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Original Research—CME

Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study

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Abstract

Objective: To determine whether single injections of autologous platelet-rich plasma (PRP) into symptomatic degenerative intervertebral disks will improve participant-reported pain and function.
Design: Prospective, double-blind, randomized controlled study.
Setting: Outpatient physiatric spine practice.
Participants: Adults with chronic (≥6 months), moderate-to-severe lumbar diskogenic pain that was unresponsive to conservative treatment.
Methods: Participants were randomized to receive intradiskal PRP or contrast agent after provocative diskography. Data on pain, physical function, and participant satisfaction were collected at 1 week, 4 weeks, 8 weeks, 6 months, and 1 year. Participants in the control group who did not improve at 8 weeks were offered the option to receive PRP and subsequently followed.
Main Outcome Measures: Functional Rating Index (FRI), Numeric Rating Scale (NRS) for pain, the pain and physical function domains of the 36-item Short Form Health Survey, and the modified North American Spine Society (NASS) Outcome Questionnaire were used.
Results: Forty-seven participants (29 in the treatment group, 18 in the control group) were analyzed by an independent observer with a 92% follow-up rate. Over 8 weeks of follow-up, there were statistically significant improvements in participants who received intradiskal PRP with regards to pain (NRS Best Pain) ($P = .02$), function (FRI) ($P = .03$), and patient satisfaction (NASS Outcome Questionnaire) ($P = .01$) compared with controls. No adverse events of disk space infection, neurologic injury, or progressive herniation were reported following the injection of PRP.
Conclusion: Participants who received intradiskal PRP showed significant improvements in FRI, NRS Best Pain, and NASS patient satisfaction scores over 8 weeks compared with controls. Those who received PRP maintained significant improvements in FRI scores through at least 1 year of follow-up. Although these results are promising, further studies are needed to define the subset of participants most likely to respond to biologic intradiskal treatment and the ideal cellular characteristics of the intradiskal PRP injectate.

Introduction

Low back pain (LBP) is a common, often confounding problem for patients and physicians. In the United States, at least 80% of adults experience at least 1 episode of LBP during their lifetime [1]. LBP is the most common cause of disability among Americans between 45 and 65 years of age [2]. Furthermore, of all musculoskeletal conditions, LBP imposes the greatest economic burden on the U.S. health care system [3]. Although most cases of LBP are self-limited, approximately 20% recur within 6 months of the initial episode and a subset of patients experience chronic symptoms thereafter. For individual patients and the national health care system, LBP imposes high physical and financial costs [4,5].

Numerous anatomic structures can cause LBP [6-8]. The intervertebral disk (IVD) accounts for 40% or more cases of chronic LBP [9]. Noninvasive imaging methods used to identify spine pathology have limited ability to determine the exact source of pain [10-13]. Diskography, although controversial, remains a provocative diagnostic test for pain generated by the IVD [14].

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The adult IVD is the largest avascular structure in the human body. Small branches of the metaphyseal arteries around the outer annulus comprise its limited vasculature. IVDs therefore rely on passive diffusion from adjacent endplate vessels for nutrition [15]. With limited vascular supply and largely indirect access to nutrition, the IVD has poor inherent healing potential. The rationale behind intradiskal injection of platelet-rich plasma (PRP) is to place a high concentration of growth factors directly at the site of collagen injury or degeneration, where they are habitually found in low concentration. We hypothesize that circulating growth factors (eg, platelet-derived growth factor, transforming growth factor, insulin-like growth factor, and vasoendothelial growth factor) and cytokines in PRP will act as humoral mediators to induce the natural healing cascade [16-18]. Preclinical, in vitro studies support this hypothesis. Analysis of PRP-infused human IVD specimens demonstrated cell proliferation and differentiation, as well as up-regulated type II collagen and proteoglycan synthesis via chondrogenesis [19]. In an animal model, intradiskal PRP led to restoration of normal cellular architecture and disk height in an experimentally injured IVD [20,21].

Readily available and cost-effective compared with surgical options, a prohealing therapy such as autologous PRP suits the pathoanatomic cascade that episodic LBP represents. In comparison with surgical management of the internally disrupted IVD, autologous PRP could be a safer and more cost-effective therapy if proven to be of benefit.

A major advantage of PRP is its breadth of potential clinical applications. Unlike an isolated growth factor, PRP is a mixture of autologous growth factors, cells, and fibrin readily accessible for use. The injection of fibrin itself may catalyze sealing of annular fissures [22]. Potential disadvantages of PRP include the relatively small amount of growth factor delivered (nanogram scale) and the variance of composition from subject to subject. Among other considerations, subject cell count and the specific harvesting system used influence the final constituent factors of the PRP graft. Although PRP has demonstrated promising results for a variety of musculoskeletal conditions, small sample sizes and lack of standardization of graft preparation have hampered research efforts. This study sought to investigate whether a single intradiskal injection of PRP, delivered to the symptomatic IVD(s), would confer clinical benefit for individuals with chronic diskogenic LBP.

Materials and Methods

Study Design

This was a prospective, double-blind, randomized, controlled study of participants with chronic lumbar diskogenic pain treated with an intradiskal PRP injection. The study was approved by the Hospital for Special Surgery Institutional Review Board and the Conflict of Interest Committee in Research (Institutional Review Board #29-025). The study was funded by the institution's Physiatry Research & Education Fund. The PRP preparation kits and centrifuge were donated by Harvest Technologies Corporation (Plymouth, MA).

