Short Communication

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Regenerative Medicine

Treatment of symptomatic degenerative intervertebral discs with autologous platelet-rich plasma: follow-up at 5–9 years

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Aim: This study assessed pain and function at 5–9 years postinjection in a subset of patients who received intradiscal platelet-rich plasma (PRP) injections for moderate-to-severe lumbar discogenic pain. **Patients & methods:** All patients received injections of intradiscal PRP in a previous randomized controlled trial. Data on pain, function, satisfaction, and need for surgery were collected at one time point of 5–9 years postinjection and compiled with existing data. **Results:** In comparison to baseline, there were statistically significant improvements in pain and function ($p < 0.001$). All improvements were clinically significant. Six patients had undergone surgery during the follow-up period. **Conclusion:** This subset of patients demonstrated statistically and clinically significant improvements in pain and function at 5–9 years postinjection.

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Keywords: autologous PRP • degenerative disc disease • intervertebral disc degeneration • long-term outcomes

Low back pain (LBP) is a leading cause of disability in the adult population, and up to 85% of people experience at least one episode of back pain at some point in time [1]. Episodes of LBP often present suddenly. However, over 75% of patients with new episodes of back pain have a previous history of back pain [2]. According to the United States Centers for Disease Control and Prevention, more than 70 million Americans today suffer from LBP, costing the country an estimated US$250 billion each year in lost wages and treatment costs – not to discount the many years of wellness lost [3–5]. This is not just a problem for the USA; WHO now ranks LBP as a leading cause of disability worldwide [6].

The most common source of chronic LBP is degenerative disc disease, which is characterized by degeneration of the intervertebral disc [7,8]. Degeneration of the intervertebral disc occurs progressively with aging, may have a genetic component, and can be exacerbated by disease and/or injury [9]. The intervertebral discs serve a mechanical function, transmitting and balancing the load from one's body weight throughout the spinal column [10]. They are the largest avascular tissues in the body and are composed of the central nucleus pulposus (NP), the outer annulus fibrosus (AF), and cartilage and bony endplates, which extend from the AF and NP and attach the disc to the vertebrae [11]. The AF is composed of organized bundles of type I collagen, whereas the NP contains type II collagen fibers, which are less organized [11]. The endplates serve to prevent collision between the discs while also providing nutrients and oxygen to the discs through passive diffusion [11]. During intervertebral disc degeneration, the development of annular fissures causes the migration of NP contents into the AF. These contents contain high concentrations of pro-inflammatory cytokines that initiate chemical sensitization of the nociceptors found in the outer AF [12]. Other processes that occur during degeneration include the loss of glycosaminoglycans, an increase in denatured type II collagen, and an increase in fibronectin fragments [10].

Most patients with degenerative disc disease in the lumbar spine recover in 6 weeks to 3 months with minimal treatment, although 20% experience recurring LBP [13]. Treatment of degenerative disc disease involves both conservative and surgical procedures [9]. Conservative treatments include rest, physical therapy, and anti-inflammatory medications, and aim to primarily reduce LBP. Surgical treatments fuse spinal segments with the aim of reducing

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discogenic pain by eliminating motion between segments of the spine [9]. In recent years, the use of autologous cell therapies to treat degenerative disc disease has increased; these include platelet-rich plasma (PRP) and bone marrow concentrate, which contains mesenchymal stem cells.

PRP has been studied extensively in the treatment of various musculoskeletal problems and is considered to be extremely rich in growth factors that promote healing and tissue formation [14]. Studies have shown that these growth factors are powerful agents in promoting proliferation, cell migration, and synthesis of extracellular matrix proteins and collagen [15–17]. Additionally, PRP has been shown to prevent the activation of inflammatory mediators [18]. Preclinical studies have demonstrated a positive restorative effect of concentrated PRP on intervertebral disc cells [19]. In a recent review article by Akeda *et al.*, they concluded that there is strong preclinical evidence for the use of intradiscal PRP, but there is a need for high quality, long-term, clinical studies [20]. Furthermore, several clinical studies have shown safety and improvements in outcomes up to 2 years following treatment in patients with discogenic LBP [20–25]. However, the long-term outcomes of intradiscal PRP injections are unknown. Thus, the purpose of this study was to determine the long-term effects of intradiscal PRP injections on pain and function in patients with discogenic LBP.

