Clinical Trial/Experimental Study

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Effect of platelet-rich plasma injections for chronic nonspecific low back pain

A randomized controlled study

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Abstract

Background: Patient with chronic nonspecific low back pain is weakened ligament, and prolotherapy is the effective treatment but their use remains controversial. These ligaments can be strengthened by platelet-rich plasma injection. We hypothesized that the effectiveness of platelet-rich plasma injection and prolotherapy may decrease pain and improved disability of patient with chronic low back pain

Methods: This study was a prospective, double-blind, randomized controlled trial and was conducted for 3 years for patient enroll and follow-up. Thirty-four patients with chronic nonspecific low back pain (duration of at least 3 months) refectory to conventional management were randomized to platelet-rich plasma injection and lidocaine injection. Patients were treated with weekly platelet-rich plasma or lidocaine injections at the lumbopelvic ligaments for 2 weeks and then weekly prolotherapy with 15% glucose for 2 weeks and followed up 6 months. Visual analog scale, Oswestry Disability Index, and Roland–Morris Disability Questionnaire were evaluated at initial, 4 weeks, 3 months, and 6 months. Four patients did not complete this trial. Three were in the platelet-rich plasma injection and 1 was in the lidocaine injection.

Results: The intensity of pain was significantly decreased in platelet-rich plasma injections at 6 months as compared lidocaine injections; between-group differences were 0.9 (95% confidence interval 0.10–1.75 [$P = .027$]). All participants were significantly decreased pain and disability index at 4 weeks, 3 months, and 6 months but there were no significant differences between groups except for visual analog scale at 6 months. The baseline parameters were no significant differences in both groups.

Conclusions: In chronic nonspecific low back pain, the platelet-rich plasma injection in combination with prolotherapy is an effective intervention and either lidocaine or platelet-rich plasma injection significantly reduced disability. And injection at the lumbopelvic ligaments using the platelet-rich plasma and prolotherapy is also an effective treatment for pain.

Abbreviations: CI = confidence interval, ODI = Oswestry Disability Index, MCID = minimal clinical important difference, RMDQ = Roland–Morris Disability Questionnaire, VAS = visual analog sale.

Keywords: injectionligamentslow back painpainplatelet-rich plasma, prolotherapyrandomized controlled trialvisual analog scale

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1. Introduction

Chronic low back pain is a growing problem worldwide for which there is currently no effective intervention and often results in decreased physical activity and increased disability. Chronic nonspecific low back pain is not attributable to a recognizable, specific pathology (eg, infection, tumor, osteoporosis, fracture, structural deformity, and inflammatory diseases, such as ankylosing spondylitis, radicular syndrome, and cauda equina syndrome). It was defined as lasting for 3 months or longer.[1,2] The structural injury of muscles, ligaments, vertebral discs, facet joints, and other soft tissue may be responsible for some cases of chronic nonspecific low back pain.[3]

Platelet-rich plasma is an autologous biological material that can be applied to tissues, where it releases platelet-derived growth factors that enhance the natural healing systems. A platelet-rich plasma injection consists of a high concentration of platelets, releasing large amounts of growth factors that bring about fast and powerful healing of connective tissue.[4] Platelet-rich plasma is applicable in the treatment of soft tissue injury, tendinopathy, chondropathy, osteoarthritis, and muscle or ligament injury.[5]

Platelet-rich plasma therapy is a safe, effective, and feasible treatment modality and is evolving as a powerful therapy for the treatment of discogenic back pain.[6] Hussein and Hussein reported that platelet-rich plasma injections into atrophied lumbar multifidus muscles represent a safe, effective method for relieving chronic low back pain and disability with long-term

patient satisfaction and a success rate of 71.2%, but this study lacked a control group.[7]

In a study by Watson and Shay,[8] prolotherapy using a variety of proliferates was found to have potential as an effective treatment for low back pain as a result of presumed ligamentous dysfunction. Yelland et al[9] reported that significant and sustained reductions of pain and disability were observed with prolotherapy for 2 years in patients with chronic low back pain, but there was no difference with saline control injections.

