up, or change scores for the VAS or ODI. Further, observations of percentages at each study site showed no obvious trends in data at a particular site. There were no adverse events reported in this study.

Discussion

The safety of this procedure continues to be supported by the lack of adverse events and consistent patient tolerance. However, results do not demonstrate a significant benefit with the given PRP intervention according to the primary outcome of this study, which was defined as a 30% improvement on both the NPRS and ODI after 8 weeks. The most liberal interpretation of results (defined as greater than 30% improvement on at least one measure) does indicate clinically meaningful benefit at 8 weeks in 44% of active group patients, but this trend is even more prevalent in the control group (63%). Based on the results of a planned futility analysis, no significant improvement in overall treatment outcomes would have been gained by continuing the study to completion. Overall, these findings

do not match the promising results of previous studies (16,21,22) but seem to suggest a strong placebo response, particularly considering the greater prevalence of reported improvement among control group patients compared with the active group. While the minimal positive outcome seen in this study does not seem to support the theoretical framework and previous trials, an overall deficiency in this framework may not necessarily be suggested. Criteria for a responsive outcome in the present study differed from that of Tuakli-Wosornu et al (16), which defined improvement on a numeric rating scale of the patients' "best pain" (least intense) around the time of evaluation to indicate improvement. "Worst pain" and "current pain" in the previous study (16) did not demonstrate improvement. The present study integrated each of these factors into one scale and tested for clinically meaningful change overall along with improvement on a separate measure altogether. This increased threshold for improvement could explain the difference in data interpretation, and further study may be needed to investigate which observations better depict clinical improvement in a real-world setting. The observation of more prevalent relief among control group patients in this study, which was not seen in the prior study, however, is not likely explained by differences in outcome criteria alone. The primary differences between the present study and previously published PRP studies with positive clinical outcomes, are the method of formulation of the PRP itself (described previously and below) and the treatment target (herein spinal pain). In the present study, concentrated plasma was used to re-suspend the platelet infranatant. This difference from prior studies (20-22) is not likely to be an explanation for lack of effectiveness of the injectate since, if anything, more potentially useful soluble factors are provided including exosomes and alpha-2-macroglobulin. A likely factor explaining a poor outcome with PRP, however, is that the intradiscal environment is a hostile related to low oxygen tension, poor vascular supply, and the limited potential for chemotaxis and proliferation of regenerative cells. Regardless of the exact mechanism of action, as some previous studies have already suggested (17,21,27,28), the present results further necessitate caution in proceeding with PRP interventions without further positive studies. Further studies should also investigate the effect of saline as an intervention instead of its use as a placebo in this study. Our data suggested it worked almost as well as the PRP group, and this warrants further investigation.

Conclusions

In the future, a third arm of a true control group would be necessary to understand the differences between PRP and saline interventions. A needle only would be advisable to obtain this kind of control. A small sample size clearly limits the ability to draw more concrete conclusions. At this juncture in time, bone marrow concentrate appears to have preliminary evidence for benefit in patients with discogenic pain and may continue to be considered as an alternative therapy (28).

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