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Randomized Trial

# Concordant Pressure Paresthesia During Interlaminar Lumbar Epidural Steroid Injections Correlates with Pain Relief in Patients with Unilateral Radicular Pain

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**Background:** Transforaminal and interlaminar epidural steroid injections are commonly used interventional pain management procedures in the treatment of radicular low back pain. Even though several studies have shown that transforaminal injections provide enhanced short-term outcomes in patients with radicular and low back pain, they have also been associated with a higher incidence of unintentional intravascular injection and often dire consequences than have interlaminar injections.

**Objectives:** We compared 2 different approaches, midline and lateral parasagittal, of lumbar interlaminar epidural steroid injection (LESI) in patients with unilateral lumbosacral radiculopathic pain. We also tested the role of concordant pressure paresthesia occurring during LESI as a prognostic factor in determining the efficacy of LESI.

**Study Design:** Prospective, randomized, blinded study.

**Setting:** Pain management center, part of a teaching-community hospital in a major metropolitan US city.

**Methods:** After Institutional Review Board approval, 106 patients undergoing LESI for radicular low back pain were randomly assigned to one of 2 groups (53 patients each) based on approach: midline interlaminar (MIL) and lateral parasagittal interlaminar (PIL). Patients were asked to grade any pressure paresthesia as occurring ipsilaterally or contralaterally to their "usual and customary pain," or in a distribution atypical of their daily pain. Other variables such as: the Oswestry Disability Index questionnaire, pain scores at rest and during movement, use of pain medications, etc. were recorded 20 minutes before the procedure, and on days 1, 7, 14, 21, 28, 60, 120, 180 and 365 after the injection.

**Results:** Results of this study showed statistically and clinically significant pain relief in patients undergoing LESI by both the MIL and PIL approaches. Patients receiving LESI using the lateral parasagittal approach had statistically and clinically longer pain relief then patients receiving LESI via a midline approach. They also had slightly better quality of life scores and improvement in everyday functionality; they also used less pain medications than patients receiving LESI using a midline approach. Furthermore, patients in the PIL group described significantly higher rates of concordant moderate-to-severe pressure paresthesia in the distributions of their "usual and customary pain" compared to the MIL group. In addition, patients who had concordant pressure paresthesia and no discordant pressure paresthesia (i.e., "opposite side or atypical") during interventional treatment had better and longer pain relief after LESI. Two patients from each group required discectomy surgery in the one-year observation period.

**Limitations:** The major limitation of this study is that we did not include a transforaminal epidural steroid injection group, since that is one of the approaches still commonly used in contemporary pain practices for the treatment of low back pain with unilateral radicular pain.

**Conclusions:** This study showed that the lateral parasagittal interlaminar approach was more effective than the midline interlaminar approach in targeting low back pain with unilateral radicular pain secondary to degenerative lumbar disc disease. It also showed that pressure paresthesia occurring ipsilaterally during an LESI correlates with pain relief and may therefore be used as a prognostic factor.

**Key words**: lumbar epidural steroid injection, interlaminar injection, low back pain, unilateral radicular pain, midline interlaminar approach, lateral parasagittal interlaminar approach, pressure paresthesia, quality of life, everyday functionality

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Low back pain has reached global epidemic proportions, with reported US lifetime prevalence rates exceeding 70% by some accounts (1). While the patient population suffering from low back pain continues to expand, the challenges of effectively treating back and radicular pain persist, and the economic expenditures for managing spinal pain are almost exponentially increasing (2). The cost of Social Security disability for low back pain continues to increase despite an array of therapeutic options (3).

Transforaminal and interlaminar epidural steroid injections are commonly used interventional pain management procedures in the treatment of radicular low back pain (4,5). According to the Centers for Medicare and Medicaid Services (CMS), in 2002, the interlaminar epidural steroid injections were utilized over 66% of the time for epidural procedures in Medicare beneficiaries with gradual decrease in frequency to 50.8% by 2006. In contrast, lumbar transforaminal epidural injection use increased from 22% of all epidural procedures to 37.6% by 2006 (6). In Medicare recipients there have also been observed changes, with an annual increase in spinal interventional techniques of 9.6% between 2000 and 2008, with some slowing of growth in more recent years (7). Daffner et al (8) showed that around $105.8 million was charged to 30,709 patients during the 90-day period preceding surgical discectomy, with 32% of the total charges for injection procedures.

The success rates of these injections vary and depend on many factors such as the duration and diversity of symptoms; the varying approaches to the central neuraxis; different formulations of anti-inflammatory medications employed; and different dose applications of the steroids used (9,10). The lumbar epidural space may be accessed using interlaminar, caudal, or transforaminal approaches (11). The interlaminar approach delivers medication more closely to the target site of pathology than does the caudal approach (5,12,13). However, the transforaminal approach requires the smallest dose of medication to reach the targeted site of pathology (5,12-14) while the caudal approach is considered to be the technically least challenging of the 3 techniques, with a minimal risk of iatrogenic dural puncture (4,5,13).

While several studies have shown that transforaminal injections provide enhanced short-term outcomes in patients with radicular low back pain due to lumbar disc herniation and spinal stenosis (15-17), these benefits should be weighed against the risk of vascular-related complications. A recent study by Manchikanti et al (18) reported a higher incidence of iatrogenic intravascular injection in a transforaminal steroid injection group than in an interlaminar group. Although complications of interventional procedures are rare, when they do occur they may be catastrophic and potentially include spinal cord infarction, paralysis, and even death (19,20).

Candido et al (21), in a randomized single-blind study, showed that interlaminar epidural steroid injections using a lateral parasagittal approach achieved more reliable anterior epidural spread than did a transforaminal approach without any observed difference in pain relief between these 2 groups. Since the midline interlaminar (MIL) epidural approach is utilized in everyday clinical practice by interventional physicians, our goal was to compare it to a parasagittal interlaminar (PIL) approach during lumbar epidural steroid injection (LESI) for patients experiencing unilateral lumbosacral radiculopathic pain, as these approaches theoretically pose a lower risk of vascular or spinal cord injury than do transforaminal injections. We also tested the role (if any) of concordant (same distribution as the patient's usual and customary pain) or discordant (noted remotely from the patient's usual and customary pain) pressure paresthesia occurring during LESI as a prognostic factor in determining the efficacy of LESI.