When used alone, prolotherapy may not be an effective treatment for chronic low back pain.[10] When combined with exercise and other interventions, prolotherapy can improve chronic low-back pain and disability. Platelet-rich plasma injection was considered as another intervention, and the efficacy of the combination of platelet-rich plasma injection and prolotherapy for low back pain has not been established.

There was no clinical study that after platelet-rich plasma injection, prolotherapy was performed in patients with chronic nonspecific low back pain. The purpose of the present study was to compare the efficacy and safety of platelet-rich plasma injection and prolotherapy against lidocaine injection and prolotherapy in a prospective, double-blind, and randomized controlled trial.

2. Materials and methods

2.1. Patients

This study was conducted with the approval of the Institutional Review Board of Incheon St. Mary's Hospital (OC11BISI0097). This study was a prospective, double-blind, and randomized controlled trial.

Beginning in December 2011, participants were enrolled. Among patients with chronic low back pain who visited the outpatient spine center at an Incheon St. Mary's Hospital in Incheon, Republic of Korea, 34 patients were enrolled in this prospective study, all of whom agreed in writing to voluntarily participate in the clinical trial and met the screening criteria. Follow-up of participants was completed in October 2014 at trial end.

The inclusion criteria were as follows: age not less than 20 years, low back pain with a duration of at least 3 months, failed standard therapy (ie, physical modality, exercise, and medication), pain scale score of 3 or higher, and voluntary informed consent signed by the patient after the objectives and methods of the clinical study had been explained. The exclusion criteria were as follows: patients with a history of acute exacerbation of low back pain, patients with lumbar radiculopathy or spinal stenosis, patients with osteoarthritis of the hip joint, patients with cancer or inflammatory spondyloarthropathy, patients receiving platelet-rich plasma injections or prolotherapy or prior lumbar spine surgery, patients who received steroid injections within the previous 6 months, patients taking nonsteroidal anti-inflammatory drugs within 1 week prior to the screening visit, subjects who were pregnant or breastfeeding, subjects deemed inappropriate for entry into this study according to the judgment of the investigator, patients with another active illness, patients with a moderate degree of cardiac disease, renal failure, or liver disease, patients with anemia (hemoglobin < 5.0 g/dL), and patients who had participated in an investigational drug study or bioequivalence study within the 3 months prior to the screening visit.

2.2. Procedures

Platelet-rich plasma was prepared using a commercially available double-spin Prosys system (Tozaiholdings Inc., Seoul, Korea). This device consisted of a disposable separation kit and a concentration kit. Blood samples (60 mL) were taken from the medial cubital vein of each patient using a syringe containing anticoagulants at a ratio of 1:10 (anticoagulant: blood). The sampled blood was used to make the platelet-rich plasma for the platelet-rich plasma injection group. The sampled blood from the control group was discarded. For the platelet-rich plasma injection group, this mixture was then centrifuged for 3 minutes to separate red blood cells from the platelet-poor plasma and buffy coat. For further concentration, the separated fraction containing the platelet-poor plasma and buffy coat was centrifuged with the concentration kit for 3 minutes. Concentrated platelet-rich plasma was obtained. This process produced about 5 to 6 mL of platelet-rich plasma for each participant.[11]

The injection sites were tenderness points in the lumbosacral spine and lumbopelvic region, taking into consideration the pattern of local and referred pain. After injection sites were anesthetized, injections were performed by 1 expert physiatrist. All patients were injected with weekly platelet-rich plasma or lidocaine injections for 2 weeks. For double blinding, syringes for injection were covered with foil. Approximately 6 mL of solution was injected at a maximum of 8 sites treated at each visit. The platelet-rich plasma group was injected about 5 to 6 mL of platelet-rich plasma and control group was injected 6 mL 0.5% lidocaine. After treatment with platelet-rich plasma or lidocaine, all patients were treated with prolotherapy with 15% glucose solution for 2 weeks. Approximately 2 mL of 15% glucose solution was injected at each site, and a maximum of 8 sites were injected. Both groups were identical except that for 2 weeks, intervention group was injected with weekly platelet-rich plasma injection while control group was injected with weekly lidocaine injection.