Patients & methods

Ethics & patient selection

This study was a 5- to 9-year follow-up of a previous randomized controlled trial. Approval was obtained from the institutional review board, and informed consent was obtained from patients who agreed to complete the follow-up survey. Only patients in the intradiscal PRP arm of the previous study were included in this follow-up study (n = 29). These patients had symptomatic degenerative intervertebral discs and had received intradiscal injections containing 3–4 ml of leukocyte-rich PRP, which were prepared using a Harvest centrifuge (Harvest Technologies Corporation [now Terumo BCT], MA, USA). The platelet concentration in the PRP was three- to five-times that in baseline whole blood. Inclusion criteria from the previous study included refractory LBP persisting for 6 months or greater, failure of conservative treatment measures, maintained intervertebral disc height of at least 50%, disc protrusion less than 5 mm on imaging, concordant pain on discography, and presence of a grade 3 or grade 4 annular fissure. Exclusion criteria included presence of a known bleeding disorder, pregnancy, infection, allergy to contrast agent, presence of a psychiatric condition, solid bone fusion preventing disc access, severe spinal canal compromise at the affected levels, extrusions or sequestered disc fragments, previous spinal surgery, spondylolysis, spondylolisthesis, discordant pain on discography, and presence of a grade 5 annular fissure.

Follow-up & data collection

After informed consent was obtained, follow-up surveys were administered either online or by phone at 5–9 years following intradiscal PRP injections. The 36-Item Short Form Survey (SF-36) pain scale and numerical rating scale (NRS) pain scores (current, best, worst) were used to assess pain. The Functional Rating Index (FRI) and SF-36 physical function scale were used to assess function. Minimal clinically important differences (MCIDs) for NRS pain, SF-36 pain, FRI, and SF-36 physical function have been shown to be 2.0, 16.9, 9.0, and 4.9 points, respectively [26–29]. The follow-up survey also included questions regarding the number of interventional spine injections and need for surgery following the intradiscal PRP injections. Satisfaction was assessed using the modified North American Spine Society questionnaire.

Patients were classified as 'successes' or 'failures' based on their responses to the follow-up survey. 'Success' was defined as meeting the MCID for both pain and function without the need for surgery. 'Failure' was defined as either needing surgery or not meeting the MCID for pain or function. For patients who did not complete the follow-up survey, electronic medical records were reviewed to determine whether they underwent surgery after the intradiscal PRP injection.

Statistical analysis

All 29 patients who were in the PRP arm of the previous randomized controlled trial were included in the analysis. Baseline continuous variables are presented as means and standard deviations, while frequencies and percentages are reported for discrete variables. Generalized estimating equation (GEE) was used for the analysis of all outcomes. This modeling technique was chosen due to its robust nature to handle data, regardless of whether or not they meet the assumption of normality [30]. Additionally, GEE allows for the clustered analysis of all observations that have been collected longitudinally and accounts for any missing data from patients who were lost to follow-up.

Table 1. Baseline characteristics.

Characteristic	Overall		
	Total	Mean or N	SD or %
Age at injection; years	29	41.1	7.4
Number of levels	29	2.4	0.9
Female sex	29	16	55
Multiple levels injected	29	14	48
Levels injected:			
– L1-L2	29	0	0
– L2-L3	29	4	14
– L3-L4	29	16	55
– L4-L5	29	25	86
– L5-S1	29	25	86
Baseline PROMs:			
– Current NRS pain	29	4.7	2.3
– Best NRS pain	29	2.8	1.9
– Worst NRS pain	29	8.0	1.4
– FRI score	29	51.5	15.9
– SF36 pain score	29	43.3	23.1
– SF36 physical function score	29	56.4	18.8

FRI: Functional rating index; NRS: Numerical rating scale; PROM: Patient-reported outcome measure; SD: Standard deviation; SF36: 36-item short form.