Primary Hypothesis

Single injections of autologous PRP into symptomatic degenerative IVDs will improve participant-reported pain and function.

Participant Recruitment

One hundred nine participants were assessed for eligibility at a single academic outpatient spine practice between May 2009 and November 2013 based on the general inclusion and exclusion criteria set forward (Table 1). Fifty-one participants were not enrolled in the study (26 did not meet inclusion criteria and 25 declined to participate). A total of 58 participants met the prediskography inclusion criteria and were randomized for inclusion into the study. After diskography, 7 participants were excluded because of either the presence of a Grade V annular fissure or the lack of concordant pain at time of injection with contrast. Three participants failed to maintain inclusion/exclusion criteria after undergoing the procedure, and 1 was lost to follow-up, yielding a follow-up rate of 92% (Figure 1).

Study Protocol

Participants with a history of chronic axial LBP who met inclusion and exclusion criteria were recruited. Participants were evaluated by 2 interventional spine and sports medicine physiatrists within the same practice and enrolled in the study if prediskography inclusion criteria were met. General demographic information, including age and gender, as well as baseline outcome scores, were obtained from participant charts and questionnaires. Baseline information was obtained from each participant before diskography via the Functional Rating Index (FRI), Numeric Rating Scale (NRS), and the 36-Item Short Form Health Survey (SF-36) questionnaires. Each participant was then required to complete repeat questionnaires that also included a modified North American Spine Society (NASS) Outcome Questionnaire at 1 week, 4 weeks, 8 weeks, 6 months, and 12 months or more postinjection.

At enrollment, typically 2 weeks before treatment, participants provided informed consent, a baseline assessment, and blood samples via venipuncture to assess white blood cell count, erythrocyte sedimentation rate, prothrombin time, and International

Table 1
Inclusion and exclusion criteria for study participation

Inclusion Criteria	Exclusion Criteria
• Refractory low back pain persisting for ≥6 mo • Failure of conservative treatment measures (oral medications, rehabilitation therapy,* and/or injection therapy) • Maintained intervertebral disk height of at least 50% • Disk protrusion less than 5 mm on magnetic resonance imaging or computed tomography scan • Concordant pain on diskography • Presence of a grade 3 or 4 annular fissure as determined by diskography • Absent contraindications (eg, spinal stenosis)	• Presence of a known bleeding disorder • Current anticoagulation therapy • Pregnancy • Systemic infection or skin infection over the puncture site • Allergy to contrast agent • Presence of a psychiatric condition (eg, posttraumatic stress disorder, schizophrenia) • Solid bone fusion preventing access to the disk • Severe spinal canal compromise at the levels to be investigated • Extrusions or sequestered disk fragments • Previous spinal surgery • Spondylolysis • Spondylolisthesis • Discordant pain on diskography • Presence of a grade 5 annular fissure with demonstrated extravasation of contrast

* Note: Our standard physical therapy prescription focuses on patient education regarding proper ergonomics, back care principles, and progressive exercise instruction to increase core strength and flexibility in a spine safe manner. The program trial is usually twice weekly for a minimum of 6 weeks.

Normalized Ratio (INR) to ensure all values were within normal limits. Just before diskography, a blood sample of 30 mL was drawn from all participants to ensure participant blinding to treatment. All blood samples were processed via a centrifuge (Harvest Technologies Corporation, Plymouth, MA) to produce 3-4 mL of autologous PRP for each participant.

The participants were randomized into 2 parallel groups, the treatment or the control group (2:1 ratio, respectively), by an independent observer who drew a card from a sealed envelope. A 2:1 ratio of sealed envelopes, containing treatment or control cards, was prepared by the independent observer before the initial participant recruitment.

A covered syringe containing 3-4 mL of PRP (treatment group) or contrast agent (control group) was then prepared under a standardized protocol. The entire syringe was covered with an opaque sleeve by an independent observer to ensure its contents were not visible. The participant was taken to the interventional

