Randomized Trial

A Randomized, Double-Blind, Active-Control Trial of the Effectiveness of Lumbar Interlaminar Epidural Injections in Disc Herniation

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Background: Among the multiple nonsurgical modalities, epidural injections are one of the most commonly utilized treatment modalities in managing chronic low back and lower extremity pain due to disc herniation and radiculitis. There is a paucity of randomized trials from contemporary interventional pain management settings utilizing fluoroscopy with long-term follow-up.

Study Design: Randomized, double-blind, active-controlled trial with 2-year follow-up.

Setting: An interventional pain management practice in the United States.

Objective: The objective was to assess the effectiveness of lumbar interlaminar epidural injections of local anesthetic with or without steroids for managing chronic low back pain of disc herniation or radiculitis.

Methods: Two groups of patients were studied, with 60 patients in each group receiving either local anesthetic only or local anesthetic mixed with betamethasone.

Outcome Measures: The primary outcome measure was defined as pain relief and functional status improvement of 50%. The outcomes were assessed by numeric rating scale (NRS) of pain and functional status with Oswestry Disability Index (ODI). Secondary outcome measures included employment status and opioid intake.

Results: Results showed significant improvement in 60% of patients in Group I and 70% of patients in Group II at the end of 2 years. In addition, in the successful groups, those with at least 3 weeks of relief (with the first 2 procedures), the improvement was 72% in Group I and 71% in Group II. Results were somewhat superior for pain relief at 6 months and functional status at 12 months in the steroid group. Thus, the results indicate that a patient's failure to respond to local anesthetic alone, may be treated with addition of steroids.

Limitations: The results of the study are limited by the lack of a placebo group.

Conclusion: Lumbar interlaminar epidural injections of local anesthetic with or without steroids is an effective modality, in patients with chronic function limiting low back and lower extremity pain secondary to disc herniation after failure of conservative modalities.

Key words: Lumbar disc herniation, lumbar radiculitis, lumbar interlaminar epidural injections, local anesthetic, steroids, randomized controlled trial, active-controlled trial

Clinical Trial: NCT00681447

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Multiple systematic reviews (1-4) and randomized trials (5-11) have been conducted assessing the effectiveness of epidural injections in the treatment of lumbar herniated disc and radiculitis administered by caudal, interlaminar, and transforaminal approaches. Benyamin et al (4) in a systematic review of lumbar interlaminar epidural injections, showed that of the multiple studies of interlaminar epidural injections, the majority were performed with an inappropriate study design, a series of 3 epidural injections, and without fluoroscopy. Among caudal and interlaminar injections, only 8 studies were performed under fluoroscopic visualization (3,4), among which there was only one randomized, controlled trial of an interlaminar approach with one-year results with 120 patients (7). Significant improvement was observed in 67% of patients with local anesthetic alone and 85% of patients with local anesthetic and steroids at the end of one year. Pinto et al (1), in a systematic review and meta-analysis of epidural corticosteroid injections in the management of sciatica, opined that epidural corticosteroid injections offer only short-term relief of leg pain and disability for patients with sciatica. However, this systematic review and analysis of evidence was flawed based on a multitude of issues including a combination of active-control and randomized placebo controlled trials, with the misclassification of local anesthetic as placebo, along with the utilization of physiotherapy evidence database criteria, which has not been validated (1,12). In contrast, multiple systematic reviews (3,4), utilizing rigorous evidence synthesis, along with robust criteria of outcomes assessment, showed good evidence for lumbar interlaminar, caudal, and transforaminal epidural injections in managing radiculitis secondary to disc herniation.

The estimated prevalence of lumbar radiculopathy or sciatica has been described as 9.8 per 100,000 cases (13). Lumbar radiculopathy secondary to disc herniation resolves spontaneously in about 50% of patients; although as many as 30% to 70% will still have pronounced symptoms after one year, with 5% to 10% of patients undergoing surgery (14,15).

With the increasing prevalence of low back pain, coupled with the exponential increase of numerous modalities of management with increasing disability and health care costs, all modalities including all interventional techniques have been under scrutiny for their overuse, abuse, utilization patterns, and clinical and cost effectiveness (16-27). Among the 3 approaches, the lumbar interlaminar route has been the most common approach; however, the evidence for lumbar interlaminar epidural injections has been overtly negative, even though a recent systematic review by Benyamin et al (4) showed positive evidence utilizing fluoroscopically performed controlled trials in contemporary interventional pain management settings. Multiple deficiencies have been encountered in the available literature and systematic reviews with study design (fluoroscopically directed verses blind), sample size, assessment of outcomes, duration of follow-up, and true placebo control (3,4,12,24-28). Significant issues also have been raised concerning bias and inappropriate study design of systematic reviews, including inclusion criteria, as well as the conclusions reached based on occasionally flawed studies. In addition, a cost utility analysis of caudal epidural injections has been illustrated for disc herniation with cost utility for one year of quality-adjusted life year (QALY) of $2,206 for disc herniation (29).