All observations were analyzed using maximum likelihood estimations. Function and pain outcomes scores were treated as a continuous response. Each model contained time as the sole predictor (treated as a fixed effect). All parameter estimates from the GEE models are reported as means and 95% CI. Bonferroni correction was used to adjust for multiple pairwise comparisons. Statistical significance was defined as $p < 0.05$. All analyses were performed with SPSS, version 22.0 (IBM Corp., NY, USA).

Results

Patient flow & baseline characteristics

Multiple attempts were made to contact the 29 patients who were part of a previous randomized controlled trial. Four patients declined to participate. A total of 21 patients consented to participate, and 19 patients completed the follow-up survey, with an average time to follow-up of 6.57 years (standard deviation: 1.44). Two patients did not complete the follow-up survey. The remaining four patients could not be reached. Information regarding need for surgery was taken from electronic medical records for two patients who did not complete the survey.

The mean age at injection was 41.1 years (standard deviation: 7.4). Multiple levels were injected in almost half of the patients (n = 14; 48%). Baseline characteristics are shown in Table 1.

Pain

Patients reported significant decreases in current, best, and worst NRS pain at 5–9 years postinjection (4.7 [3.9–5.6] to 1.3 [0.8–1.9], 2.8 [2.1–3.5] to 0.5 [0.1–1.0], and 8.0 [7.5–8.5] to 4.9 [3.9–5.9], respectively; $p < 0.001$). SF-36 pain scale scores (higher = better) were also significantly improved (80.4 [72.4–88.4] from 43.3 [35.0–51.5] at baseline; $p < 0.001$). All changes in pain scores were clinically significant, according to predefined MCID criteria (Figures 1 & 2; Table 2).

Physical function

Significant improvements in function were observed at 5–9 years postinjection, as assessed using the SF-36 physical function scale (where higher scores indicate better function) and FRI (where lower scores indicate better function). SF-36 physical function scale scores improved from 56.4 (CI: 49.7–63.1) at baseline to 82.9 (CI: 74.8–90.9) at 5–9 years postinjection. The FRI scores improved from 51.5 (CI: 45.8– 57.2) at baseline to 22.4 (CI: 14.6–30.3) ($p < 0.001$). All changes in function met MCID criteria for clinical significance (Figures 2 & 3).

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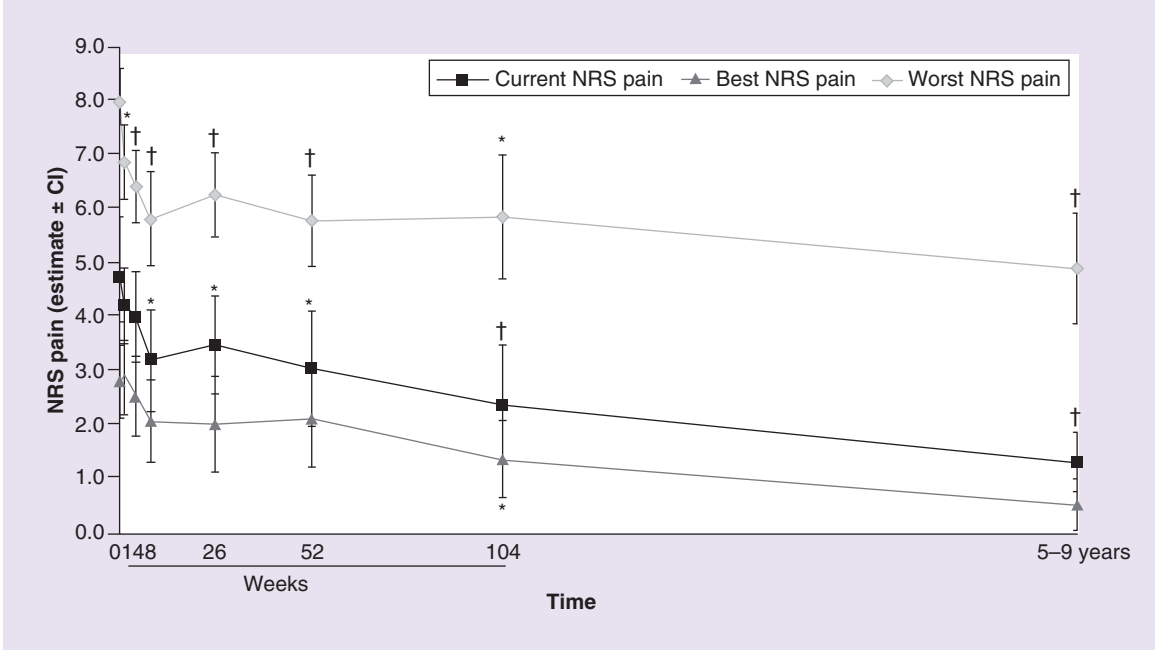