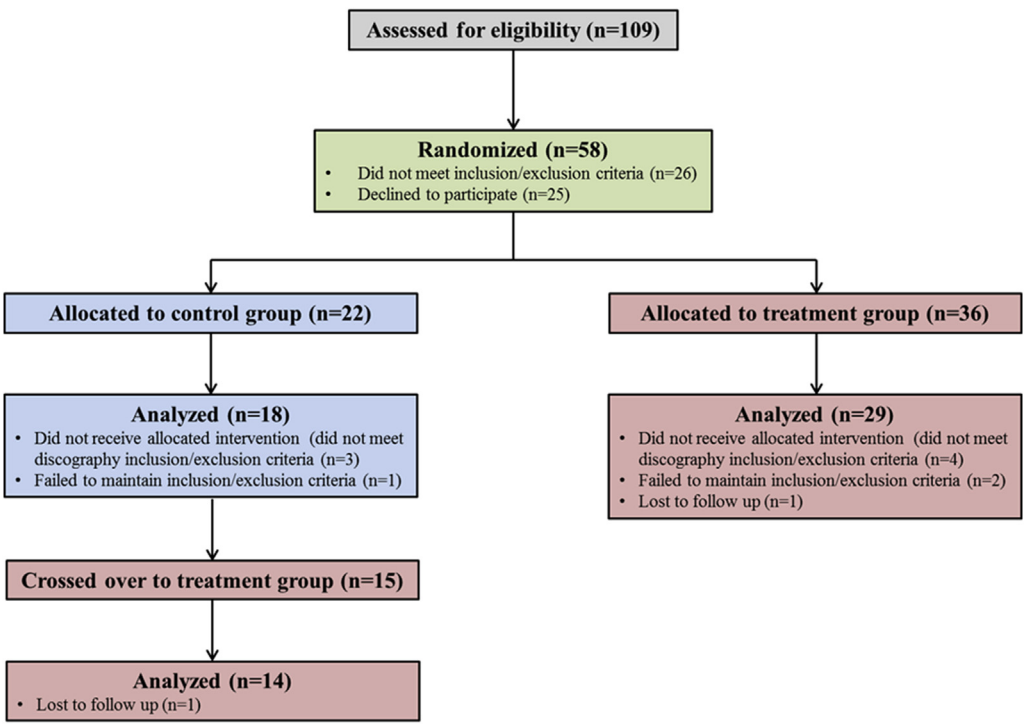

Figure 1. Flow chart of study participant enrollment, randomization, and analysis.

procedure suite and placed prone on the fluoroscopy table. After a standardized sterile preparation, local anesthesia was administered. With a standard double-needle, extrapedicular technique, a 25-gauge spinal needle was advanced through a 20-gauge introducer needle into the mid-portion of the suspected disk levels, as well as into a control level. Anteroposterior and lateral fluoroscopic imaging confirmed proper needle position. A volume of 1-2 mL of contrast agent (Omnipaque 180, Amersham Health, Princeton, NJ) was injected while the participant's pain response and disk architecture were recorded.

As soon as the participant endorsed concordant pain reproduction and there was evidence of contrast filling an annular fissure, the covered syringe was attached to the needle hub by an independent physiatrist to maintain blinding. No extension tubing was used during the injection. Only disk levels that elicited concordant pain with evidence of incomplete annular disruption ($<$2 mL) were then injected additionally with either 1-2 mL of PRP or 1-2 mL of contrast agent. Both the physician and participant remained blinded. If more than one disk was symptomatic with reproduction of concordant pain, the PRP or contrast was divided into equal doses and injected into each of the affected disks. All participants had a peripheral intravenous access placed and received 1 g of cefazolin (Ancef; GlaxoSmithKline, Philadelphia, PA) 30 minutes before the procedure.

Postdiskography computed tomography scan images, when obtained, were used by the treating physician to visualize and categorize the architecture of the IVD according to the Dallas Discogram Classification [23]. This same information could later be used for surgical decision-making if necessary. The treating physicians remained blinded to the computed tomography scan images during the initial 8-week follow-up period.

Follow-up questionnaires were then administered by an independent observer at the designated time points. After 12 months, a small subset of participants were tracked annually for up to 2 years. All participants who had no clinical improvement (ie, those who did not meet or surpass the minimal clinically significant outcome measure improvements) at 8 weeks were unblinded. If they were initially in the control group, they were offered intradiskal PRP for their symptomatic disk(s). Those in the PRP group who had no clinical improvement were managed with other continued conservative treatments, or went on to surgery.

Outcome Measures

Primary outcomes measures included postprocedure improvements in pain, function, and participant satisfaction. Secondary outcomes were untoward side effects, including increased pain, bleeding, infection, and neurologic deficits. Four internationally validated surveys were used as outcome measures: the FRI, the NRS, the SF-36, and the modified NASS Outcome Questionnaire. Only the physical functioning and pain sections were scored on the SF-36 [24,25]. The FRI was designed for participants with spinal disorders to measure participant perception of function and pain related to performing dynamic movements and holding static positions [26]. The minimum clinically important difference (MCID) of the FRI is a 9-point change [27]. The NRS for pain is commonly presented as a 100-mm horizontal line on which pain intensity is indicated by a point between 0, ie, "no pain at all" and 10, ie, "worst pain imaginable." Participants were asked to tick an integer representing current pain, pain at best, and pain at worst [28]. The MCID of the NRS is a 2-point change [29]. A change of 4.9 and 10 points constitute a MCID in the SF-36 physical functioning and SF-36 pain scores, respectively [28,30]. The modified NASS Outcome Questionnaire measures participant satisfaction with the procedure. The questionnaire used in this study is a version of a questionnaire used in prior studies by other authors [31,32].

A sample size of participants (48 treatment participants, 24 control participants) was estimated by power analysis to achieve greater than 80% power to detect a 9-point change in FRI score with estimated standard deviations of plus or minus 15 in a 2-way repeated measures analysis of variance model with 5 time points.