Despite the developing evidence, with ever-increasing investigations and modalities of treatments, epidural injections are one of the most commonly performed interventions for managing chronic low back and lower extremity pain secondary to disc herniation and other pathologies (1-4,20-22,24,27,29-36). As a group, however, utilization statistics have shown the highest increases for sacroiliac joint injections at 331%, followed by 308% for facet joint interventions, and 130% for epidural injections per 100,000 fee-for-service Medicare recipients (23). Surprisingly, however, the highest increases were seen with lumbar transforaminal epidural injections, of 665% (22,23), and lumbar facet joint radiofrequency thermoneurolysis, of 544% (23). A combination of caudal and lumbar interlaminar epidural injections showed an increase of 25% from 2000 to 2011 (22.23).

This study was designed to evaluate the effectiveness of lumbar interlaminar epidural injections of local anesthetic with or without steroids, in managing chronic intractable persistent pain of low back and lower extremity secondary to disc herniation or radiculitis after failure of conservative management. This is the final report of a 2-year follow-up of 120 patients in a randomized, double-blind, active-control evaluation. This is a continuation of the previously published one-year follow-up of 120 patients (7).

Methods

This trial was conducted with the approval of the Institutional Review Board (IRB) and registered with the

U.S. Clinical Trial Registry (NCT00681447). The design of the study was randomized, double-blind, and active control. The study was performed in a private practice, interventional pain management setting, and a specialty referral center in the United States. The trial was conducted based on Consolidated Standards of Reporting Trials (CONSORT) guidance (37,38).

There was no external support or funding in performance of this randomized double-blind evaluation. The study was conducted with internal resources of the practice of the first author.

Participants

All the participants were recruited from the practice presenting for interventional pain management. Eligible patients were provided with IRB approved protocol and all signed informed consent.

Interventions

The protocol consisted of 2 groups, and the patients were randomly assigned to one of the 2 groups based on the protocol. Group I patients were treated with lumbar interlaminar epidural injections with lidocaine 0.5%, 6 mL, preservative free. Group II patients were treated with lumbar interlaminar epidural injections of 0.5% preservative-free lidocaine, 6 mL, mixed with 1 mL of non-particulate betamethasone.

Pre-Enrollment Evaluation

All patients underwent appropriate assessment. This assessment included demographic data, medical and surgical histories, along with coexisting disease(s); physical examination findings; pain rating scores using numeric rating scale (NRS); functional assessment using the Oswestry Disability Index (ODI); radiologic findings; work status; and opioid intake prior to enrollment.

Inclusion and Exclusion Criteria

Inclusion criteria focused on disc herniation or radiculitis. Furthermore, patients must have been at least 18 years of age with chronic low back and lower extremity pain of 6 months with function-limiting intensity. All participants must have been capable of understanding the study protocol, able to provide voluntary written informed consent, and had an unrestricted ability to participate in outcome assessments.

Patients with previous lumbar surgery, radiculitis secondary to spinal stenosis, and radiculitis without disc herniation were excluded. Patients with uncontrolled or unstable psychiatric disorders, medical illness, opioid use, and those with an inability to participate in outcome assessments were also excluded. Pregnant and lactating women, and patients with a history of or potential for adverse reaction(s) to local anesthetics or steroids were excluded as well.

Description of Interventions

All patients were treated in a sterile operating room in an ambulatory surgery center. All procedures were performed by one physician with appropriate monitoring. Intravenous sedation was provided as indicated.

The procedure, in short, included identification of the lumbar interlaminar epidural space with loss of resistance technique and fluoroscopic visualization, followed by confirmation by non-ionic contrast medium. The epidural space was entered based on the disc herniation between L5 and S1, or one space below the disc herniation level if it was at higher levels. After confirmation of the entry into the epidural space, injections were performed in Group I with 6 mL of lidocaine hydrochloride and in Group II with 5 mL of lidocaine and 1 mL of non-particulate betamethasone.