## Methods

This prospective randomized study was approved by the Advocate Health Care Institutional Review Board. We assessed 137 patients. All patients who were 18 years old or older, had unilateral lumbosacral radiculopathic pain, and who were referred for LESI for symptomatic pain management were considered eligible to participate. Twenty-three patients did not meet inclusion criteria and/or had exclusion criteria; 8 patients refused to participate. We enrolled 106 patients in the study (Fig. 1).

Inclusion criteria were degenerative lumbar disc disease, including protruding or bulging discs, desiccated discs, and herniated discs, where at least 50% of the disc height was preserved respective to contiguous levels based on contemporaneous (≤ 3 months old) MRI findings, with pathology primarily at a single disc level. Exclusion criteria were patients who required injections for multi-level disease; who had discogenic pain without radiculopathic pain; a history of previous spinal surgery; those who had undergone LESI(s) in the past year; those who had allergies to methylprednisolone, lidocaine, or iodine-based contrast medium; those

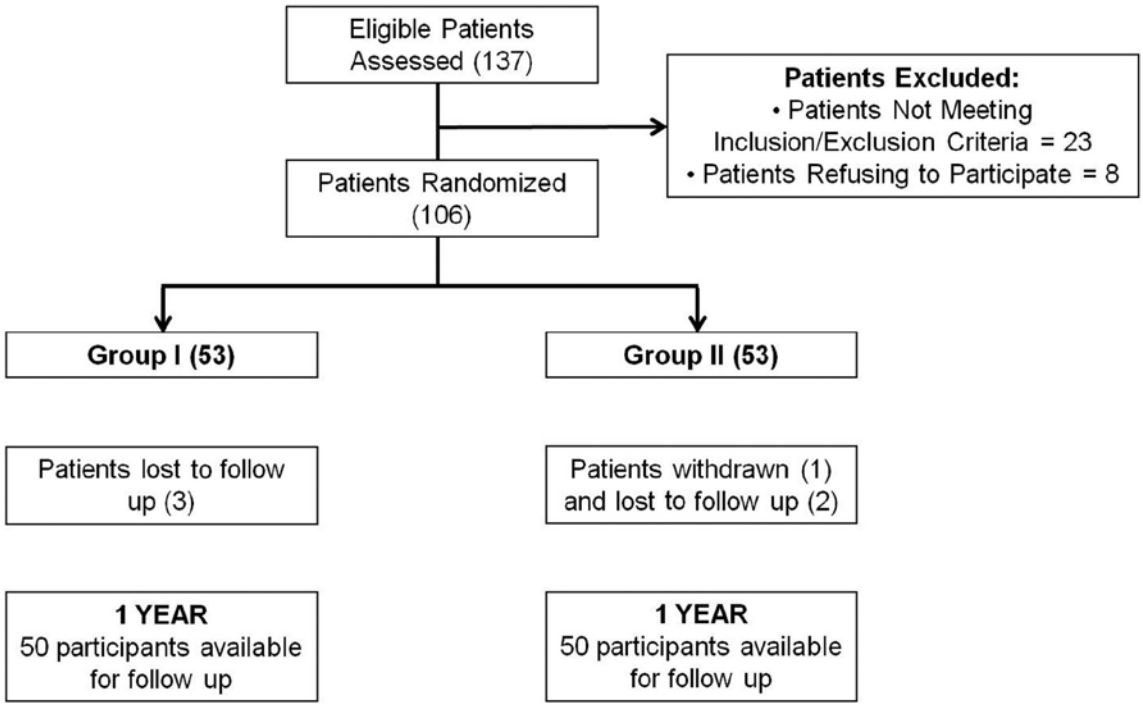


Fig.1. *CONSORT Flow Diagram. Group I – Patients received LESI using a midline interlaminar approach. Group II – Patients received LESI using a lateral parasagittal interlaminar approach.*

concurrently using systemic steroid medications or who manifested opioid habituation.

In single-blind fashion, all patients were randomly assigned to one of 2 groups using computer-generated randomization numbers, which were kept in sealed envelopes. Group allocation was revealed to the interventional physician immediately before performing the procedure. Physicians performing the LESI were not involved in the collection or analysis of data. Group I (53 patients) received LESI using a midline interlaminar (MIL) approach, and patients from group II (53 patients) received LESI using a lateral parasagittal interlaminar (PIL) approach ipsilateral to the side of the patient's pain.

After explaining all risks, benefits, and alternative treatment options for patients, informed, written consent was obtained. Patients were placed in the prone position on the fluoroscopy table. Monitors were applied and vital signs were assessed. A baseline fluoroscopic image was obtained using the anteroposterior view to assess anatomical landmarks. A full sterile skin prep using chlorhexidine solution and sterile draping was performed. After local infiltration of the skin and subcutaneous tissues using 1% plain lidocaine 5 mL total via a 27-gauge, 1.5-inch needle, the epidural space was entered via the MIL or PIL approach at the L3-L4, L4-L5, or L5-S1 interspace, depending on previously obtained MRI images matched to clinical symptoms and dermatome charts. An 18-gauge, 3.5-inch Tuohy-type epidural needle was slowly advanced towards the epidural space using a continuous loss-of-resistance to air technique under intermittent fluoroscopic guidance. After confirming that there was no blood, cerebrospinal fluid or paresthesia obtained by the advancing needle tip, the fluoroscopy unit was rotated into the lateral position and images were obtained to verify that the needle was in the peridural space during contrast injection. Three mL of iohexol contrast medium was incrementally injected, seeking demonstration of epidural spread on anteroposterior and lateral views. After confirming that there was no intravascular, subarachnoid, or subdural spread of contrast medium, 120 mg of methylprednisolone acetate (2 mL) combined with 1 mL 1% lidocaine preservative free and 1 mL

normal saline preservative free (total volume = 4 mL) was injected into the epidural space. All injections were timed and were completed within 3 seconds.

The patients were taught the definition of paresthesia, which was defined as a "tingling, pricking, or radiating abnormal sensation to one thigh, leg, or foot in a discrete segmental location." They were asked to confirm whether they felt pressure paresthesia or not, and if responding in the affirmative, whether a paresthesia was in a distribution of their "usual and customary pain" (concordant) or if it was distinct from their "usual and customary pain" (discordant). They were also asked to grade the severity of pressure paresthesia on a scale from 0 to 3 (0 = no paresthesia, 1 = mild paresthesia, 2 = moderate paresthesia and 3 = severe paresthesia) ipsilaterally or contralaterally. ". Whenever the paresthesia occurred before the injection of the corticosteroid/local anesthetic mixture, injections were halted and patients were reevaluated regarding the location of the needle tip to ensure that it was in the proper location as defined above.