Figure 1. Numerical rating scale pain scores. Parameter estimates and CIs for current (black square), best (dark gray triangle), and worst (light gray diamond) pain scores at baseline (0 weeks), 1 week, 4 weeks, 8 weeks, 26 weeks, 52 weeks, 104 weeks, and 5–9 years are shown. A score of 0 represents no pain, whereas a score of 10 represents worst possible pain. Statistical significance was determined via generalized estimating equations. *$p < 0.05$ versus baseline (time 0); †$p < 0.001$ versus baseline (time 0).
NRS: Numerical rating scale.

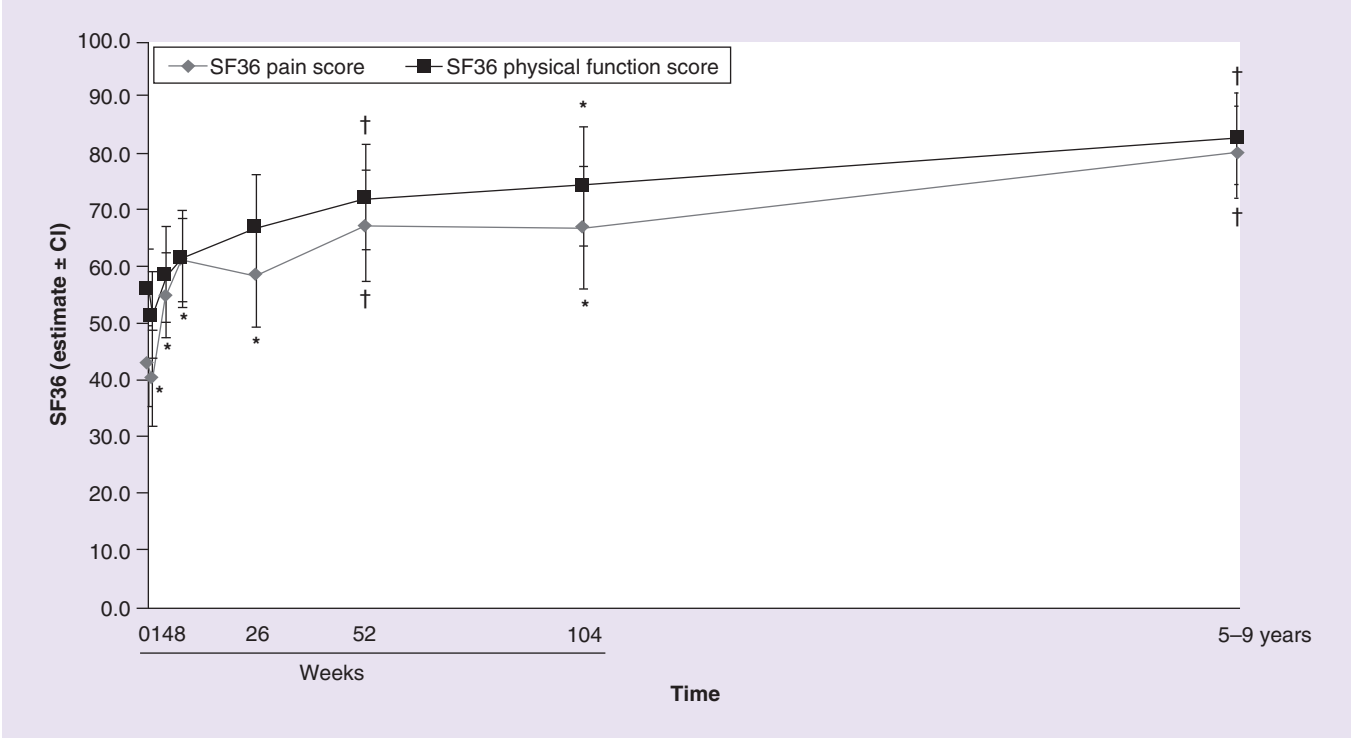

Figure 2. 36-Item Short Form Survey pain and physical function scores. Parameter estimates and CIs for SF36 pain (black square) and SF36 physical function (gray diamond) scores at baseline (0 weeks), 1 week, 4 weeks, 8 weeks, 26 weeks, 52 weeks, 104 weeks, and 5–9 years are shown. Statistical significance was determined via generalized estimating equations. *$p < 0.05$ versus baseline (time 0); †$p < 0.001$ versus baseline (time 0).

Table 2. Patient-reported outcome measures at 5–9 years postinjection.

PROM	Overall		
	Total	Parameter estimate	95% CI
Current NRS pain	29	1.3	0.8–1.9
Best NRS pain	29	0.5	0.1–1.0
Worst NRS pain	29	4.9	3.9–5.9
FRI score	29	22.4	16.6–34.7
SF36 pain score	29	80.4	72.4–88.4
SF36 physical function score	29	82.9	74.8–90.9

FRI: Functional rating index; NRS: Numerical rating scale; PROM: Patient-reported outcome measure; SF36: 36-item short form.