Additional Interventions

All patients were provided with treatments as assigned unless unblinding occurred, or if an emergency situation arose. Interlaminar lumbar epidural injections as per the protocol were provided based upon the initial response following the epidural procedure and deteriorating pain relief below 50%. If patients were nonresponsive to epidural injections and were not unblinded, they continued with conservative medical management without epidural injections in addition to a structured exercise program and drug therapy.

Co-Interventions

All patients at their request continued drug therapy either with opioids or nonsteroidal antiinflammatory agents, generally at a lower level than initial doses. They also continued their structured exercise program and employment. Medications were adjusted based on their necessity, either discontinuing them, lowering the dosage, or in rare circumstances increasing the dosage. No additional physical therapy, occupational therapy, or any other interventions were offered beyond the protocol.

Objectives

The objective of this trial was to evaluate the effectiveness of lumbar interlaminar epidural injections

with or without steroids for managing chronic low back and lower extremity pain secondary to disc herniation or radiculitis.

Outcomes

All patients were assessed with primary and secondary outcomes at predefined intervals of 3, 6, 12, 18, and 24 months. Significant improvement was the primary outcome, defined as at least 50% improvement with pain relief and functional status. This significant outcome measure is robust and also superior to the generally utilized measures of 20% to 30% improvement (39-41). Opioid intake, employment, and work status were considered as secondary outcome measures.

Consistent relief lasting at least 3 weeks with the initial 2 epidural injections was deemed as successful.

The NRS pain scale (0 – 10); functional assessment using the ODI (0 – 50 scale); employment status; and opioid intake in terms of morphine equivalents were measured. On the NRS scale, 0 represents no pain and 10 represents the worst pain imaginable (42). Based on the ODI scores (0% – 20%: minimal disability; 20% – 40%: moderate disability; 40% – 60%: severe disability; 60% – 80%: crippled; 80% – 100%: bed-bound or exaggerating their symptoms) (43,44), the value and validity of the NRS and ODI have been described (42-44).

Opioid intake was calculated in each patient by conversion into morphine equivalent dosages (45).

Assessment of employment and work status was a difficult issue. Consequently, we assigned each of the patients to one of 4 categories designated as "employable" which included those who were unemployed due to pain, employed but on sick leave, laid off, or working. The other categories included housewife with no desire to work outside the home, retired, disabled, and elderly at least 65 years of age, eligible for social security and Medicare.

Sample Size

The sample size was determined based on previous assessments. Sample size calculations required a total of 110 patients with 55 patients in each group, considering a 0.05 two-sided significance level, with a power of 80%, and an allocation ratio of 1:1. Consequently, for this assessment, we utilized a sample of 120 patients with 60 patients in each group, allowing for a 10% attrition or non-compliance rate.

Randomization

Random assignment was carried out by allocating 60 patients into each group.

Sequence Generation

Simple randomization was adopted with a computer-generated random allocation sequence.

Allocation Concealment

A study coordinator randomized the patients and an operating room nurse prepared the drugs appropriately.

Implementation

One of the coordinators of the study enrolled the patients and assigned them to their respective groups.

Blinding (Masking)

Blinding or masking was carried out at all stages of the trial following the computer generation random allocation sequence with proper allocation concealment. All patients and all the medical personnel who administered the interventions were blinded. Injections used for both groups were clear and indistinguishable from each other. Additional blinding precautions included the incorporation of study patients with other patients undergoing routine treatments so that the physician performing the procedures did not know whether or not study patients were being treated.

Statistical Methods

Statistical package for Social Sciences version 9.01 (SPSS Inc, Chicago, IL) was used for data analysis. Chi-squared statistic, Fisher's exact test, one-way analysis of variance (ANOVA), t-test, and paired t-test were used for categorical and continuous data comparison. Outcomes of the participants were measured at 6 points. Repeated measures analysis of variance was performed with Bonferroni post hoc analysis. A *P* value of less than 0.05 was considered significant.

Intent-to-Treat-Analysis

The last follow-up data or initial data were utilized in patients who dropped out of the study or for whom no other data were available for intent-to-treat analysis.

In addition, changes in the NRS were assessed utilizing the last follow-up score, best case scenario, and worst case scenario. The intention-to-treat analysis with last follow-up visit was used if there were no significant differences.