Pain scores on an 11-point numeric rating scale (NRS) were recorded at rest and during movement, 20 minutes before the procedure and on days 1, 7, 14, 21, 28, 60, 120, 180 and 365 after the injection. All patients completed the Oswestry Disability Index (ODI) questionnaire at the same time points. The ODI has been designed to provide information regarding how patients' back and radicular pain has affected their ability to manage everyday life. It contains 10 sections regarding impairments like pain and abilities including personal care, lifting, walking, sitting, standing, sleeping, social life, sex life and traveling. Patients provide scores between 0 to 5, where 0 means "normal" and 5 means "complete impairment." The total scores could range from 0 to 50, but for this study scores were multiplied by 2 and were presented as a percentage (0-100%).

Patients were asked to report any side effects following the injection; their use of pain medications; and were asked to grade their satisfaction with the LESI procedure on a scale from 1 to 5 (1 = complete dissatisfaction, 2 = dissatisfied, 3 = somewhat satisfied, 4 = satisfied, 5 = complete satisfaction).

## Statistical Analysis

The sample size estimated for this study was 96, based on a difference in pain scores at $\alpha = 0.05$, power = 0.95, and effect size 0.36. We considered a difference of 50% in pain scores to be clinically significant improvement. To allow potential dropouts from the study, we included 106 patients (53 per group). We used G*Power software (version 3.1.5) (Heinrich Heine University, Dusseldorf, Germany) for this sample size calculation (22).

Descriptive analysis and testing the difference between the midline and lateral parasagittal groups were done by Pearson Chi-Square or Fisher's Exact Test (if treated variables were measured on categorical scale) with effect size statistics (Phi or Cramer's V) if testing was significant. If treated variables were measured on an interval/ratio scale, we tested differences between the 2 groups by using Student's t-test for independent samples t-test (with or without equal variance assumed). For testing equality of variances we used Levene's test.

A Double Multivariate Analysis of Variance using General Linear Model Repeated Measures procedure was done as a main statistical analysis. In this analysis, the dependent variables were NRS at rest and during movement and ODI score within factor Time (measured at 10 time points: 0, 1, 7, 14, 21, 28, 60, 120, 180 and 365 days) and between factor Group (MIL and PIL). If interaction between group and time was significant, the separate analysis of dependent variables was performed, with Bonferroni adjusted significance alpha level. For this type of statistical testing, we used multivariate test statistics – Pillai's trace. In all necessary post-hoc analyses, we used Bonferroni alpha-level adjustment.

For testing the relationship between 2 categorical variables we used the Chi-square test for independence. If the results confirmed that 2 categorical variables were not independent, we tested the effect size by using Cramer's V test. If the effect size was between 0.1 and 0.3, it was considered weak; if more than 0.3, moderate; and when more than 0.5 it was considered high. For testing the correlation between ordinal variables we used the Spearman rho coefficient. Because we had multiple comparisons, we also used Bonferroni adjusted alpha levels. When comparing rho coefficients between 2 groups (midline and lateral parasagittal) for ODI scores, NRS at rest, and NRS during movement, we used an appropriate test for the difference between 2 independent groups.

For testing only one dependent variable in the model (morphine equivalents or satisfaction) we used General Linear Model Repeated Measures. First, we tested the difference between MIL and PIL at different time points. If interaction was significant, we employed a separate analysis (based on different times) by using Student's t-test for independent samples, with Bonferroni adjustment of significance level (0.05/5 =

0.01). However, if interaction was not significant, we analyzed the significance of factor Group and repeated factor Time. If factor Time was significant, we employed a simple contrast analysis with baseline time point as a reference. This further analysis used Bonferroni adjustment of significance level (0.05/5 = 0.01).

The difference in time when patients received additional injections was analyzed by using independent samples t-test. Correlation between ipsilateral and contralateral paresthesia and the time when patients received their second injection was analyzed by the Spearman rho coefficient.

Statistical analyses were performed using SPSS Software Version 20 (IBM Corporation, Armonk, NY).

## Results

From 106 patients enrolled in this study, 6 were lost to follow-up. The remaining 100 patients were between 24 and 78 years old; 56 were women and 44 were men. There was no difference between groups in regard to gender, age, weight, or height (Table 1). The patients had radicular low back pain an average of 14 months before injection (range 0.5 to120 months). There was no difference between the MIL and the PIL groups in duration of preprocedure radicular pain. Most injections were performed at the L5-S1 level (66%), 32% at the L4-L5 level, and only 2% at the L3-L4 level (Table 1).

All patients were asked about the presence of pressure paresthesia during LESI, and to both grade whether that paresthesia was in the same distribution as their "usual, customary and daily type pain" – concordant pressure paresthesia (CPP) or whether it was distinct from that pain – discordant pressure paresthesia (DPP), as well as the severity of the paresthesia and whether or not it was brief or sustained (> one minute duration was considered sustained). In the PIL group, 78% of patients had CPP, compared to only 50% of patients in the MIL group ($P$ = 0.002). Also, in the MIL group 36% of patients had DPP versus only 10% in the PIL group (Table 2).

Chi-square test for independence showed that there was a relationship between CPP and group assignment. The effect size was 0.355 (Cramer's V), which means that the relationship was "moderate." When only an ipsilateral pressure paresthesia was assessed, a relationship was also present and the effect size was 0.315 (Cramer's V). Fifty-percent of the patients from the MIL group did not have a CPP on the side of their

Table 1. *Demographic Characteristics of patients.*

| | | Midline | Lateral Parasagittal | *P*-value |
|---|---|---|---|---|
| Gender | Female | 30 | 26 | 0.546 |
| | Male | 20 | 24 | |
| Age | | 48.9±14.4 | 48.8±13.6 | 0.966 |
| Height (cm) | | 167.3±10.1 | 167.9±9.3 | 0.750 |
| Weight (kg) | | 79.3±17.5 | 83.5±19.7 | 0.263 |
| Duration of Symptoms (months) | | 13.8±20.5 | 14.3±23.9 | 0.546 |
| Level of Injection | L3-L4 | 0 | 2 | 0.278 |
| | L4-L5 | 18 | 14 | |
| | L5-S1 | 32 | 34 | |