2.3. Outcome measures

Patients underwent an initial visit prior to the first injection and received follow-up visits at 4 weeks, 3 months, and 6 months after the final injection. At each visit, patient safety was evaluated through physical and neurological examinations. The visual analog scale (VAS), Oswestry Disability Index (ODI), and Roland–Morris Disability Questionnaire (RMDQ) were evaluated by a blind investigator. The primary outcome was the VAS, and ODI and RMDQ were considered the secondary outcomes. The study flowchart is shown in Figure 1.

2.4. Randomization and blinding

Thirty-four patients were randomized to platelet-rich plasma injection or lidocaine injection with the random number table envelop method developed using block randomization (block sizes of 4 or 6) by the Catholic Research Coordinating Center. The envelope was opened by a research nurse after the patient enrolled and scheduled injection. Patient and physiatrist were blinded to the group through the trial.

2.5. Statistical analysis

The sample size was roughly calculated based on: a mean difference in the VAS score of 1.5 points reduction of chronic low

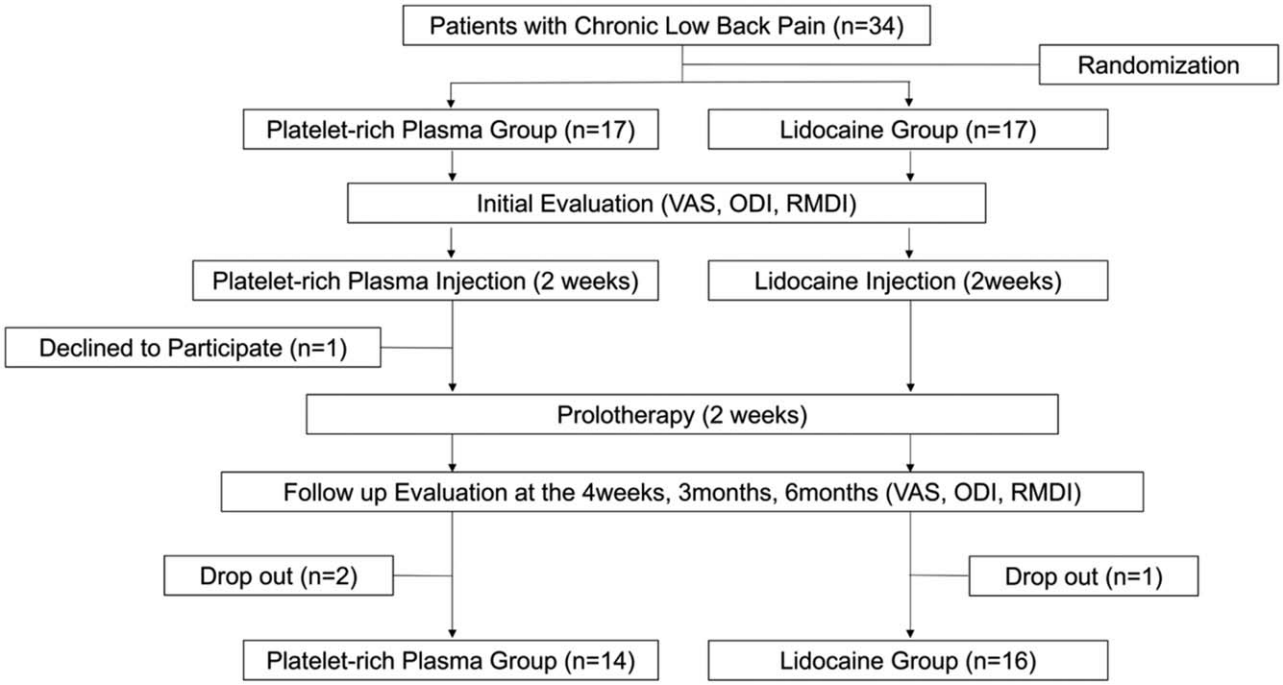

Figure 1. Study flowchart. ODI = Oswestry Disability Index, RMDQ = Roland–Morris Disability Questionnaire, VAS = visual analog sale.

back pain, with an expected standard deviation of 1.2 (the preset alpha value was 0.05, with a statistical power of 0.8). A group size of approximately 17 was required (a total of 34 patients).