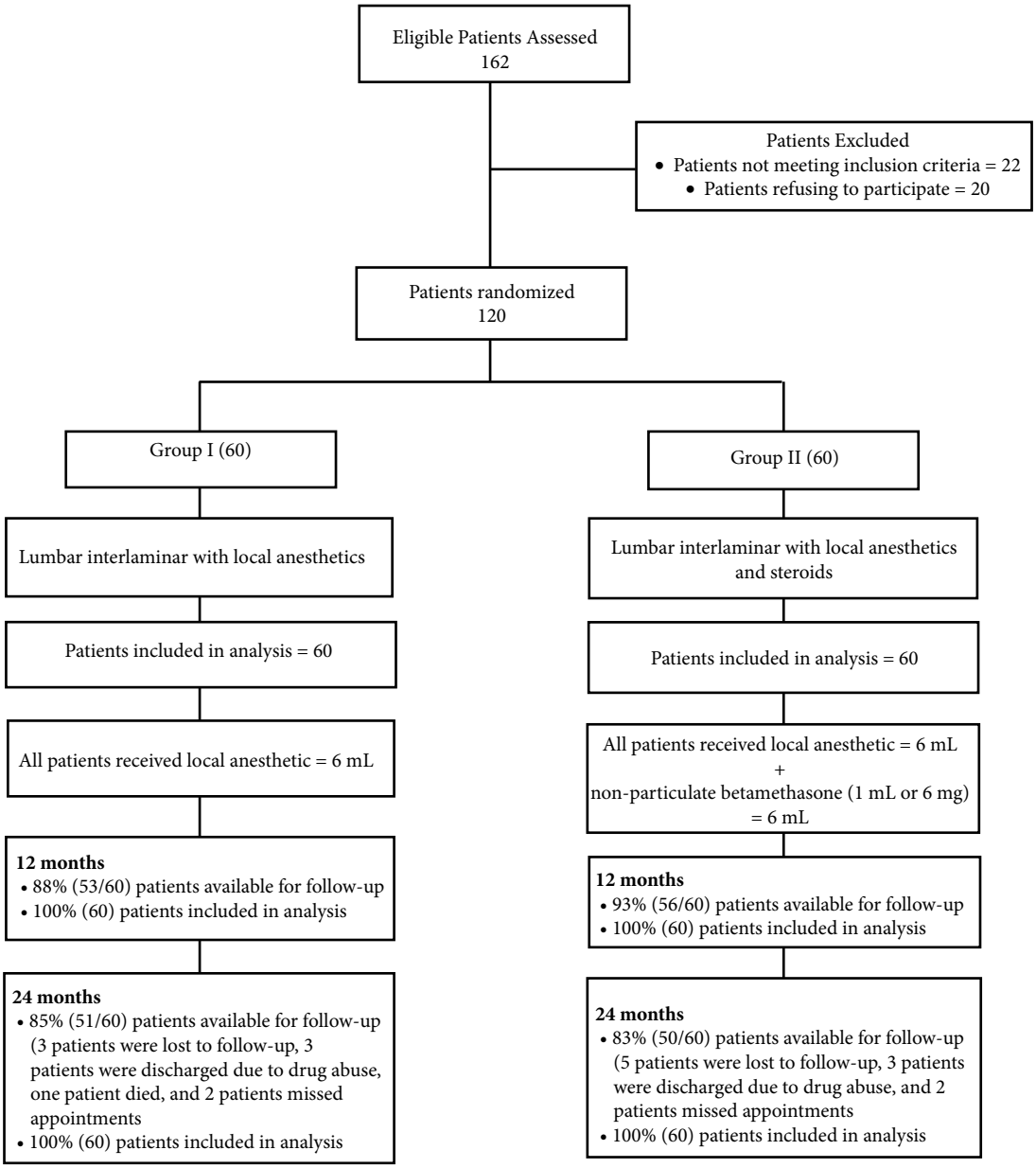

Fig. 1. *Schematic presentation of patient flow at 2-year follow-up.*

Results

Patient Flow

Patient flow is shown in Fig. 1.

Recruitment

The trial recruitment period lasted from January 2008 to May 2010.

Table 1. *Baseline demographic and clinical characteristics.*

		Group 1 (60)	Group II (60)	*P* value
Gender	Male	38% (23)	62% (37)	0.011
	Female	62% (37)	38% (23)	
Age	Mean ± SD	49.0 ± 14.1	40.6 ± 12.5	0.001
Weight	Mean ± SD	201.8 ± 49.4	181.8 ± 41.1	0.018
Height	Mean ± SD	66.2 ± 3.4	68.1 ± 4.7	0.013
Duration of Pain (months)	Mean ± SD	135.0 ± 120.3	133.2 ± 108.5	0.933
Onset of Pain	Gradual	77% (46)	57% (34)	0.020
	Injury	23% (14)	43% (26)	
Numeric Rating Score	Mean ± SD	8.2 ± 0.8	8.0 ± 1.0	0.237
Oswestry Disability Index	Mean ± SD	30.3 ± 4.7	29.6 ± 5.2	0.443
Disc Herniation * (levels)	L3/4	1.7% (1)	0%	0.133
	L4/5	3.3% (2)	13.3% (8)	
	L5/S1	95% (57)	86.7% (52)	

*Multiple patients presented with disc herniation at more than one level.