Statistical Analysis

Overall summary statistics were calculated in terms of means and standard deviations for continuous variables and frequencies, and percentages for discrete variables. Baseline group differences for continuous variables were evaluated using independent sample *t*-tests, and χ^2/Fisher exact tests were used for the discrete variables. To assess the differences in participant reported outcome measures between PRP and control groups over time and to adjust for missing data at any given time point and the variation of the duration of follow-up time, generalized linear mixed-effect models were built. Multiple models were built to evaluate model fit based on variance-covariance structures. On the basis of the results from the -2 Log Likelihood, the Akaike Information Criterion, and Schwarz Bayesian Criterion, final models with an unstructured variance-covariance structure were reported [33]. Analysis of the within-group changes over time for the PRP group were assessed with a similar model. Bonferroni corrections were applied to the analyses of inter- and intragroup changes over time by multiplying the corresponding *P* values by factors of 3 and 5, respectively, to account for multiple comparisons [34,35]. The effective level of significance was .05 for all reported *P* values. Differences in mean PRP group scores at discrete follow-up time points compared with those at baseline were assessed using paired *t*-tests. Measures of the

Table 2
Baseline patient characteristics and patient reported outcome scores between control and PRP groups

	Control Mean or N	Control SD or %	PRP Mean or N	PRP SD or %	*P* Value
N	18		29		
Age	43.80	8.91	41.40	8.08	.359
Female gender	16	84.2%	15	51.7%	.031

PRP = platelet-rich plasma; SD = standard deviation.

association between treatment group and participant-reported satisfaction were calculated using odds ratios with observed level of significance determined by Pearson χ^2 test. Statistical significance for measures of association was set to .05. All analyses that estimated marginal means for levels of factors and factor interactions were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY).

Results

PRP Versus Control Evaluation

From 2009 to 2013, 109 participants were assessed for lumbar back pain for potential eligibility by the senior investigator (G.E.L.). Of those participants, 26 failed to meet the full inclusion and exclusion criteria, and 25 declined to participate in the study. The final number of participants that were randomized was 58 participants (53.2%). Of those 58 participants, 36 were randomized to the treatment group (62.1%) and 22 were randomized to the control group (37.9%). In the treatment group, 29 of the 36 participants were used for analysis (80.6%), whereas 18 of the 22 control group participants were used (81.2%).

Demographic characteristics in the 2 study groups are reported in Table 2. Mean age between the 2 groups were not significantly different. The control group had a mean age of 44 years and the treatment group had a mean age of 41 years ($P = .36$). There was a significantly greater proportion of female patients who were randomized to the control group (84.2%) than there was in the treatment group (51.7%) ($P = .03$) (Table 2).

During the 8-week follow-up period in the comparative component of the study, the PRP group demonstrated significant improvement in several outcome measures. The interaction effect of the between group comparisons over 8 weeks showed a significant effect in FRI score, indicating that the PRP group had significantly changed over 8 weeks compared with changes in the control group ($P = .03$) (Table 3). Participant-reported NRS best pain score showed a significant difference over 8 weeks compared with the control group ($P = .02$). Group changes over 8 weeks were not found to be significant in the self-reported current pain, worst pain, SF-36 Pain, and SF-36 Function scores ($P = .16$, $P = .09$, $P = .08$, and $P = .44$ respectively) (Table 3). Changes in PRP and control groups over time are illustrated in Figures 2-7.

At 8 weeks, participants who received PRP were more likely to report satisfaction with their treatment than

Table 3
Results of patient-reported outcome scores between control and PRP groups over time

Outcome	Time	Control Mean	SD	PRP Mean	SD	*P* Value*
FRI	Baseline	45.37	15.61	51.47	15.62	.027
	1 wk	45.99	15.74	49.83	15.72	
	4 wk	44.17	17.14	43.25	16.68	
	8 wk	44.45	19.60	37.99	19.60	
SF-36 Pain	Baseline	47.92	21.13	43.28	21.11	.079
	1 wk	47.22	21.76	40.52	21.76	
	4 wk	47.22	19.98	55.17	19.98	
	8 wk	52.78	22.19	61.29	22.19	
SF-36 Physical Function	Baseline	56.11	18.54	56.40	18.52	.435
	1 wk	51.28	20.04	51.63	20.46	
	4 wk	60.97	21.43	58.43	21.17	
	8 wk	57.08	22.91	61.70	22.89	
Current Pain	Baseline	4.61	2.21	4.74	2.21	.157
	1 wk	4.78	1.99	4.21	1.99	
	4 wk	4.61	2.21	4.00	2.21	
	8 wk	4.39	2.59	3.09	2.59	
Best Pain	Baseline	2.08	1.74	2.81	1.78	.015
	1 wk	2.44	1.82	2.88	1.83	
	4 wk	2.28	1.82	2.53	1.83	
	8 wk	2.72	2.12	2.00	2.06	
Worst Pain	Baseline	7.72	1.53	7.98	1.56	.086
	1 wk	7.39	1.95	6.86	1.94	
	4 wk	7.11	1.91	6.41	1.88	
	8 wk	6.83	2.33	5.82	2.33	

PRP = platelet-rich plasma; SD = standard deviation; FRI = Functional Rating Index; SF-36 = 36-Item Short Form Health Survey.
* *P* value indicates significance of interaction effect of treatment over time.

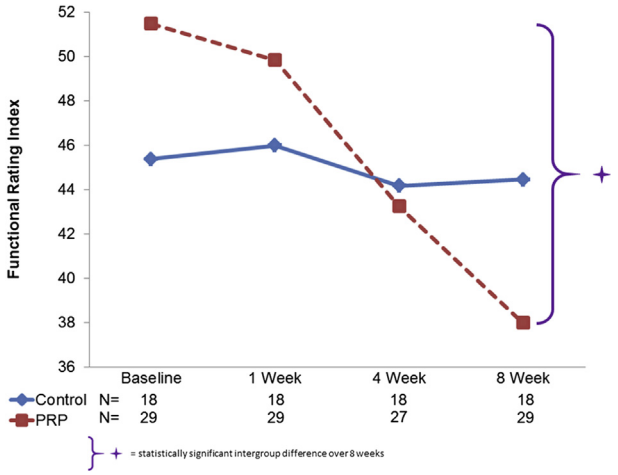

Figure 2. Change in Functional Rating Index over time from baseline to 8 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number observations analyzed at the given time point.

