ORIGINAL ARTICLE

A Randomized Double-Blind Controlled Pilot Study Comparing Leucocyte-Rich Platelet-Rich Plasma and Corticosteroid in Caudal Epidural Injection for Complex Chronic Degenerative Spinal Pain

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■ **Abstract**

Objectives: To compare the efficacy and safety between leucocyte-rich platelet-rich plasma (LR-PRP) and corticosteroid in fluoroscopically guided caudal epidural injection for patients with complex chronic lumbar spinal pain.

Study Design: A prospective randomized controlled double-blinded study.

Methods: Fifty eligible patients with complex chronic degenerative spinal pain were randomly assigned with a 1:1 allocation ratio to receive caudal epidural injection of corticosteroid (triamcinolone acetonide, 60 mg) or LR-PRP (isolated from 60 mL autologous blood) under fluoroscopic guidance. Levels of low back pain, quality of life, and complications (or adverse effects) were evaluated at 1, 3, and 6 months after treatment. Pain levels and quality of life were assessed using the VAS and Short Form 36-Item Health Survey (SF-36), respectively.

Results: No significant difference was shown at baseline between the 2 groups. Compared with the pretreatment values, there were significant reductions in the VAS score in both groups. A significantly lower VAS score at 1-month follow-up was detected in patients who received corticosteroid injection. However, the scores were lower in the LR-PRP group at 3- and 6-month follow-up. SF-36 responses at 6 months showed significant improvement in all domains in the LR-PRP group. There were no complications or adverse effects related to treatment at 6-month follow-up in either group.

Conclusions: Both autologous LR-PRP and corticosteroid for caudal epidural injections under fluoroscopic guidance are equally safe and therapeutically effective in patients with complex chronic lumbar spinal pain. However, LR-PRP is superior to corticosteroid for a longer pain-relieving effect and improvement in quality of life. ■

Key Words: degenerative spinal pain, epidural-caudal injection, leucocyte-rich platelet-rich plasma, low back pain

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INTRODUCTION

Degenerative diseases of the lumbar spine are a common cause of pain and disability. In addition to becoming

increasingly prevalent, chronic pain resulting from spinal degenerative disease significantly increases the socioeconomic burden.[1] This disorder is commonly correlated with the complex heterogeneous condition of spine degeneration.[2] The clinical approach to managing degenerative spinal pain can be highly variable.[3] Treatments are aimed towards pain relief and return to an acceptable level of function. Over the past 3 decades, epidural corticosteroid injections have become a standard part of the multimodal pain management algorithm for the treatment of low back pain, whether as a result of chronic spinal deformities or conditions associated with acute radicular pain. They are also frequently used in the treatment of chronic degenerative spine pain.[3] Despite the widespread use of epidural corticosteroid injections as a modality for chronic degenerative spine pain, its effectiveness remains controversial.[3,4]

Platelet-rich plasma (PRP) is a biological blood-derived product with platelet concentrations 3 to 5 times greater than the physiological baseline.[5] PRP has the potential to enhance the body's natural healing response through the various actions of its related growth factors.[6] In recent years, PRP injections have gained considerable attention as a treatment modality for musculoskeletal conditions, such as tendinopathies, muscle strain injuries, ligament tears, and osteoarthritis.[7–11] Although the therapeutic role of PRP in discogenic pain and facet joint pain is promising, the role of epidural PRP injections is less clear.[12,13]

This prospective randomized controlled clinical study aimed to compare the efficacy and safety of leucocyte-rich PRP (LR-PRP) against the long-acting depot-corticosteroids by caudal route for chronic degenerative spine pain of nonmalignant origin in which conservative therapies have failed or primary invasive therapies are not indicated.

METHODS

Eligibility and Patient Selection

This randomized controlled double-blinded clinical trial with a 1:1 allocation ratio was approved by the Ethics Committee of Hospital HM Delfos, Barcelona, Spain, and conducted by the principles of the Declaration of Helsinki at Clinica Vertebra Barcelona Spine & Pain Surgery Center, Barcelona, Spain. Written informed consent was obtained from patients before enrollment. Consecutive patients with well-established complex degenerative lumbar spinal conditions who were diagnosed through MRI or neurophysiological studies were eligible to enroll in this study. The lumbar pain that was radiating or nonradiating to the buttocks and groin should have lasted for at least 3 months.