Statistical analyses were performed using SPSS software version 18.0 (SPSS Inc., Chicago, IL). One way analysis of variance power analysis was performed with the help of the Catholic Research Coordinating Center to compare the average values of each group. As a result, this study was conducted on 17 subjects of each group considering a dropout rate of 10%. Independent *t* tests were used to evaluate differences in baseline characteristics. Repeated-measure analysis of variance was used to test for significant differences between initial and follow-up measurements; posthoc tests were done using Bonferroni correlation. A *P*-value $<.05$ was considered statistically significant. Concurrent validity was tested through linear regression analysis between VAS, ODI, and RMDQ at initial, 4 weeks, 3 months, and 6 months. Alternate forms reliability was tested with Cronbach alpha between VAS, ODI, and RMDQ.

3. Results

Thirty-four patients were recruited for this study. There were 6 male and 10 female patients in lidocaine injection group and 6 male and 8 female patients in platelet-rich plasma injection group. The mean age was 50.5 ± 17.0 years in lidocaine injection group versus 51.0 ± 18.1 years in in platelet-rich plasma injection group ($P = .939$). The body mass index was 25.1 ± 4.1 in lidocaine injection group versus 22.9 ± 2.7 in platelet-rich plasma injection group ($P = .095$). The duration of pain was 12.7 ± 13.5 months in lidocaine injection group versus 16.2 ± 16.7 months in platelet-rich plasma injection group ($P = 0.535$). The baseline parameters of the patients according to the clinical variables are presented in Table 1. Patients were separated into the platelet-rich plasma injection group or the lidocaine injection group, each containing 17 patients. In the platelet-rich plasma group, 1 patient did not receive the treatment process, and 2 patients failed to follow-up, finally 14 patients completed the study. Sixteen patients of the lidocaine injection group were included in the analysis after 1 failed to follow-up. There were no significant differences between the 2 groups in terms of sex, age, body mass index, and duration of pain.

The intensity of pain was significantly decreased at 6 months among patients who received platelet-rich plasma injections as compared to those who received lidocaine injections; between-group differences were 0.9 (95% confidence interval [CI] 0.10–1.75 ($P = .027$). There was no significant difference of the VAS at baseline, 4 weeks and 3 months 0.2 (95% CI −1.15 to 0.74), 0.0 (95% CI −1.41 to 1.46), and 0.7 (95% CI −0.54 to 1.97). All participants experienced significantly decreased pain at 4 weeks, 3 months, and 6 months (Table 2). These findings met the minimal clinical important difference (MCID). In patients with low back pain, MCID values are suggested 1.5 for the VAS and a 30% change from baseline.[12]

The findings concerning disability assessed by the ODI and RMDQ are shown in Table 3. Significant improvement in disability indices was observed in both groups compared with

Table 1

Baseline characteristics of the patients.

Variables	Lidocaine injection (n = 16)	Platelet-rich plasma injection (n = 14)
Male	6 (37.5%)	6 (42.9%)
Female	10 (62%)	8 (57.1%)
Age (yr)	50.5 ± 17.0	51.0 ± 18.1
Body mass index	25.1 ± 4.1	22.9 ± 2.7
Duration of pain (mo)	12.7 ± 13.5	16.2 ± 16.7

Values are presented as mean ± standard deviation or number.

Table 2

Visual analog scale score.

Time of Measurement	Lidocaine injection (n = 16)	PRP injection (n = 14)	95% CI lower	95% CI upper	*P*-value
Base line	5.7 ± 1.4	5.9 ± 1.2	−1.15	0.74	.660
4 wk	4.3 ± 1.5	4.3 ± 2.2	−1.41	1.46	.975
3 mo	4.2 ± 1.3	3.5 ± 2.0	−0.54	1.97	.251
6 mo	3.5 ± 1.2	2.6 ± 1.0	0.10	1.75	.027

Values are presented as mean ± standard deviation or number.
CI = confidence interval, PRP = platelet-rich plasma.