Table 2. *Pressure Paresthesia during LESI Injection.*

| | | Midline | Lateral Parasagittal | *P*-value |
|---|---|---|---|---|
| Pressure Paresthesia | CPP | 25 (50%) | 39 (78%) | 0.005 |
| | DPP | 18 (36%) | 5 (10%) | |
| | No pressure paresthesia | 7 (14%) | 6 (12%) | |
| Severity of CPP | Severe paresthesia | 6 (12%) | 15 (30%) | 0.019 |
| | Moderate paresthesia | 13 (26%) | 17 (34%) | |
| | Mild paresthesia | 6 (12%) | 7 (14%) | |
| | No paresthesia | 25 (50%) | 11 (22%) | |
| Severity of DPP | Severe paresthesia | 4 (8%) | 1 (2%) | 0.019 |
| | Moderate paresthesia | 10 (20%) | 2 (4%) | |
| | Mild paresthesia | 4 (8%) | 2 (4%) | |
| | No paresthesia | 32 (64%) | 45 (90%) | |

CPP- concordant pressure paresthesia
DPP – discordant pressure paresthesia

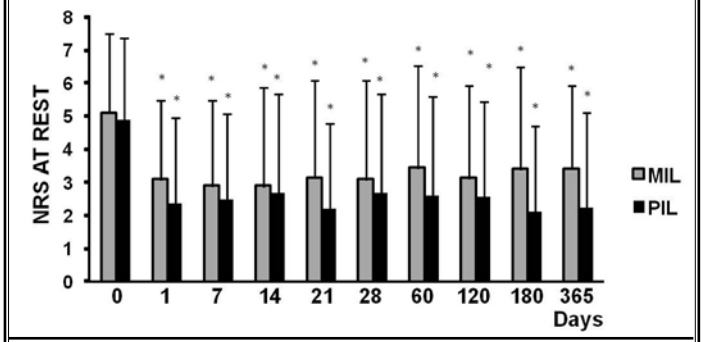


Fig. 2. *The Numeric Rating Scale (NRS) pain score at rest. Plots show mean NRS pain scores at rest (mean ± SD) at different time points. MIL - midline interlaminar approach; PIL - lateral parasagittal interlaminar approach.*

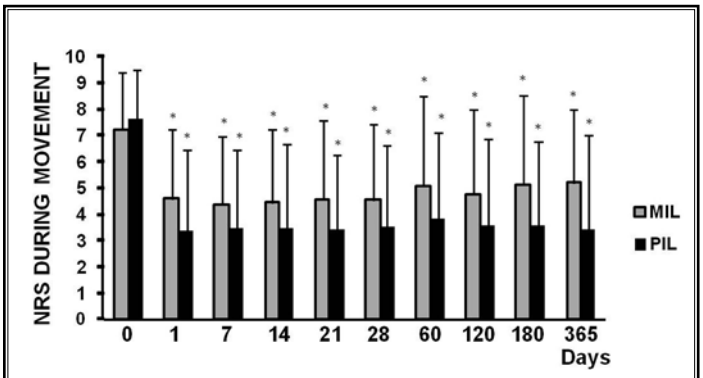


Fig. 3. *The Numeric Rating Scale (NRS) pain score during movement. Plots show mean NRS pain scores at rest (mean ± SD) at different time points. MIL - midline interlaminar approach; PIL - lateral parasagittal interlaminar approach.*

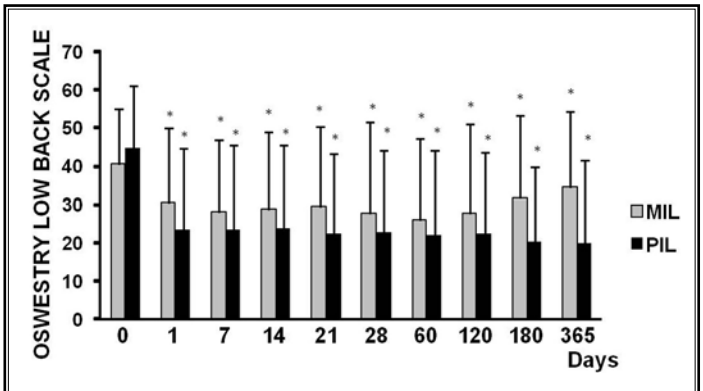


Fig. 4. *Oswestry Disability Index (ODI) Scores. Plots show mean ODI scores (mean ± SD) at different time points. ODI scores could range from 0 to 100% where higher scores mean more impairment. MIL - midline interlaminar approach; PIL - lateral parasagittal interlaminar approach.*

radicular pain, and only 12% of the other half who did have a CPP had severe paresthesia. However, 78% from the PIL group had an ipsilateral paresthesia, and 30% of patients had severe paresthesia (Table 2).

When assessed for the presence of a DPP, there was a relationship with group assignment. The effect size was 0.316 (Cramer's V). However, we noticed results opposite from the CPP correlation. Only 10% of patients receiving LESI using a PIL approach had any DPP, while 36% of patients from the MIL group had one. No patient in either group experienced a sustained paresthesia (defined as lasting > one minute) regardless of whether or not it was a CPP or DPP or whether or not it was mild, moderate, or severe.

The average pain score on the 11-point NRS before injection was 5.1 ± 2.4 at rest and 7.2 ± 2.2 during movement in the MIL group, and 4.9 ± 2.5 at rest and 7.6 ± 1.9 during movement in the PIL group. Unilateral lumbosacral radiculopathic pain reduction compared to the basal level at rest (Fig. 2) and during movement (Fig. 3) was clinically and statistically significant for both the midline and lateral parasagittal LESI approaches. The average ODI score before the procedure was higher in the PIL group than in the MIL group (44.9% vs. 40.6%) but was not statistically significant. Patients in both groups showed significant improvement over time (Fig. 4).

A multivariate test was conducted on 3 dependent variables (NRS at rest, NRS during movement and ODI scores) based on multivariate statistics using Pillai's Trace which was transformed on univariate F-statistics (Table 3). An analysis showed that the interaction between factors Time and Group (last row in the first section of Table 3) was significant. The next step was to perform separate analyses of each of the dependent variables (see next section in Table 3), with Bonferroni significance correction (0.05/3=0.017). In the separate analysis for each dependent variable we also used General Linear Model Repeated Measures, but because we had a single dependent variable, the intercept and Group factors were tested directly with univariate F-statistics (without multivariate statistics Pillai's Trace).