Exclusion criteria included: diabetes mellitus, pregnancy, history of ongoing malignant disorder, autoimmune diseases, active infection of the area to be injected, hematologic disorders, use of antiplatelet medication, or nonsteroidal anti-inflammatory drugs (NSAIDs) for 3 days before treatment, use of epidural or systemic corticosteroids within 3 weeks before treatment, mild or severe anemia, platelet counts of less than 150,000/mL, and indications for imperative open spine surgery.

After enrollment into the study, participants underwent a medical check-up that included clinical history, physical examination, laboratory tests, imaging (MRI, plain x-rays), and medication history. Eligible participants were then randomly assigned to receive epidural injection of corticosteroid (corticosteroid group) or LR-PRP (LR-PRP group).

Outcome Measures

All participants completed the VAS and the Spanish version of the Short Form 36-Item Health Survey (SF-36) during a personal interview with a medical doctor to assess their quality of life before and after the intervention. The SF-36 consists of 2 distinct parts: a physical dimension, represented by the physical component summary (PCS), and a mental dimension, represented by the mental component summary (MCS). All scales in the questionnaire contribute to PCS and MCS scoring in differing proportions.[14] The primary endpoint of this study was the improvement of VAS score in spinal pain; the secondary endpoint was the change in quality of life after single epidural injection.

Procedures

The preparation and handling of LR-PRP was done using sterile techniques at the Regenerative Medicine Laboratory in the surgery area of Clinica Vertebra Barcelona, Spine & Pain Surgery Center. Autologous blood (60 mL) was collected from the basilic or cephalic vein of each patient's upper limb, and 5 mL of acid citrate dextrose was added to the blood sample as an anticoagulant. The blood mixtures were centrifuged for 14 minutes at 1,568 *g*, resulting in 3 layers: a lower layer composed of red blood cells, an intermediate layer

composed of white blood cells, and an upper layer composed of plasma. The intermediate and upper layers were collected and were ready for injection after quantification using a laboratory analyzer. Local anesthetic agents were not added to the preparation, as the anesthetic could affect platelet activation through altering the pH of the solution.[15,16]

The patient was placed in the prone recumbent position and maintained in light sedation by intravenous administration of midazolam. The skin at the dorsal sacral area was carefully prepared and draped. An 18-gauge Tuohy epidural needle was accessed to the S3–4 epidural space under fluoroscopic guidance. The correct placement of the needle was verified by injection of 2 mL non-ionic iohexol contrast medium. In patients assigned to the LR-PRP group, a total of 20 mL LR-PRP mixture (16.5 mL of LR-PRP and 3.5 mL of non-ionic iohexol contrast medium) was injected through the Tuohy 18-gauge needle. The spread of the solution along the epidural space was closely monitored under fluoroscopy with anteroposterior and lateral views throughout the course of administration. In the corticosteroid group, patients received epidural injection of 20 mL corticosteroid mixture (60 mg of triamcinolone acetonide [Celestone cronodose; Merck Sharp & Dohme (Kenilworth, NJ, USA)] and 3.5 mL iohexol contrast medium in normal saline) using the same methodology as described with the LR-PRP group.

All patients were transferred from the operating room to the recovery area in the recumbent supine position. Patients were discharged home 90 minutes later provided that no acute complications or secondary effects were observed. Patients were instructed to rest for at least 24 to 48 hours after caudal epidural injection and encouraged to drink sufficient amount of water. An oral analgesic (paracetamol 1 g every 8 hours) was prescribed for pain management in the first 48 to 72 hours. Patients were instructed to avoid NSAIDs, corticosteroids, and any other analgesics or medications that might affect platelet function. The study protocol did not have any limitations on patients' daily activity after discharge from hospital.