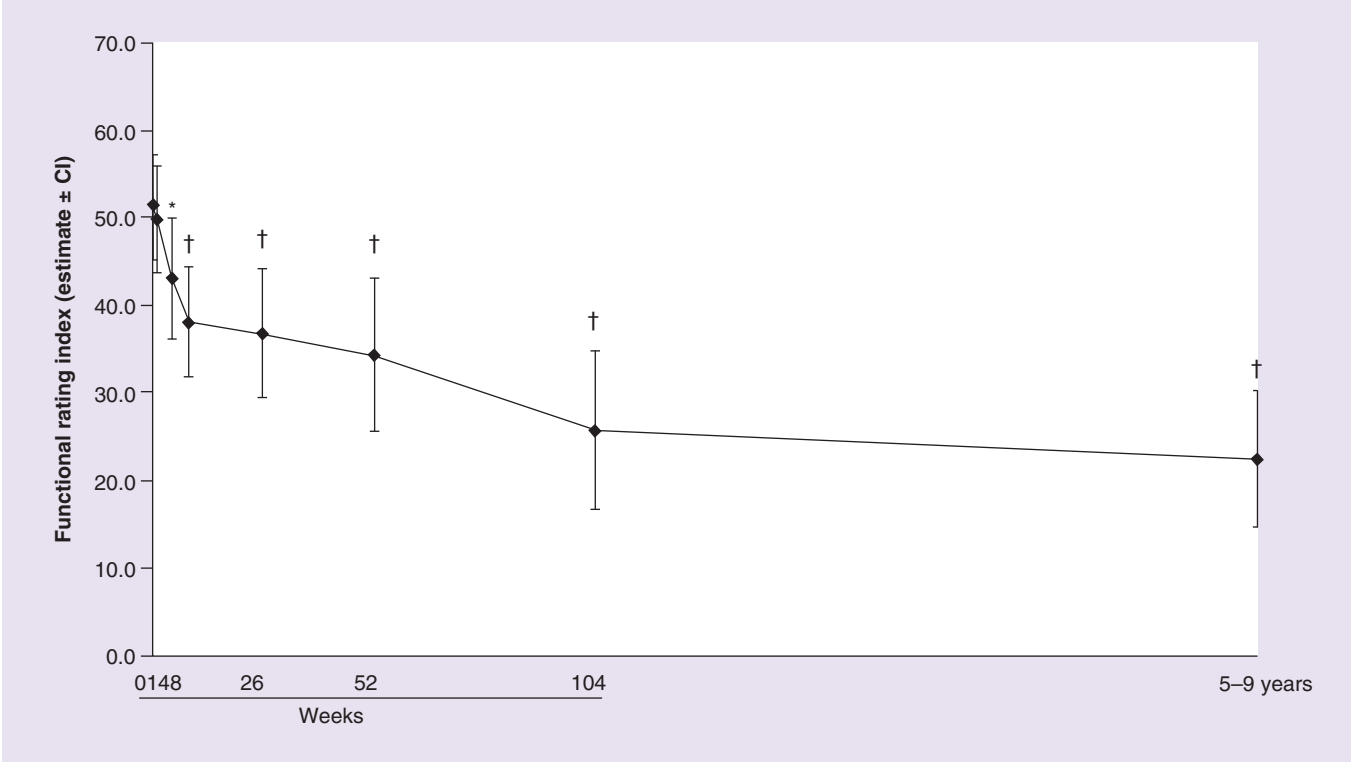

Figure 3. Functional rating index scores. Parameter estimates and CIs at baseline (0 weeks), 1 week, 4 weeks, 8 weeks, 26 weeks, 52 weeks, 104 weeks, and 5–9 years are shown. Statistical significance was determined via GEEs. *$p < 0.05$ versus baseline (time 0); †$p < 0.001$ versus baseline (time 0).

Pain medication usage, additional injections & patient satisfaction

Of the 19 patients who completed the survey, eight (42%) indicated that they had taken pain medications following the injection. Four (21%) patients required additional spinal injections, including epidural steroid injections and zygapophyseal joint injections. At the time of their 5- to 9-year follow-ups, 11 (58%) patients expressed satisfaction with the intradiscal PRP injection. Two (11%) patients felt that the injection had helped them, but they would not go through it again for the same outcome. Six (32%) patients felt that they were the same or worse compared with before the injection, although three of them reported clinically and statistically significant improvements in pain and function.

Success of intradiscal PRP injections

Successes and failures were determined using data from 21 patients (72%). Of these, 15 (71%) patients reported clinically and statistically significant improvements in both pain and function at 5–9 years postinjection, and were classified as successes. Six (29%) patients underwent surgery at the affected levels and were classified as failures. All

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Table 3. Effect of age, sex, and number of levels on success.

Parameter	Failure (n = 6)		Success (n = 15)		p-value
	Mean or N	SD or %	Mean or N	SD or %	
Females (vs males)	4	67%	8	53%	0.66
Age at injection (years)	43.5	2.6	39.2	8.8	0.26
Number of levels	1.8	1.0	2.4	0.7	0.16
Multiple levels injected	3	50%	8	53%	>0.99

SD: Standard deviation.

surgeries took place at an average of 4 years following the injection (range: 1–7 years). Two patients believed that the intradiscal PRP injection delayed their need for surgery. Sex, age at the time of injection, and the number of levels injected had no effect on success of the injection (Table 3).