Based on this analysis we can conclude that factor "Time" was significant for all 3 variables,

Table 3. *Multivariate test on three dependent variables (NRS at rest, NRS during movement and OLBP scores)*

| Dependent variable(s) | Effects | Pillai's Trace | F | *P* - value | Partial eta squared |
|---|---|---|---|---|---|
| OLBP, NRS Rest and NRS Movement | Intercept | 0.817 | 142.995 | <0.001 | 0.817 |
| | Group | 0.060 | 2.060 | 0.111 | 0.060 |
| | Time | 0.755 | 8.205 | <0.001 | 0.755 |
| | Time*Group | 0.479 | 2.451 | 0.001 | 0.479 |
| NRSR | Intercept | - | 193.227 | <0.001 | 0.663 |
| | Group | - | 2.481 | 0.118 | 0.025 |
| | Time | 0.474 | 9.002 | <0.001 | 0.474 |
| | Time*Group | 0.139 | 1.616 | 0.123 | 0.139 |
| NRSM | Intercept | - | 356.338 | <0.001 | 0.784 |
| | Group | - | 5.091 | 0.026 | 0.049 |
| | Time | 0.642 | 17.926 | <0.001 | 0.642 |
| | Time*Group | 0.141 | 1.637 | 0.117 | 0.141 |
| OLBP | Intercept | - | 270.001 | <0.001 | 0.734 |
| | Group | - | 3.186 | 0.077 | 0.031 |
| | Time | 0.504 | 10.161 | <0.001 | 0.504 |
| | Time*Group | 0.288 | 4.053 | <0.001 | 0.288 |
| OLBP for Midline group | Intercept | - | 172.042 | <0.001 | 0.778 |
| | Time | 0.518 | 4.892 | <0.001 | 0.518 |
| OLBP for Lateral Parasagittal group | Intercept | - | 103.581 | <0.001 | 0.679 |
| | Time | 0.667 | 9.122 | <0.001 | 0.667 |

but not for the factor "Group" (Table 3). Since the interaction between factors Group and Time was significant for the ODI score (fourth section in Table 3), we separated the 2 groups (midline MIL and lateral parasagittal PIL), and conducted univariate Analysis of Variance Repeated Measures procedure, where factor Time was tested with multivariate statistics Pillai's Trace, and Intercept was tested with univariate F-statistics (without multivariate statistics Pillai's Trace).

Next, we conducted a post-hoc analysis, based on multiple comparisons of all levels of factors Group and Time, with Bonferroni adjustment alpha-level, which confirmed only the difference between baseline pain scores and ODI scores and other time points, but no statistically significant difference between the 2 groups (midline and parasagittal).

We also measured the non-parametric coefficient correlation (Spearman rho) between Pressure paresthesias, CPP and DPP with differences in NRS at rest, NRS during movement, and ODI scores compared with the scores before injection. All coefficients are shown in Table 4. The second column in Table 4 showed statistically significant negative (indirect) correlations between CPP differences in pain scores at rest and during movement for the PIL group and only NRS at rest for the MIL group during the first month after injection. The third column in Table 4 showed no statistically significant correlations between DPP and differences in pain scores in the PIL, and positive (direct) correlation between DPP and differences in pain scores at rest in the MIL group during the first month.

An important fact is that the correlation between pain relief and pressure paresthesia was indirect when the paresthesia was identified on the ipsilateral side (CPP) and direct when identified on the contralateral side (DPP) which means that a more severe pressure paresthesia ipsilaterally and a less severe paresthesia contralaterally is related to better pain relief.

We also followed the use of any analgesic medications in these patients before and after LESI and there was no difference between the 2 groups. Before injections 64% of patients in the MIL group used pain medication; 36% used opioids and 62% used nonsteroidal anti-inflammatory drugs (NSAIDs). In the PIL group, 54% used pain medications before injection; 28% used opioids and 54% used NSAIDs. After LESI, patients reduced their use of pain medications, particularly the aggregate amount of opioids they were taking. Opioid

Table 4. *Nonparametric correlations (Spearman's rho) between pressure paresthesia (CPP-concordant and DPP-discordant) Diffreences in the pain scores (NRS at rest and during movement) and OLBP scores at different time points.*

| | | Pressure Paresthesia | CPP | DPP |
|---|---|---|---|---|
| NRS Rest Difference 1 day | MIL | -0.427 | -0.454 | 0.443 |
| | PIL | -0.451 | **-0.488*** | 0.325 |
| NRS Rest Difference 7 day | MIL | **-0.506*** | **-0.563*** | **0.581*** |
| | PIL | -0.397 | **-0.497*** | 0.255 |
| NRS Rest Difference 14 day | MIL | -0.458 | **-0.512*** | **0.528*** |
| | PIL | **-0.513*** | **-0.566*** | 0.336 |
| NRS Rest Difference 21 day | MIL | **-0.570*** | **-0.567*** | **0.486*** |
| | PIL | -0.423 | **-0.532*** | 0.240 |
| NRS Rest Difference 28 day | MIL | **-0.511*** | **-0.526*** | **0.482*** |
| | PIL | **-0.505*** | **-0.589*** | 0.233 |
| NRS Rest Difference 60 day | MIL | **-0.481*** | -0.443 | 0.472 |
| | PIL | -0.420 | -0.443 | 0.263 |
| NRS Rest Difference 120 day | MIL | -0.319 | -0.351 | 0.469 |
| | PIL | -0.384 | **-0.478*** | 0.280 |
| NRS Rest Difference 180 day | MIL | -0.357 | -0.351 | 0.339 |
| | PIL | -0.382 | **-0.506*** | 0.326 |
| NRS Rest Difference 365 day | MIL | -0.422 | -0.470 | 0.261 |
| | PIL | -0.435 | **-0.567*** | 0.333 |
| NRS Movement Difference 1 day | MIL | -0.326 | -0.307 | 0.285 |
| | PIL | **-0.546*** | **-0.576*** | 0.344 |
| NRS Movement Difference 7 day | MIL | -0.435 | -0.394 | 0.347 |
| | PIL | **-0.547*** | **-0.660*** | 0.363 |
| NRS Movement Difference 14 day | MIL | -0.413 | -0.398 | 0.395 |
| | PIL | **-0.530*** | **-0.659*** | 0.313 |
| NRS Movement Difference 21 day | MIL | -0.497 | -0.442 | 0.410 |
| | PIL | **-0.498*** | **-0.662*** | 0.310 |
| NRS Movement Difference 28 day | MIL | -0.409 | -0.411 | 0.409 |
| | PIL | **-0.556*** | **-0.694*** | 0.254 |
| NRS Movement Difference 60 day | MIL | -0.364 | -0.312 | 0.380 |
| | PIL | **-0.495*** | **-0.601*** | 0.307 |
| NRS Movement Difference 120 day | MIL | -0.093 | -0.103 | 0.349 |
| | PIL | **-0.486*** | **-0.605*** | 0.244 |
| NRS Movement Difference 180 day | MIL | -0.238 | -0.223 | 0.273 |
| | PIL | -0.462 | **-0.579*** | 0.280 |
| NRS Movement Difference 365 day | MIL | **-0.484*** | -0.440 | 0.192 |
| | PIL | -0.473 | **-0.684*** | 0.364 |
| OLBP Difference 1 day | MIL | -0.193 | -0.183 | 0.199 |
| | PIL | -0.255 | -0.311 | 0.287 |
| OLBP Difference 7 day | MIL | -0.402 | -0.369 | 0.304 |
| | PIL | -0.342 | -0.399 | 0.337 |
| OLBP Difference 14 day | MIL | -0.381 | -0.400 | 0.410 |
| | PIL | -0.306 | -0.372 | 0.381 |
| OLBP Difference 21 day | MIL | -0.428 | -0.455 | 0.420 |
| | PIL | -0.311 | -0.332 | 0.325 |
| OLBP Difference 28 day | MIL | -0.320 | -0.340 | 0.397 |
| | PIL | -0.276 | -0.287 | 0.224 |