All patients were contacted via telephone interview within 24 hours after the procedure by an experienced nurse for any procedure-related adverse reactions. Patients arranged to return to the outpatient clinic at 1, 3, and 6 months after treatment, and a visiting medical doctor assessed the patient's VAS score, current analgesic medication, and activities of daily living. Patients were also asked to complete the SF-36 at 6 months after treatment. The medical doctor who assessed the post-treatment VAS and SF-36 questionnaires was unaware of the treatment groups.

Randomization and Blinding

Eligible patients were randomized in permuted blocks using a computer-generated list under a 1:1 sampling ratio in 2 groups. The allocation of treatment for each patient was concealed in an opaque envelope according to the randomization sequence. The envelope was opened by a research nurse after the patients were enrolled and scheduled for epidural injection. Patients were blinded to the treatment group through the study period. All caudal injections were performed by the same experienced expert, and he was not involved in the subsequent steps. All the reviewers for outcome assessment were blinded to group assignment.

Statistical Analysis

The sample size in each group was approximately 23 patients (a total of 46 patients), calculated to detect a mean difference in the VAS score of 1.5 points in post-treatment reduction of chronic spinal pain, with an expected standard deviation of 1.2 (the preset alpha value was 0.05, with a statistical power of 0.8). Data were imported and analyzed using SPSS version 16 software (IBM Corp., Armonk, NY, U.S.A.). Data normality was described by mean and variance. Variables were compared with the normal distribution using the independent *t*-test, paired *t*-test, and analysis of variance. Non-normal variables were evaluated using Kruskal–Wallis, Wilkinson-signed rank, and Mann–Whitney tests, as appropriate. Pearson and Spearman correlation coefficients were used to evaluate the relation between quantitative variables. Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 50 patients (25 patients in each group) were enrolled in this study. No significant differences were found in the demographic data between the 2 treatment groups (Table 1). The VAS scores measured at baseline (before treatment) and at 1, 3, and 6 months after treatment in the corticosteroid and LR-PRP groups are presented in Table 2. Caudal epidural administration of triamcinolone acetonide or LR-PRP significantly

Table 1. Patient Demographic Data

Characteristics	Corticosteroid Group (n = 25)	LR-PRP Group (n = 25)	P Value
Age (mean ± SD)	61 ± 12.60	68 ± 13.06	NS
Sex (M:F)	10:15	11:14	NS

Data were analyzed with the unpaired t-test.
LR-PRP, leukocyte rich platelet-rich plasma; NS, nonsignificant; SD, standard deviation.

Table 2. Visual Analog Scale Scores

Time of Measurement	Corticosteroid Group (n = 25)	LR-PRP Group (n = 25)
Baseline VAS score	7.18 ± 0.95	7.48 ± 1.12
VAS score after epidural injection		
1 month	4.40 ± 0.92*	5.20 ± 0.69*
3 months	6.28 ± 0.86*	5.70 ± 0.97*
6 months	7.53 ± 0.60	6.08 ± 0.99*

Data are expressed as mean ± standard error of the mean. Data were analyzed with 1-way repeated-measures analysis of variance.
LR-PRP, leukocyte-rich platelet-rich plasma.
*P < 0.001 compared with the baseline VAS score.

improved the levels of lumbar pain (via VAS scores) up to 6 months after treatment.

Compared with the LR-PRP group, significantly lower VAS scores were shown in the corticosteroid group at 1 month after caudal epidural injection. However, significantly lower VAS scores were reported in patients who received LR-PRP injections at 3- and 6-month follow-ups (Figure 1).

Compared with the baseline measurements, the SF-36 questionnaire completed at 6 months after treatment showed significant improvements in the bodily pain domain in both groups. Only patients who received LR-PRP had significant improvement in other domains of physical function (including physical functioning, role-physical, general health, and PCS-36). Furthermore, the scores in all the domains of health-related quality of life were consistently higher in the questionnaires of the LR-PRP-treated patients at 6 months after treatment (Table 3).

No complications or adverse effects related to treatment were observed or reported at the 6-month follow-up in either the corticosteroid or LR-PRP group. Only 1 male patient in the LR-PRP group experienced itching in the pelvic area, which was progressively alleviated after treatment with diphenhydramine.