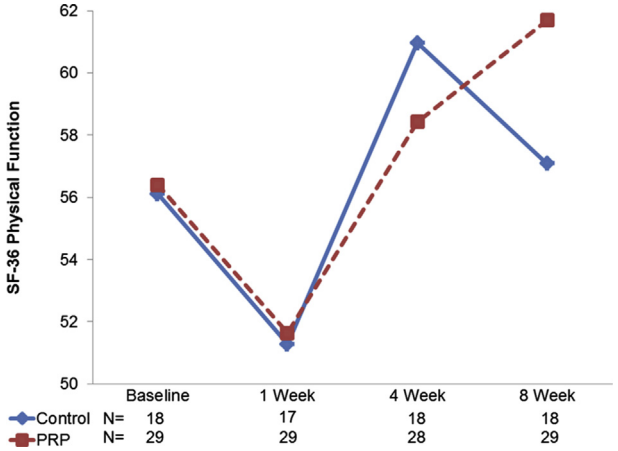

Figure 4. Change in 36-Item Short Form Health Survey (SF-36) Physical Function over time from baseline to 8 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number of observations analyzed at the given time point.

those in the control group. Among the PRP group, 56% (15/27) of the participants were satisfied with or would undergo the same treatment compared with 18% (3/17) of control participants. The odds of a participant in the control group being dissatisfied was 5.83 times the odds of a participant in the PRP group being dissatisfied (odds ratio: 5.83, 95% confidence interval: 1.17 to 37.47, $P = .01$) (Table 4).

PRP Longitudinal Data

Longitudinal analysis of the PRP group consisted of 28 participants who reached the 6-month follow-up time point and 21 participants who reached the 1-year time point. Statistically significant improvements from baseline to 6 months were observed in NRS Worst Pain (1.66-point change) ($P < .01$), FRI (12.92-point change) ($P < .01$), and SF-36 Pain (14.67-point change) ($P = .03$). Statistically significant improvements from baseline to 1 year were observed in NRS Worst Pain (2.12-point change) ($P < .01$), FRI (17.49-point change) ($P < .01$), SF-36 Pain (24.51-point change) ($P < .01$), and SF-36 Physical Functioning scores (16.80-point change) ($P < .01$) (Table 5). PRP and control group outcomes were not compared after 8 weeks.

Safety

There were no reported complications after the intradiskal injection of PRP or additional contrast.

Discussion

This preliminary study was designed to evaluate the clinical effectiveness of intradiskal autologous PRP for a subset of participants with chronic lumbar diskogenic

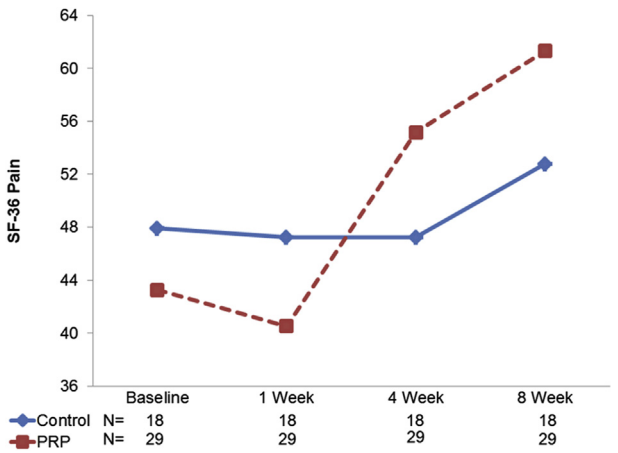

Figure 3. Change in 36-Item Short Form Health Survey (SF-36) Pain Score over time from baseline to 8 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number of observations analyzed at the given time point.

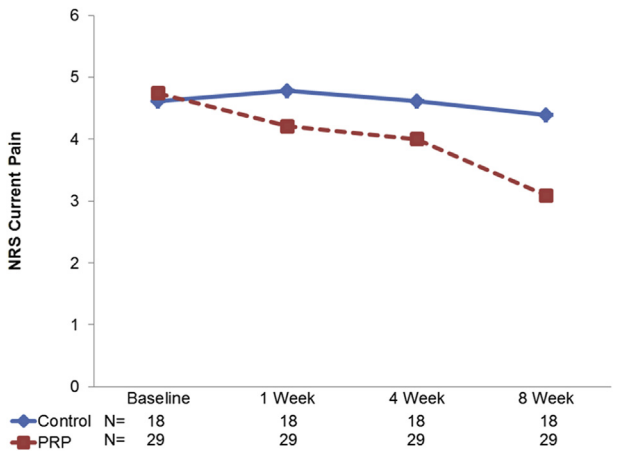

Figure 5. Change in Numeric Rating Scale (NRS) Current Pain over time from baseline to 8 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number of observations analyzed at the given time point.