Table 4 (cont.). *Nonparametric correlations (Spearman's rho) between pressure paresthesia (CPP-concordant and DPP-discordant) Diffreences in the pain scores (NRS at rest and during movement) and OLBP scores at different time points.*

| | | Pressure Paresthesia | CPP | DPP |
|---|---|---|---|---|
| OLBP Difference 60 day | MIL | -0.234 | -0.261 | 0.358 |
| | PIL | -0.250 | -0.261 | 0.202 |
| OLBP Difference 120 day | MIL | -0.069 | -0.115 | 0.344 |
| | PIL | -0.266 | -0.307 | 0.185 |
| OLBP Difference 180 day | MIL | -0.148 | -0.226 | 0.278 |
| | PIL | -0.262 | -0.278 | 0.246 |
| OLBP Difference 365 day | MIL | -0.213 | -0.327 | 0.073 |
| | PIL | -0.253 | -0.399 | 0.132 |

usage was calculated as morphine equivalents (23) (Fig. 5). Our results also showed that patients who received LESI by using an MIL approach used more opioid medications postinjection compared with patients from the PIL group (Fig. 5). Even though patients from the MIL group used more opioids than patients from the PIL group, General Linear Model for Repeated Measures showed no interaction between factors Time and Group (Table 5). Results showed that only factor Time was significant, which means that both groups had a significant reduction in opioid consumption following LESI. Further post-hoc analysis with Bonferroni correction showed a statistically significant difference only between baseline and days one and 7.

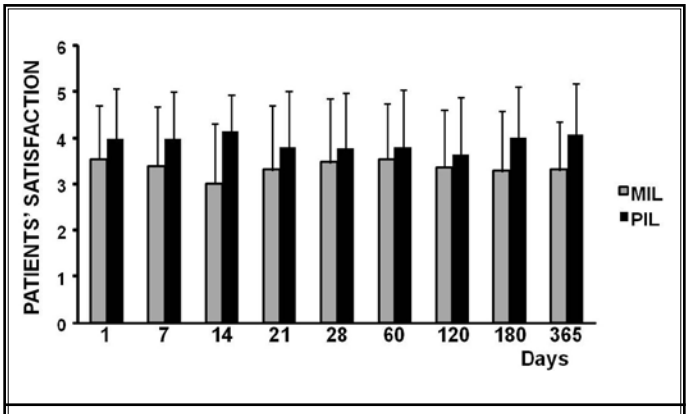


Fig. 5. *The use of opioid medications. Plots show mean opioid use measured by using morphine equivalent converting table (23). MIL - midline interlaminar approach; PIL - lateral parasagittal interlaminar approach.*

Table 5. *General Linear Model for repeated measures for morphine equivalents*

| Dependent variable | Effects | Pillai's Trace | F | *P*-value | Partial eta squared |
|---|---|---|---|---|---|
| Morphine Equivalents | Intercept | - | 18.035 | <0.001 | 0.155 |
| | Group | - | 1.694 | 0.196 | 0.017 |
| | Time | 0.212 | 2.695 | 0.008 | 0.212 |
| | Time* Group | 0.033 | 0.339 | 0.959 | 0.033 |

We also evaluated patients for side effects after injection. The most frequent side effects within the first year following injection included: discomfort and pain at the injection site (30% of patients from MIL and 22% of patients from PIL); headache, nonpositional, not related to dural puncture (12% of patients from MIL and 22% of patients from PIL); and nausea (14% of patients from MIL and 6% of patients from the PIL group). However, there was no difference between these 2 groups in the frequency of side effects.

All patients were also asked to grade their overall procedure-related satisfaction on a scale from one to 5 (Fig. 6). Results showed that there was an interaction between factors Time and Group for this variable, and that the factor "Group" was significant (Table 6). Because of this significant interaction, we performed a separate analysis (based on different times) of independent samples t-tests, with Bonferroni adjustment (0.05/5 = 0.01). Based on this separate analysis, there was a statistically significant difference between the 2 groups, and better satisfaction in the PIL group on days 7, 14, 180, and 365.

If patients required additional injections, they received them using the same approach as they were randomly assigned to at the beginning of the study. During one year, the total number of injections was not different between these 2

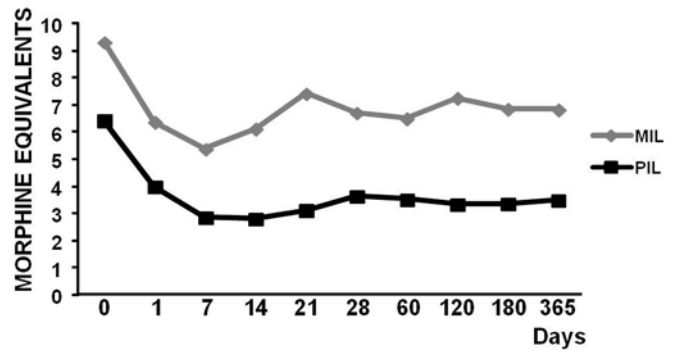


Fig. 6. *Patients' Satisfaction. Plots show mean satisfaction grade (mean ± SD) at different time points. Patient's satisfaction was graded on the scale 1 to 5. MIL - midline interlaminar approach; PIL - lateral parasagittal interlaminar approach..*