DISCUSSION

The results of this randomized controlled trial (RCT) showed promising results in terms of pain control for patients with chronic nonmalignant pain of spinal origin. Both the corticosteroid and LR-PRP treatment groups showed significant reduction in pain perception at 1 month after epidural injection, but the patients who received epidural LR-PRP treatment had further significant improvements in pain relief and quality of life at 6 months after treatment. This finding suggests that LR-PRP, but not corticosteroids, has a sustained analgesic effect over time in patients with chronic degenerative spinal pain of complex origin.

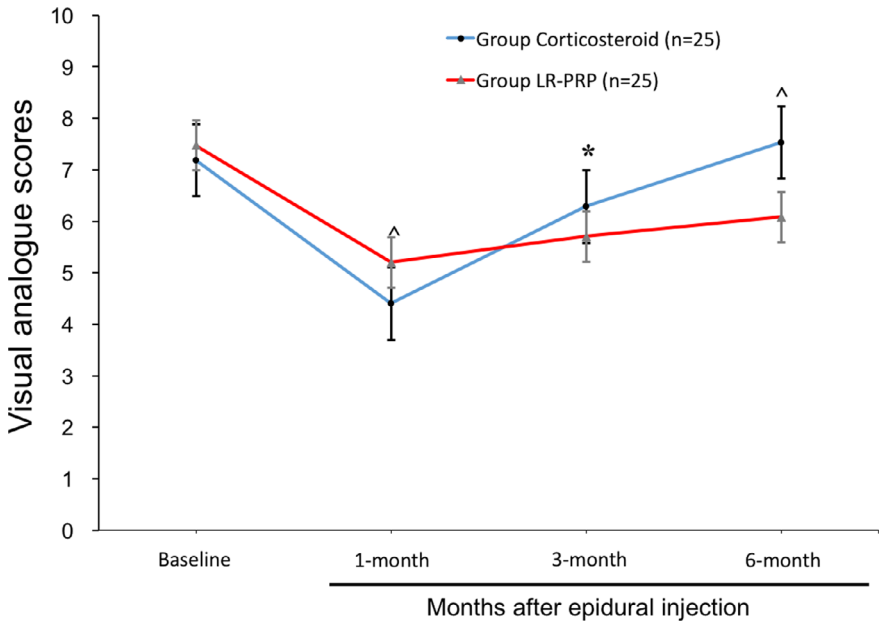

Figure 1. The VAS scores of lumbar spinal pain between the 2 treatment groups. LR-PRP, leukocyte-rich platelet-rich plasma. Results are shown as mean ± SEM. Data were analyzed with 1-way repeated-measures analysis of variance. *P < 0.05 and ^P < 0.01.

Table 3. Outcomes of Physical Health Dimension SF-36 Questionnaire (Spanish Version)

	Physical Functioning	Role-Physical	Bodily Pain	General Health	Physical Component Summary
Corticosteroid group					
Baseline	34.74 ± 18.42	26.42 ± 33.14	53.42 ± 26.40	53.14 ± 17.12	141.1 ± 70.18
6 months	35.42 ± 21.32	31.14 ± 39.42	60.14 ± 28.14	54.24 ± 23.14	151.74 ± 84.24
P values	0.291	0.711	0.008	0.82	0.39
LR-PRP group					
Baseline	31.30 ± 20.80	27.20 ± 32.14	54.10 ± 28.73	52.24 ± 22.11	140.10 ± 75.12
6 months	59.74 ± 22.57	57.40 ± 40.10	79.42 ± 17.42	56.16 ± 19.23	226.14 ± 61.02
P values	0.001	0.001	0.001	0.0001	0.001
Between-group *P* values	0.001	0.0001	0.0001	0.0008	0.0001

Results are shown as mean ± standard deviation. Data were analyzed with 1-way repeated-measures analysis of variance. LR-PRP, leukocyte-rich platelet-rich plasma; SF-36, Short Form 36-Item Health Survey.