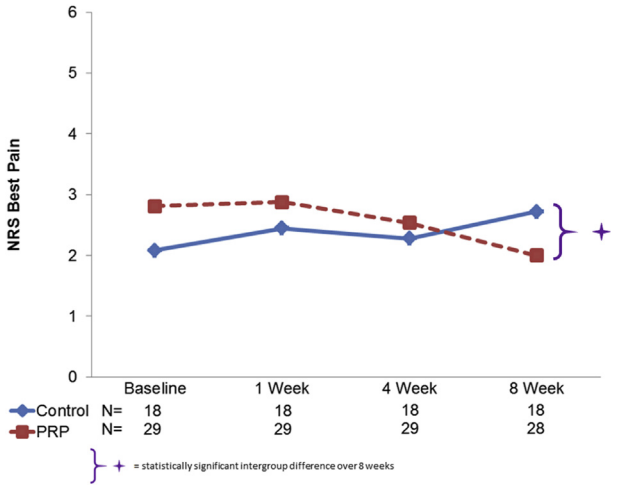

Figure 6. Change in Numeric Rating Scale (NRS) Best pain over time from baseline to 8 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number of observations analyzed at the given time point.

pain. To our knowledge, this is one of the first clinical studies investigating the efficacy of an intradiskal cell therapy in a double-blind, randomized controlled study design.

The strengths of this study were its double-blind, randomized, controlled trial design, the rigorous participant selection process, the high follow-up rate, and long term data (ie, at least 1 year) in the majority of participants. Although the number of participants was relatively low, this study detected statistically significant improvements in NRS Best Pain, FRI, and NASS satisfaction between the treatment and control groups over 8 weeks. In addition, the beneficial effects of PRP were sustained for at least 1 year with respect to the FRI Index. No participant in the treatment group experienced complications, including progressive disk herniation, neurologic injury, or disk space infection.

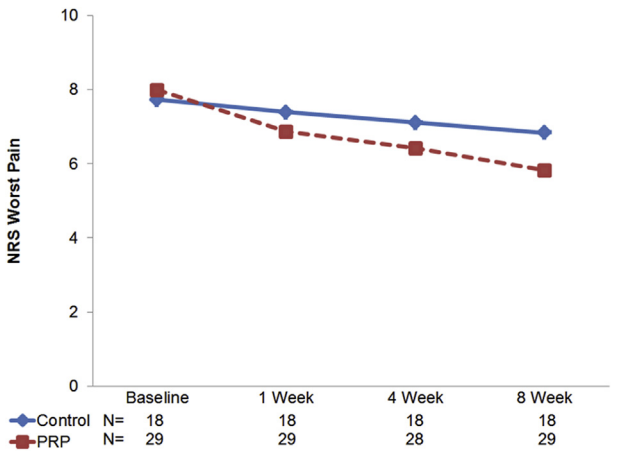

Figure 7. Change in Numeric Rating Scale (NRS) Worst Pain over time from baseline to 8 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number of observations analyzed at the given time point.

Meticulous participant selection was critical for the study. Inclusion and exclusion criteria were rigorous, thus explaining the 4-year time period necessary to enroll 51 eligible participants. Among the authors, it was agreed that PRP is a targeted annular therapy. If the disk protrusion was significant (>5 mm) and the endplates were degenerated, targeted annular therapy would likely be of no clinical or functional benefit. Complete, Grade V annular fissures also were excluded, because then the injectate would likely flow out of the disk into the epidural space. This would allow little to no opportunity for the PRP graft to effect an intradiskal pro-healing change.

Interestingly, participants who elicited concordant pain at 2 levels and were treated with PRP for both disks showed superior improvements in all outcome measures at 1 year compared with those participants who elicited concordant pain at one level and subsequently received treatment for the single disk. There were no significant differences in mean outcome measure scores at baseline between these 2 subgroups.

The least amount of contrast necessary to elicit a pain response was injected in the IVD with the intention of leaving sufficient space in the disk to accommodate PRP volume. We did not use a pressure-controlled manometry system because in the authors' experience, these systems require greater volume of contrast to elicit a pain response compared to manual administration. In most participants, a pain response was elicited with injection of less than 1 ml of contrast. In a small group of participants, 2 mL of contrast was required. In the authors' experience, a disk that is not completely disrupted will typically only hold 3-4 mL of injectate. This limited the volume of PRP in most participants to between 1 and 2 mL. Furthermore, for each participant, treatment was limited to 1 injection at the time of diskography to minimize the possibility of adverse reaction from multiple disk punctures [36].

One limitation of the study was the limited follow-up time of only 8 weeks for the control group. Having a longer follow-up interval on the control participants (6 months, 1 year) would possibly enable detection of greater differences between groups over time. Although there were statistically significant differences between PRP and control groups over 8 weeks, these changes were not detected in all outcome measures, and the changes in NRS pain scores were modest at best. In retrospect, there were some participants in the study who had more disk degeneration and larger protrusions than others, which likely increased some of the variability in witnessed responses. Finally, there was no data collection on cell counts or biochemical analysis of the PRP and there was no routine radiologic follow-up to see if morphologic disk changes occurred with clinical improvement. Future studies should include these data to better learn about the effects of cell therapy on lumbar disk disease.

Table 4
North American Spine Society (NASS) satisfaction at 8 weeks

Outcome	Score	Control		PRP		Odds Ratio	95% Confidence Interval		*P* Value
		N	%	N	%		Lower	Upper	
NASS satisfaction at 8 wk	1 or 2	3	17.6%	15	55.6%	5.83	1.17	37.47	.010
	3 or 4	14	82.4%	12	44.4%				

The NASS Patient Satisfaction Index:
1 = The procedure met my expectations.
2 = I improved less than I had hoped, but I would undergo the same procedure again for the same results.
3 = The procedure helped, but I would not undergo the same procedure again for the same results.
4 = I am the same or worse than before the procedure.