Table 6 *General Linear Model for repeated measures for patients' satisfaction.*

| Dependent variable | Effects | Pillai's Trace | F | *P*-value | Partial eta squared |
|---|---|---|---|---|---|
| Satisfaction | Intercept | - | 1545.11 | <0.001 | 0.940 |
| | Group | - | 8.888 | 0.004 | 0.083 |
| | Time | 0.096 | 1.208 | 0.303 | 0.096 |
| | Time*Group | 0.236 | 3.508 | <0.001 | 0.236 |

groups (1.88 ± 1.14 in the MIL group and 1.82 ± 0.94 in the PIL group). Around half of the patients from both groups (25 from the MIL group and 27 from the PIL group) received a second injection. However, the time between injections was statistically and clinically significant between these groups. Patients who received LESI using the PIL approach received their second injection 6 weeks later than patients who had received their LESI by the MIL approach (9.76 ± 10.15 MIL; 15.78 ± 10.41 PIL). Thirteen patients from the MIL group and 11 from the PIL group received a third injection. Patients from the PIL group received this third LESI 9 weeks later than patients from the MIL group (17.54 ± 10.68 MIL; 26.64 ± 15.96 PIL). Five patients required a fourth injection (3 from the MIL group and 2 from the PIL group), with more than 7 months after the first such injection (19.00 ± 8.72 MIL; 48.00 ± 4.24 PIL) (Fig. 7).

We also tested the correlation between CPP and DPP and the timing of when patients received their second injection. Spearman's rho was 0.350 (P = 0.012) for CPP and -0.337 (P = 0.016) for DPP demonstrating that patients who had a more significant paresthesia ipsilaterally and less significant paresthesia contralaterally had longer pain relief and required a second injection after a longer time interval than patients who had less significant pressure paresthesia ipsilaterally and more significant paresthesia contralaterally.

Only 4% of patients required surgery within the first year, 2 from the MIL group (average 36 weeks after the first injection) and 2 from the PIL group (average 38 weeks after the first injection).

## Discussion

The results of this study showed statistically and clinically significant pain relief in patients undergoing LESI by both a PIL approach as well as an MIL approach. Patients receiving LESI using the PIL approach had statistically and clinically longer pain relief than patients received LESI using an MIL approach. They also had slightly better quality of life and improvement in everyday functionality; they used less pain medication than patients who received LESI via MIL.

The literature is still emerging regarding the efficacy of epidural steroid injections (including interlaminar, transforaminal and caudal) in treating low back pain due to degenerated and herniated lumbar discs. Even though results of the SPORT trial conducted by orthopedic surgeons showed that patients with lumbar disc herniation treated with lumbar epidural steroid injections had no improvement in short or long-term outcomes compared with patients who did not receive these injections(24), there are multiple studies showing a statistically significant beneficial effect for these injections(9-11, 15-17, 21, 25-28).

However, there is still an unresolved debate as to whether interlaminar or transforaminal approaches are superior for treating patients with radicular low back pain, as multiple advantages and disadvantages of each technique have been described. Some studies have shown enhanced analgesic effectiveness of the transforaminal approach over interlaminar injections (16,17). This has translated into an increasing utilization of transforaminal injections over interlaminar epidural steroid injections. Other studies have shown no difference between these 2 approaches (25-27). Rados et al (26) randomized 64 patients with unilateral radicular pain to receive either LESI or transforaminal epidural steroid injections (TFESIs) and found no difference between these 2 approaches with signifi-

cant improvements in function and pain relief in both groups (26). Candido et al (21) also found no difference in postprocedure pain relief scores between TFESI and LESI using a lateral parasagittal interlaminar approach, the same approach we used in the current study. Several meta-analyses and systematic reviews of randomized controlled clinical trials have demonstrated that LESI is an approach that delivers the anti-inflammatory medication closely to the target site of pathology, and that doing so results in at least short-term benefits (4,11,12,28). Benyamin et al (11), in a meta-analysis, analyzed 15 randomized and 11 nonrandomized trials testing the effectiveness of LESI and found good results in all studies wherein combinations of local anesthetics and corticosteroids were utilized.

There remain some concerns regarding the accuracy and efficacy of LESI; the data on the complications of each procedure has been limited to date. McGrath et al (29) reported a very low incidence of minor complications exclusive of major complications from a retrospective review of 4,265 epidural steroid injections with no clear-cut explanation for the difference in complication between LESI and TFESI. Manchikanti et al (18) reported a higher incidence of unintentional intravascular injection in a TFESI group. There are many published reports illustrating serious complications associated with transforaminal injections, including spinal cord or brainstem infarction (30), severe spinal cord injury (31), seizure (30), and quadriplegia (20). In addition, it has been shown that radiation exposure for patients and interventional pain physicians is higher during TFESI than during LESI (21).

A large, prospective randomized controlled trial demonstrated that LESI were mostly effective in providing short-term symptomatic relief (32). The failure of long-term success with LESI may relate to a suspected deficient spread of steroid to cover the proposed targeted site of nociception at the anterior or ventral epidural space. With interlaminar administration, the epidural injection flow was shown to be highly variable. Steroids may be prevented from migrating from the posterior epidural space to the anterior or ventral epidural space by the presence of epidural ligaments or scar tissue (11). Whitlock et al (33) evaluated the influence of needle position and the steroid injectate spread in 406 LESI. They concluded that midline injections were less likely to result in unilateral flow than more laterally placed injections. Botwin et al.[34] reported that only 36% of patients who received LESIs had injectate spread of contrast medium into the ventral epidural area. However,

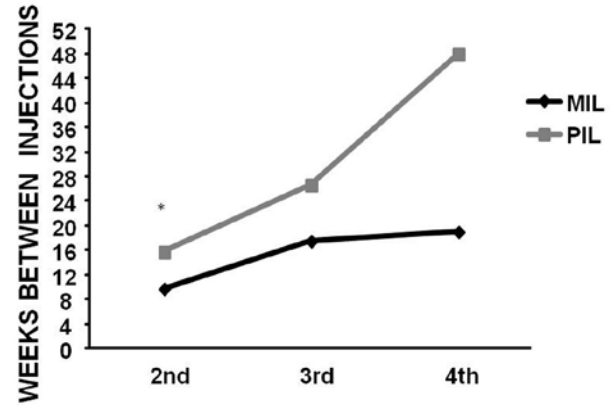


Fig. 7. *Time when received additional LESI injection. Plots show mean time in weeks (mean ± SD) after initial injection, when patients received additional injections (2nd, 3rd and 4th). MIL - midline interlaminar approach; PIL - lateral parasagittal interlaminar approach.*

all 25 studied patients had either lumbar spinal stenosis or a herniated nucleus pulposus, and all injections were performed using a midline approach (34). This may be one of the reasons the lateral parasagittal interlaminar approach was shown to be superior in the study by Bloomeber et al (35) as well as in the present study.