Degenerative spinal disease results from the combined effects of aging and adverse loading. The degenerative process usually starts within the disc, then extends to the end plates and bone marrow of the adjacent vertebral bodies. This process eventually progresses to involve distant structures, leading to osteoarthritis of the facet joints, hypertrophy of the ligamentum flavum, and spinal canal stenosis.[2] Chronic degenerative spinal pain is complex in origin, arising from various structures of the spine. Degenerative changes within intervertebral discs and endplates alter the loading patterns on vertebral bodies and the associated spinal structures, and cause increased stress on the facet joints, spinal ligaments, and tendons. This can affect the surrounding nerves and result in low back pain or radicular pain. The low back pain is a result of tissue inflammation, nerve compression, and abnormal motion instability.[17] Chronic pain induced by degenerative discs has been shown to be closely related to generation of inflammatory pain mediators such as phospholipase A2, nitric oxide, prostaglandin E, and interleukin-1, found in the degenerative disc.[18,19] It has been hypothesized that the disc material with inflammatory substances causes inflammation of the nerve root, resulting in venous congestion and pain.[20]

Numerous modalities of treatments have been applied to manage chronic degenerative spinal pain.[21,22] In addition to other treatment modalities (eg, surgical interventions), epidural injections are one of the most commonly utilized treatments in the management of severe chronic degenerative spinal pain.[23] It can be considered as first-line treatment for patients who have severe comorbidities, psychosocial conditions, or chronic functional limitation.

There has been emerging clinical evidence to support the use of PRP therapy (ie, intervertebral disc injections, lumbar facet joint injections, and sacroiliac joint injections) as potential treatment options for degenerative spinal pain.[7,12,13] However, there is still a lack of high-quality RCTs on caudal epidural PRP injections in treating degenerative spinal pain. In this RCT, caudal epidural LR-PRP injections guided by fluoroscopy led to a significant reduction in pain scores and improvement of life quality in patients with degenerative spinal pain when compared to either pretreatment values or those in the corticosteroid group.

Despite the extensive use of epidural steroid injections, debate continues on their effectiveness due to the lack of well-designed, randomized, controlled studies. Fair evidence was shown for caudal epidural steroid injections in managing chronic axial or discogenic pain and spinal stenosis.[15] The caudal epidural approach has multiple advantages when compared to transforaminal and interlaminar approaches, including more effect on targeting of the low lumbar sacral area and more spreading of injectate to ventrolateral epidual space possibilities to the ventrolateral epidural space for the injectate. Under fluoroscopy guidance, caudal epidural injections are considered as the safest procedures with minimal risk of inadvertent dural puncture.[24]

PRP has recently been proposed for treatment of degenerative spinal pain. The therapeutic role of PRP in discogenic pain and facet joint pain is promising; however, the role of epidural PRP injections is less clear.[25] Our study shows the ability of caudal epidural LR-PRP injections for degenerative spinal pain to provide significant pain relief and improvement of quality of life in 6 months and to potentially prevent surgical interventions. The results of this study have significant implications for caudal epidural LR-PRP injections in interventional pain management practices.

It has been theorized that PRP promotes tissue healing through the release of different growth factors

(such as platelet-derived growth factor, insulin-like growth factor 1, vascular endothelial growth factor, transforming growth factor ß1, epidermal growth factor), along with the potential to promote cell differentiation and the reconstitution of human tissue.[5,26,27] This treatment can optimize healing in pathological human tissue and can alter nociceptive neuron hyperexcitability through a complex cascade of healing processes.[5,28]

At the writing of this article, there has yet to be a standard procedure for PRP production. Numerous formulations and techniques for PRP production exist, and various approved commercial PRP preparation kits are available. In addition, there are no universal PRP end products.[25,29] Individual patient factors such as age and comorbidities can cause differences in PRP-related growth factors and overall composition. Based on platelet and leukocyte counts as well as PRP activation, PRP can be classified into 4 types. The use of LR-PRP may produce a more intense local inflammatory response.[30–32]

It remains unclear whether PRP containing leukocytes has a beneficial effect on tissue healing. It has been reported that leukocytes in PRP have positive anti-infectious, immunoregulatory, and angiogenetic effects.[33] PRP containing leukocytes has also been shown to improve healing in soft tissue injuries complicated by infection, as well as to inhibit the growth of some infection-causing bacteria.[34]