Discussion

Although the short-term effects of intradiscal PRP injections have been demonstrated in the literature, long-term effects extending 5 years and beyond have not been reported. This study conducted follow-ups at 5–9 years postintradiscal PRP injection in patients who had symptomatic intervertebral disc degeneration and were previously enrolled in a randomized controlled trial. The findings showed clinically and statistically significant improvements in pain and function compared with baseline. About 71% of patients were classified as successes; the remaining 29% of patients required spinal surgery and were classified as failures. There were no effects of sex, age, and number of levels injected on success of the injection.

Degenerative disc disease, which is characterized as intervertebral disc degeneration, is the most common source of LBP in adults and accounts for 40% of chronic LBP [8]. It can be caused by genetic, mechanical (e.g., excessive loading), or environmental factors (e.g., smoking) [31]. The intervertebral discs are avascular, flexible joints that absorb compressive forces and facilitate load transmission. When degeneration occurs, loss of the extracellular matrix and an upregulation of pro-inflammatory factors are most commonly seen. Calcification of the endplate leads to a reduction in its permeability, which blocks the transport of nutrients into the disc [31]. There is also increased loading on neighboring joints, resulting in chronic discogenic pain. Treatments for degenerative disc disease often include conservative therapy and progress to surgical interventions if needed.

The use of PRP in the treatment of musculoskeletal disorders has increased in recent years [14]. PRP is prepared from autologous whole blood and contains a high concentration of platelets, which are thought to supply and release growth factors that promote healing and tissue formation [32]. These growth factors are contained within the platelet α granules and include platelet-derived growth factor, transforming growth factor β, and basic fibroblast growth factor, among others [14,32,33]. Studies have shown that they are powerful agents in regulating cell proliferation, stimulating angiogenesis, promoting cell differentiation, and influencing the synthesis of extracellular matrix proteins (e.g., proteoglycan, collagen) [14]. PRP was first used by Ferrari *et al.* in 1987 as an autologous transfusion component in open heart surgery to avoid homologous blood product transfusion [34]. Since then, it has been studied extensively in the treatment of musculoskeletal disorders, including tendinopathies and osteoarthritis, although its long-term effects have been reported in only a small number of studies [14].

The restorative effects of PRP on intervertebral disc cells have been demonstrated in both cell culture and animal models. In a study in which the L4-L5 intervertebral disc of adult rats was injured with a 21-gauge needle, treatment with PRP immediately postinjury led to the retainment of morphologic features, less inflammatory cells, and a higher fluid content, compared with the sham group [35]. Similar findings were found in other animals [36,37]. Furthermore, clinical studies have shown safety and improvements in outcomes at various time points up to 2 years following treatment. A randomized controlled trial showed improvements in pain and function up to 2 years in patients receiving intradiscal PRP versus contrast agent (control) [21,22]. Levi *et al.* reported improvements in pain and function up to 6 months following an intradiscal PRP injection for discogenic LBP [23]. Most recently, Akeda *et al.* isolated PRP releasate from clotted PRP and injected it intradiscally into patients with discogenic LBP. No patients experienced adverse effects, and pain scores were decreased up to 6 months after treatment [24].

Our current study complements these studies and shows that improvements in pain and function were sustained at a much longer follow-up of 5–9 years following intradiscal PRP treatment. Importantly, improvements in all outcomes met the MCID criteria for clinical significance. Less than half of the patients required pain medication

after the injection, and less than a third of the patients required additional spinal injections. These results suggest that PRP treatment leads to sustained improvements in pain and function in this cohort of patients with discogenic LBP.

There were six patients who needed surgery after their intradiscal PRP injections and were classified as failures. These surgeries were performed at a range of 1–7 years postinjection. The remaining 15 patients with available data were classified as successes, as they all reported clinically and statistically significant improvements in pain and function. Previous studies have shown an association between aging and worsening of intervertebral disc degeneration. It has been suggested that age may be a factor in determining the ability of intervertebral disc cells to heal [38]. However, in our study, age had no effect on the success of the injection. The number of levels injected, as well as whether multiple levels were injected, also had no effect.