Candido et al (21) showed 100% anterior epidural spread when using a PIL, performed in a manner analogous to that which we used. This lateral parasagittal interlaminar approach has been described by Boon et al (36) in a study of 36 cadavers conducted in 2003. They suggested that this approach should be considered in patients with disc herniation, osteoarthritis, and other conditions where the interlaminar space is significantly diminished or compromised (36). Furthermore, Kim et al (37) showed that an alternative needle placement is necessary even for TFESI for patients who have far lateral herniations of the lumbar disc, because a conventional TFESI approach was effective only in patients who had intraspinal herniations of the lumbar disc (37). However, those authors have not studied the PIL approach, which may prove to be a solution for circumventing the observed limitations even for those patients.

There exist several anatomical impediments which have been postulated to decrease the accuracy of an interlaminar injection such as ligamentum flavum calcification, interspinous ligament calcification, spinous process contact, and the absence of posterior epidural fat and the presence of midline fat density superficial

to the ligamentum flavum (most common in the L5-S1 area) (38,39). Even though the L4-L5 level is considered to be the most common level for identifying pathology amenable to these injections (40), in our study the most frequent injections were done at L5-S1 (66%). The most prevalent of suspected impediments to successful injection is commonly indentified at the L5-S1 level. Injection at this level may increase the risk of dural puncture and lead to a false loss of resistance and inaccurate delivery of injectate due to the absence of posterior epidural fat and the presence of a midline fat density superficial to the ligamentum flavum (39). For all these reasons, the PIL approach may provide a more suitable alternative to the MIL approach due to its documented evidence of a primarily unilateral flow of steroids at the targeted site of nociception, while avoiding the anatomical impediments noted above. However, the study of and literature support for this approach remains limited and more investigations of it will be necessary to determine its true place in the armamentarium of interventionalists.

Inflammatory responses are likely to be localized at the nerve root/intervertebral disc interface (34). A possible explanation for the superior efficacy of the PIL technique compared to MIL is consistent with an application of medication in closer approximation to the affected disc and nerve root, where all cytokines important in the inflammatory reaction have been released (41-43). Steroids inhibit synthesis and release of those inflammatory mediators, neuropeptides, substance P, phospholipase A2, prostaglandins, TNF-$\alpha$, interferon-$\gamma$, etc.; and reduce edema and stabilize cell membranes (40,44-48). Even though corticosteroids reduce inflammation, Manchikanti et al (49-52) showed in 4 different studies a similar improvement in patients who received LESI using either local anesthetics alone or combined with corticosteroids (betamethasone). Local anesthetics alone may possess anti-inflammatory effects as well (53,54). Additionally, there is a possibility that injection of any solution into the epidural space has at least a temporary beneficial effect, due to washing out the accumulated mediators in proximity to and in contact with the affected disc and nerve root.

The data from the present study showed that CPP and no DPP during interventional treatment are more likely to have better and longer pain relief following LESI. "Paresthesia seeking" is not dissimilar to the use of provocation during discography procedures wherein a pressure-related increase in volume applied to a disrupted intervertebral disc may lead to useful clinical information. Although the incidence of neurologic complications following epidural analgesia is exceedingly low, the clinical significance of such pressure-induced paresthesia is unknown, but is likely distinct from needle-nerve contact induced paresthesia. However, there is a paucity of data regarding induced paresthesia during epidural steroid injections. The first observation was made by Evans (55) in 1930 that patients who experienced more pain in the distribution of the affected sciatic nerve had better results from intrasacral epidural injections. Schwarzer et al (56) discussed the provocation response during lumbar facet joint injections. The only similar observation to the present work was a retrospective analysis of 207 patients receiving TFESI (57). Plastaras et al (57) showed that 70% of patients had typical pain reproduction during the procedure, but there was no difference in pain relief compared with the 30% of patients who did not have pain reproduction.

There is no study reporting any correlation between pressure paresthesia and analgesic benefit in patients undergoing LESI. Our data indicate that pressure paresthesia occurring during LESI in the same distribution of the usual, customary and daily radicular pain could be used as an indicator of proper achievement of the medication target, thus increasing the likelihood of an improved outcome towards pain resolution, hence becoming a prognosticator. Furthermore, these results suggest that pressure paresthesia occurring during LESI is not essentially insignificant and that it should not be ignored. However, paresthesia occurring before the injection of therapeutic medications might be indicative of a potential needle-nerve contact and possible neurological injury and further advancement of the epidural needle should be immediately halted when it occurs. In our study, we used fluoroscopic guidance to assure correct needle placement; to record whether the needle moved; and to avoid intravascular, subdural, and subarachnoid injections. In all our studied patients, no one experiencing a pressure paresthesia reported any transient or persistent neurological injury and no paresthesia, regardless of laterality or severity, was sustained. The use of lidocaine in the injected solution with a subsequent alleviation of usual and customary discomfort may also be an indicator of proper achievement of the medication target, thus increasing the likelihood of an improved outcome towards pain resolution. However, a multicenter study with a larger number of patients is needed to test and prove our hypothesis.

There are several limitations of this study. The major limitation of this study is that we did not include a TFESI

group, since that is one of the approaches commonly used in contemporary interventional pain medicine for the treatment of low back pain with unilateral radicular type pain. Another limitation was operator variability. Even though the injections were performed by 3 board certified, fellowship trained physicians with at least 10 years of clinical practice experience each, variabilities in tactile placement of needles and pressure on the epidural needle and air in the loss of resistance syringe may be factors affecting results.

## Conclusion

The results of this study showed that both approaches (MIL and PIL) of LESI significantly improved pain scores, quality of life, and everyday functionality, and reduced the usage of pain medications as well. However, the PIL approach was more effective than the MIL approach in targeting low back pain with radicular pain secondary to degenerative lumbar disc disease. Patients receiving PIL injections had longer durations of pain relief and required additional injections after longer intervals than did patients receiving MIL. This study also showed that pressure paresthesia occurring ipsilaterally during an LESI correlates with pain relief and can be used as a prognostic factor.

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### Conflict of interest

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association, (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might post a conflict of interest in connection with the submitted manuscript.

### Disclaimer

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