Riboh et al. investigated the effects of leukocyte concentration on the efficacy of PRP therapy on knee osteoarthritis and found no difference between LR-PRP and leukocyte-poor PRP in terms of efficacy and safety.[35] Yerlikaya et al. compared the effects of leukocyte-rich and leukocyte-poor PRP on pain and functionality in patients with lateral epicondylitis and found that the amount of leukocytes in the PRP did not significantly affect pain levels and post-injection local inflammatory reactions.[36] However, another study conducted by Mishra et al. found no significant difference in VAS scores at week 12, but significant improvements were found in LR-PRP group compared to control group at week 24.[30]

In our study, we did not compare the efficacies of epidural PRPs with different leukocyte concentrations. However, our study showed that caudal epidural LR-PRP injections provided a longer duration of pain relief that extended for at least 6 months and improved the quality of life at 6 months when compared to pretreatment values and the corticosteroid group.

It was hypothesized that the local inflammatory actions of leukocytes may accelerate the healing process, which may be a beneficial effect on long-term healing. Further investigations are required to clarify the effect of leukocyte concentrations on caudal epidural PRP. The ideal interventional or biologic therapy for degenerative spinal pain should alleviate pain and slow or reverse the catabolic metabolism within the spinal structures.[37] Epidural LR-PRP injections offer the possibility of inhibiting degenerative changes, and may provide a better treatment alternative in the future.

This study could be the first RCT-designed study to investigate the efficacy of caudal epidural LR-PRP for patients with degenerative spinal pain. PRP and its derivatives have been used for various other epidural administrations (eg, autologous conditioned serum and platelet lysate preparations).[38–40] Bhatia et al investigated the efficacy of PRP in patients with chronic prolapsed intervertebral discs. The 10 patients in the study reported good results at their 3-month follow-up, suggesting that PRP may be a good alternative to epidural steroids and surgery.[38] Centeno et al. reviewed the use of epidural platelet lysate injections as an alternative to corticosteroid injections for the treatment of lumbar radicular pain and found significant pain reduction and functional improvement throughout the 2-year follow-up period.[39] They concluded that platelet lysate injections have the potential to be a promising substitute for corticosteroid injections. Kumar et al. and Becker et al. found that lumbar epidural injections of autologous conditioned serum can be used to treat lumbar radicular pain with significant effect.[40,41]

In our study, 5 domains in SF-36 were assessed, including physical functioning, role-physical, bodily pain, general health, and PCS. An analysis of the SF-36 outcomes at the 6-month follow-up showed significant improvements in each domain in the LR-PRP group, whereas the corticosteroid group only showed improvement in the bodily pain domain when compared to pretreatment values. The LR-PRP group also showed significantly more improvement in each domain when compared to the corticosteroid group, indicating LR-PRP may have a beneficial effect on health-related quality of life outcomes.

This study was limited by a relatively short follow-up period of 6 months and by the lack of a placebo-controlled group. Long-term studies might be needed to observe the effects of LR-PRP. However, placebo-controlled caudal epidural injections are neither realistic nor ethical, even though the pseudo-therapeutic effects

of placebos have been well documented.[42] Placebo control trials measure absolute effect and demonstrate the existence of the effect, whereas active control trials, such as the present study, not only illustrate the effectiveness of caudal epidural PRP, but also compare the effects of LR-PRP to corticosteroid.

The results of our study suggested that progressive healing could have played a significant role in the clinical improvement of the LR-PRP group, as the analgesic effects and quality of life improvements of the LR-PRP injections were predominantly found in the later stages of the follow-up period (ie, 3 months and 6 months). In comparison, the corticosteroid group only showed short-term clinical improvement, which was then followed by a decline at the 1-month follow-up. Autologous LR-PRP may be a better injectable biological alternative than corticosteroids in the treatment of degenerative spinal chronic pain of complex origin.

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CONFLICTS OF INTEREST

All authors declare that there were no conflicts of interest in conducting this study.

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