before the injections. These improvement findings met the MCID. In patients with low back pain, MCID values are suggested 10 for the ODI, and 5 for RMDQ, and a 30% change from baseline.[12] All participants had significantly decreased disability indices at 4 weeks, 3 months, and 6 months, but there were no significant differences of the ODI at baseline, 4 weeks, 3 months, and 6 months; between-group difference were, −0.5 (95% CI −8.11 to 7.11), −1.8 (95% CI −8.54 to 5.10), −6.1 (95% CI −1.80 to 14.15), and −4.1 (95% CI −3.67 to 11.80). There were no significant differences of the RMDQ at baseline, 4 weeks, 3 months, and 6 months; between-group difference were, −0.6 (95% CI −3.16 to 1.98), −1.0 (95% CI −2.34 to 4.50), −1.6 (95% CI −1.32 to 4.40), and −1.6 (95% CI −0.67 to 3.92).

Calculation of validity revealed the decreased pain were predictive of disability at initial (ODI β = 0.85, *P* = .000, RMDQ β = 0.84, *P* = .000), 4 weeks (ODI β = 0.85, *P* = .000, RMDQ β = 0.88, *P* = .000), 3 months (ODI β = 0.81, *P* = .000, RMDQ β = 0.78, *P* = .000), and 6 months (ODI β = 0.68, *P* = .000, RMDQ β = 0.65, *P* = .000). Reliability was calculated using Cronbach alpha revealed good alpha values regardless of period (alpha 0.88).

Effect sizes were large for the ODI (lidocaine group −1.14, platelet-rich plasma group −1.69), RMDQ (lidocaine group −1.54, platelet-rich plasma group −2.83) and VAS (lidocaine group −1.57, platelet-rich plasma group −2.75) between baseline and 6 months.

There were no severe adverse events reported regarding changes in vital signs and physical examination findings during the trial. Only 2 patients in the platelet-rich plasma group and 3 patients in the lidocaine group reported that pain increased around the injection sites. All patients resolved within 1 week.

4. Discussion

This study evaluated the efficacy of platelet-rich plasma injection and prolotherapy in patients with chronic low back pain. Platelet-rich plasma injections combined with prolotherapy significantly decreased pain at 6 months as compared to lidocaine injections combined with prolotherapy. There were no remarkable adverse events in physical and neurological examinations throughout the study.

Our study results are similar to previous studies of prolotherapy for chronic low back pain.[9] The pain rating score significantly decreased from 5.9 initially to 2.6 at 6 months after platelet-rich plasma injection and prolotherapy. All patients with low back pain had decreased disability indices at 3 and 6 months. In the platelet-rich plasma injection group, the ODI decreased from 32.7 initially to 16.1 at 6 months, and the RMDQ decreased from 12.2 initially to 4.0 at 6 months. In the same follow-up time period in the lidocaine injection group, the ODI decreased from 32.2 to 20.2, and the RMDQ decreased from 11.6 to 5.6.

Hussein and Hussein[7] conducted that platelet-rich plasma injected into low back pain accompanied with atrophied lumbar multifidus muscles. Patients demonstrated a significant improvement of pain from 8.8 to 4.6 and ODI from 36.7 to 14.7 by 6 months. These results are consistent with the present study. Platelet-rich plasma contains a natural concentration of autologous growth factors and cytokines, then has regenerative ability to repair injured tissues.

Prolotherapy combined with platelet-rich plasma injection decreased pain and improved disability in patients with chronic low back pain. A previous systemic review[10] documented that prolotherapy alone did not have evidence of effectiveness as an intervention for patients with chronic low back pain; however, ligament injection and different solutions used may be effective

Table 3

Disability index.

Time of Measurement	Lidocaine injection (n = 16)	PRP injection (n = 14)	95% CI lower	95% CI upper	*P*-value
Oswestry Disability Index					
Base line	32.2 ± 10.5	32.7 ± 9.8	−8.11	7.11	.894
4 wk	22.5 ± 8.3	24.3 ± 9.7	−8.54	5.10	.609
3 mo	24.8 ± 8.0	18.7 ± 12.3	−1.80	14.15	.122
6 mo	20.2 ± 7.9	16.1 ± 11.9	−3.67	11.80	.288
Roland–Morris Disability Questionnaire					
Base line	11.6 ± 3.9	12.2 ± 2.9	−3.16	1.98	.642
4 wk	8.9 ± 4.4	7.9 ± 4.7	−2.34	4.50	.522
3 mo	8.2 ± 3.7	6.6 ± 3.9	−1.32	4.40	.277
6 mo	5.6 ± 3.2	4.0 ± 2.9	−0.67	3.92	.158