There were several limitations in this study. First, the sample size was small, as only patients who were enrolled in the previous randomized controlled trial were included in this study. Second, as this study focused only on the PRP group from the initial study, there was no follow-up of the control group. The control group from the initial study was given the option to receive PRP after the 8-week follow-up, and the majority of control subjects elected to receive PRP or went on to surgery, meaning follow-ups from this group were not obtained after 8 weeks postinjection. Third, not all patients included in the study could be reached for follow-up. However, for the patients who did not complete the follow-up survey, we were able to review electronic medical records and determine that two patients underwent spinal surgery at the affected levels. Fourth, the survey captured information about the need for pain medication, additional spinal injections, and surgery postinjection. However, patients may have also undergone other treatments, such as physical therapy and acupuncture. We cannot conclude that the intradiscal PRP injection was the sole contributor to patient-reported improvements in pain and function.

Conclusion

This study is the first to report long-term results of intradiscal PRP treatment in patients with symptomatic intervertebral disc degeneration. Improvements in all pain and functional outcomes were sustained over time and met the definition of clinical significance. Nearly 75% of patients were classified as successes, and a third of the patients who underwent surgery believed that the PRP injection prolonged their need for surgery. There were no significant associations between success and age, the number of levels injected, or whether multiple levels were injected. Future studies evaluating the effectiveness of PRP in LBP will need to be done in larger populations, and we should investigate ways of optimizing the PRP preparation for intradiscal application. In addition, future studies analyzing the success of patients according to the cellular characteristics of the blood drawn and the platelet yield in PRP may provide more insight into when the treatment is most effective.

Translational perspective

Previous studies have shown short-term benefits of intradiscal PRP injections for the treatment of degenerative disc disease; however, this study provides strong evidence that intradiscal PRP injections provide sustained and long-term improvements in pain and function. Thus, PRP injections have the potential to become the first line of treatment for degenerative disc disease, as the long-term effects may outweigh the lower cost of other treatments that are needed more frequently. PRP injections may also be a viable option for patients who prefer not to undergo surgery, as they may be effective in delaying the need for surgery. Further studies should analyze the long-term effects of this treatment on a larger scale, investigate whether or not higher concentrations of platelets would improve outcomes, and compare PRP to other autologous cell preparations, such as bone marrow concentrate, that have also shown promise [39].

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, informed consent has been obtained from the participants involved.

Summary points

- This study assessed the long-term outcomes of pain and function following intradiscal platelet-rich plasma (PRP) injections for the treatment of symptomatic intervertebral disc degeneration.
- Numerical rating scale (NRS) pain scores, SF-36 pain, SF-36 physical function, and the Functional Rating Index were used to assess pain and function of the patients at follow-up, and the Generalized Estimating Equations method was used to analyze all variables.
- Patients reported significant decreases in current, best, and worst NRS pain at 5–9 years postinjection, as well as SF-36 pain scores.
- Patients reported significant improvements in function, as assessed using the SF-36 physical function scale and Functional Rating Index, at 5–9 years postinjection.
- All improvements in pain and function met the predefined criteria for clinical significance.
- Of the 19 patients who completed the 5- to 9-year follow-up survey, 58% expressed satisfaction with the intradiscal PRP injection.
- Of the 21 patients with available follow-up data, 71% reported clinically and statistically significant improvements in both pain and function at 5–9 years postinjection and were classified as successes, whereas 29% underwent surgery at the affected levels during the follow-up period and were classified as failures.
- Sex, age at the time of injection, and the number of levels injected had no effect on success of the injection.
- Results from this study show that improvements in pain and function were sustained at a much longer follow-up of 5–9 years following intradiscal PRP treatment for moderate-to-severe lumbar discogenic pain. It is the first study to report such long-term results for PRP as a treatment for intervertebral disc degeneration. It is important to note that patients may have also undergone other treatments, such as physical therapy and acupuncture. Thus, we cannot conclude that the intradiscal PRP injection was the sole contributor to patient-reported improvements in pain and function.

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