A priori power analysis had indicated that a sample size of 72 participants (48 treatment participants, 24 control participants) was necessary to achieve greater than 80% power to detect a 9-point change in FRI score with estimated standard deviations of plus or minus 15 in a 2-way repeated measures analysis of variance model with 5 time

Table 5
Results of patient-reported outcome scores for PRP group over time

Outcome	Time	N	Mean	SD	*P* Value*
FRI	Baseline	29	51.47	15.62	Ref
	1 wk	29	49.83	15.72	1.000
	4 wk	27	43.25	16.68	.001
	8 wk	29	37.99	19.60	<.001
	6 mo	28	38.55	21.80	.001
	1 y	21	33.98	20.35	.001
	P value over time†		<.001		
SF-36 Pain	Baseline	29	43.28	21.11	Ref
	1 wk	29	40.20	21.76	>.999
	4 wk	29	55.17	19.98	.015
	8 wk	29	61.29	22.19	.001
	6 mo	28	57.95	25.45	.030
	1 y	21	67.79	23.51	.001
	P value over time†		<.001		
SF-36 Physical Function	Baseline	29	56.40	18.52	Ref
	1 wk	29	51.63	20.46	.353
	4 wk	28	58.43	21.17	>.999
	8 wk	29	61.70	22.89	.923
	6 mo	28	67.14	24.18	.195
	1 y	21	73.20	19.38	<.001
	P value over time†		<.001		
Current Pain	Baseline	29	4.74	2.21	Ref
	1 wk	29	4.21	1.99	.436
	4 wk	29	4.00	2.21	.215
	8 wk	29	3.09	2.59	.001
	6 mo	28	3.60	2.49	.091
	1 y	21	3.15	2.38	.063
	P value over time†		.007		
Best Pain	Baseline	29	2.81	1.78	Ref
	1 wk	29	2.88	1.83	>.999
	4 wk	29	2.53	1.83	>.999
	8 wk	28	2.00	2.06	.036
	6 mo	28	2.00	2.33	.308
	1 y	21	2.10	2.20	>.999
	P value over time†		.040		
Worst Pain	Baseline	29	7.98	1.56	Ref
	1 wk	29	6.86	1.94	.001
	4 wk	28	6.41	1.85	<.001
	8 wk	29	5.82	2.33	<.001
	6 mo	28	6.32	2.12	<.001
	1 y	21	5.86	2.20	.002
	P value over time†		<.001		

PRP = platelet-rich plasma; SD = standard deviation; FRI = Functional Rating Index; SF-36 = 36-Item Short Form Health Survey.
* *P* value compares difference from baseline using paired *t*-test.
† *P* value indicates significance of overall change over time.

points. However, stopping rules were applied because of logistical concerns (ie, time and financial constraints) and an overwhelming number of control patients requesting to be unblinded from the study protocol and requesting the treatment specifically after the 8-week follow-up period (n = 15, 68.2%). As a result, the comparative analysis was modified from 5 time points to 4. Given the new parameters of the study, we were slightly underpowered to detect the demonstrated difference in FRI score at 8 weeks between the study groups. As an additional consequence, the variance-covariance matrix of the original power analysis was not used for actual analysis of collected data. However, given the sample sizes used for this study, we were adequately powered to detect a 10-point difference between groups with a four time point study design.

Conclusion

Participants who received intradiskal PRP experienced significantly greater improvements in FRI, NRS—Best Pain, and NASS satisfaction scores compared with those who received contrast agent alone over 8 weeks. Additionally, the significant improvement in FRI score was sustained for up to 1 year or more after PRP injection. Under sterile conditions, intradiskal PRP seems to have an excellent safety profile. There were no reported complications after injection among enrolled participants. Although these results are encouraging, further studies are needed to determine who the best candidates are for this treatment, what the optimal PRP concentration and composition is, whether multiple injections improve or worsen outcomes, and how the cellular physiology responsible for IVD regeneration can be considered to optimize the therapeutic effect.