Values are presented as mean ± standard deviation or number.
CI = confidence interval, PRP = platelet-rich plasma.

for pain and disability. Platelet-rich plasma injection in patients with low back pain has the effect of soft tissue healing, vascularization of grafts, and tissue regeneration. Platelet-rich plasma consisted of platelet concentration of small plasma. Platelets are effective for hemostasis and are a source of growth factors, which are important for chemotaxis, neovascularization, synthesis of the extracellular matrix, and scar formation.[13]

Platelet-rich plasma is under investigation as a new developing therapy for low back pain. Platelet-rich plasma has been used for various injections, including intradiscal, intrafacet, epidural, spinal fusion, intraligament, and intramuscular.[14] This study is similar to those related to ligament and muscular injections. Platelet-rich plasma injection with prolotherapy improved pain and disability for long periods after injections into the lumbosacral spine and lumbopelvic region.

The platelet-rich plasma injection group experienced an improvement in disability in the form of improved lumbar function at 3 months and 6 months. The results of the present study are consistent with those of earlier studies[15] of platelet-rich plasma injections that reported significant improvements in pain and disability in patients with low back pain. Significant improvement in lumbar functional capacity was reported following platelet-rich plasma injections compared to steroid injections in the long-term period (3 and 6 months).

Kim et al[16] performed intra-articular prolotherapy in the sacroiliac joint, resulting in relieved pain that was sustained at 15 months, compared to the control group. Intra-articular prolotherapy produced dense fibrous tissue to strengthen the attachment of ligaments, tendons, joint capsules, and other structures. In our study, platelet-rich plasma injection and prolotherapy strengthened tendons, muscles, ligaments, facet joints, and other soft tissue around the lumbosacral spine and lumbopelvic region.

Possible adverse events to platelet-rich plasma injection and prolotherapy for chronic low back pain relate to the injection sites and material, but they are extremely rare.[7,15,17,18] A previous study[15] reported adverse events of platelet-rich plasma injections consisting of pain immediately after injection, but in all patients, the pain was relieved in a few hours without any pharmacological interventions. In the present study, there were no severe complications or adverse events in the follow-up period. Only 2 patients (11.8%) in the platelet-rich plasma injection group and 3 patients (17.6%) in the lidocaine injection group documented increased pain around the injection site, and any pain was relieved in all patients within 1 week.

This study had some limitations. First, it was a relatively small number of patients and a short-term study. Second, it was not enrolled the treatment of chronic low back pain patients associated with intervertebral degeneration. This study performed platelet-rich plasma injection of tenderness points in the lumbosacral spine and lumbopelvic region. Although Platelet-rich plasma has been used in several different injections such as intradiscal injection and other injection procedures including intrafacet, epidural, intraarticular, intraligament, and intramuscular.[14,19] A recent review article[19] suggested a possibility of application of platelet-rich plasma treatment for intervertebral disc degeneration. Many clinical trials conducted safety and efficacy of intradiscal injection therapy using platelet-rich plasma. In further studies, large sample sizes and stricter patient selection criteria for the cause of low back pain may provide more robust results and support for these findings.

In conclusion, platelet-rich plasma injection and prolotherapy is an effective intervention for chronic nonspecific low back pain. This study confirmed that platelet-rich plasma injection with prolotherapy improved pain at 6 months. Platelet-rich plasma injection or lidocaine injection in combination with prolotherapy reduced the disability for long periods and were safe procedures for all of the patients. These results will help disseminate evidence in a useful and understandable way for patients and clinicians. Clinicians and researchers were interested in these results and methods of platelet-rich plasma injection and prolotherapy. Future study will be necessary to determine the ideal injection material and protocol for individual patient conditions by many researchers.

Author contributions

Conceptualization: Jae Min Kim.
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Investigation: Jae Min Kim.
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Visualization: Jae Min Kim.
Writing – original draft: Jae Min Kim.
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