References

1. Andersson GB. Epidemiological features of chronic low-back pain. Lancet 1999;354:581-585.
2. Frank JW, Brooker AS, DeMaio SE, et al. Disability resulting from occupational low back pain. Part I: What do we know about primary prevention? A review of the scientific evidence on prevention before disability begins. Spine (Phila Pa 1976) 1996;21:2908-2917.
3. Frymoyer JW, Cats-Baril WL. An overview of the incidences and costs of low back pain. Orthop Clin North Am 1991;22:263-271.
4. Cassidy JD, Cote P, Carroll LJ, Kristman V. Incidence and course of low back pain episodes in the general population. Spine (Phila Pa 1976) 2005;30:2817-2823.
5. Dunn KM, Hestbaek L, Cassidy JD. Low back pain across the life course. Best Pract Res Clin. Rheumatol 2013;27:591-600.
6. Burdorf A, Sorock G. Positive and negative evidence of risk factors for back disorders. Scand J Work Environ Health 1997;23:243-256.
7. Garg A, Moore JS. Epidemiology of low-back pain in industry. Occup Med 1992;7:593-608.
8. Deyo RA, Phillips WR. Low back pain. A primary care challenge. Spine (Phila Pa 1976) 1996;21:2826-2832.
9. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine (Phila Pa 1976) 1995;20:1878-1883.
10. Rothman RH. A study of computer-assisted tomography. Spine (Phila Pa 1976) 1984;9:548.
11. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331:69-73.
12. Modic MT, Obuchowski NA, Ross JS, et al. Acute low back pain and radiculopathy: MR imaging findings and their prognostic role and effect on outcome. Radiology 2005;237:597-604.
13. Borenstein DG, O'Mara JW Jr, Boden SD, et al. The value of magnetic resonance imaging of the lumbar spine to predict low-back pain in asymptomatic patients: A seven-year follow-up study. J Bone Joint Surg Am 2001;83-A:1306-1311.
14. Walker J 3rd, El Abd O, Isaac Z, Muzin S. Discography in practice: A clinical and historical review. Curr Rev Musculoskelet Med 2008;1:69-83.
15. Bogduk N. Clinical Anatomy of the Lumbar Spine and Sacrum. 4th ed. New York, NY: Elsevier; 2005, 147-148.
16. Mishra A, Woodall J Jr, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. Clin Sports Med 2009;28:113-125.
17. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: A review. Curr Rev Musculoskelet Med 2008;1:165-174.
18. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: From basic science to clinical applications. Am J Sports Med 2009;37:2259-2272.
19. Chen WH, Lo WC, Lee JJ, et al. Tissue-engineered intervertebral disc and chondrogenesis using human nucleus pulposus regulated through TGF-beta1 in platelet-rich plasma. J Cell Physiol 2006;209:744-754.
20. Gullung GB, Woodall JW, Tucci MA, James J, Black DA, McGuire RA. Platelet-rich plasma effects on degenerative disc disease: Analysis of histology and imaging in an animal model. Evid Based Spine Care J 2011;2:13-18.
21. Obata S, Akeda K, Imanishi T, et al. Effect of autologous platelet-rich plasma-releasate on intervertebral disc degeneration in the rabbit anular puncture model: A preclinical study. Arthritis Res Ther 2012;14:R241.
22. Allon AA, Aurouer N, Yoo BB, Liebenberg EC, Buser Z, Lotz JC. Structured coculture of stem cells and disc cells prevent disc degeneration in a rat model. Spine J 2010;10:1089-1097.
23. Sachs BL, Vanharanta H, Spivey MA, et al. Dallas discogram description. A new classification of CT/discography in low-back disorders. Spine (Phila Pa 1976) 1987;12(3):287-294.
24. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: Normative data for adults of working age. BMJ 1993;306:1437-1440.
25. Jenkinson C, Layte R, Coulter A, Wright L. Evidence for the sensitivity of the SF-36 health status measure to inequalities in health: Results from the oxford healthy lifestyles survey. J Epidemiol Community Health 1996;50:377-380.
26. Feise RJ, Michael Menke J. Functional rating index: A new valid and reliable instrument to measure the magnitude of clinical change in spinal conditions. Spine (Phila Pa 1976) 2001;26:78-86; discussion 87.
27. Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimally clinically important difference in lumbar spine surgery patients: A choice of methods using the Oswestry disability index, medical outcomes study questionnaire short form 36, and pain scales. Spine J 2008;8:968-974.
28. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. J Gen Intern Med 2007;22:1453-1458.

29. Childs JD, Piva SR, Fritz JM. Responsiveness of the numeric pain rating scale in patients with low back pain. Spine (Phila Pa 1976) 2005;30:1331-1334.
30. Daltroy LH, Cats-Baril WL, Katz JN, Fossel AH, Liang MH. The North American spine society lumbar spine outcome assessment instrument: Reliability and validity tests. Spine (Phila Pa 1976) 1996;21:741-749.
31. Schofferman J, Anderson D, Hines R, Smith G, White A. Childhood psychological trauma correlates with unsuccessful lumbar spine surgery. Spine (Phila Pa 1976) 1992;17(6 Suppl):S138-S144.
32. Slosar PJ, Reynolds JB, Schofferman J, Goldthwaite N, White AH, Keaney D. Patient satisfaction after circumferential lumbar fusion. Spine (Phila Pa 1976) 2000;25:722-726.
33. Littell RC, Pendergast J, Natarajan R. Tutorial in biostatistics: Modelling covariance structure in the analysis of repeated measures data. Stat Med 2000;19:1819.
34. Bland JM, Altman DG. Multiple significance tests: The Bonferroni method. BMJ 1995;310:170.
35. Bhandari M, Whang W, Kuo JC, Devereaux PJ, Sprague S, Tornetta P III. The risk of false-positive results in orthopaedic surgical trials. Clin Orthop Relat Res 2003;413:63-69.
36. Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino JA, Herzog R. 2009 ISSLS prize winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: A ten-year matched cohort study. Spine (Phila Pa 1976) 2009;34:2338-2345.

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CME Question

In this study, adults with chronic ($\geq$ 6 months), refractory, moderate-to-severe lumbar diskogenic pain were randomized to receive an intradiskal injection of either platelet rich plasma (PRP treatment) or a contrast agent (control). At 8 weeks post-injection, patients receiving PRP treatment had significantly greater improvement from baseline than controls on:

a. FRI Function
b. SF-36 Pain
c. SF-36 Physical Function
d. NRS Worst Pain

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