Demographics

Baseline demographic and clinical characteristics are shown in Table 1. The assessment of the data showed a larger female population than male population in Group I and a larger male population in Group II. Patients in Group I were heavier than in Group II, gradual pain onset was higher in Group I, and finally, Group I had higher baseline pain rating scores.

Pain Relief and Functional Assessment

Pain relief and functional assessment results are shown in Table 2. There were significant differences in pain rating and ODI between Group I and Group II. There were also significant differences in average pain and ODI scores within the groups over a period of 2 years from baseline. Overall there was significantly higher improvement in pain relief in the steroid group at 6 months, and in ODI scores at 6 months and 12 months.

The proportion of patients showing significant improvement with a reduction in NRS and ODI of 50% or more from baseline is shown in Fig. 2, with 60% in Group I and 70% in Group II at the end of 2 years when all participants were considered. However, the improvement was 72% and 71% in the successful groups in Group I and Group II respectively.

Therapeutic Procedural Characteristics

The majority of lumbar interlaminar epidural injections (90%) were performed between the L5 and S1 interspaces, 9% between L4 and L5, and 1% between L3 and L4. Therapeutic procedural characteristics are shown in Table 3. Patients receiving consistent relief with the initial 2 procedures lasting at least 3 weeks were considered successful. There were a larger number of patients failing to respond in the local anesthetic group compared to local anesthetic with steroid group (10 versus 1 or 17% versus 2%). Consideration of all participants showed an average number of procedures per 2 years of 5.3 ± 1.3 in Group I and 6.1 ± 2.3 in Group II and total relief of 60.0 ± 39.7 weeks in Group I and 67.8 ± 29.1 weeks in Group II over a period of 2 years.

There were a significantly larger number of patients in Group I who failed to respond compared to Group II (Group I = 10 versus Group II = 1).

Employment Characteristics

Employment characteristics of both groups through 2 years are shown in Table 4.

Opioid Intake

Table 5 shows the characteristic features of opioid intake. Even though there were no differences between

Table 2. *Comparison of numeric rating scales of pain and Oswestry Disability Index for 2 years.*

Time Points	Numeric Pain Rating Scale		Oswestry Disability Index	
	Group I (60)	Group II (60)	Group I (60)	Group II (60)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Baseline	8.2 ± 0.8	8.0 ± 1.0	30.3 ± 4.7	29.6 ± 5.2
3 months	3.9* ± 1.6 (78%)	3.5* ± 1.0 (88%)	15.8* ± 6.3 (73%)	14.0* ± 4.2 (82%)
6 months	4.1* ± 1.6 (70%#)	3.5* ± 1.0 (88%)	16.1* ± 6.6 (63%#)	13.5* ± 4.2 (87%)
12 months	4.0* ± 1.6 (72%)	3.4* ± 1.2 (85%)	15.9* ± 6.9 (68%#)	13.0* ± 4.2 (87%)
18 months	3.9* ± 1.8 (67%)	3.6* ± 1.3 (80%)	15.7* ± 7.5 (67%)	13.3* ± 5.0 (80%)
24 months	4.1* ± 1.7 (63%)	3.7* ± 1.4 (70%)	16.1* ± 6.8 (63%)	13.5* ± 4.8 (73%)
Group Difference	0.677		0.140	
Time Difference	0.001		0.001	
Group by Time Interaction	0.05		0.015	

The lower value indicates better condition.
* significant difference with baseline values within the group ($P < 0.001$).
# significant difference with Group II within the time period ($P < 0.05$).
(_____) illustrates proportion with significant pain relief (≥ 50%) from baseline.

Table 3. *Therapeutic procedural characteristics with procedural frequency, average relief per procedure, and average total relief in weeks over a period of 2 years.*

	Successful Subjects		Failed Subjects		All Subjects	
	Group I (50)	Group II (59)	Group I (10)	Group II (1)	Group I (60)	Group II (60)
Average number of procedures for one year	**3.9 ± 1.2**	**4.1 ± 1.0**	**2.0 ± 1.0**	**2.0**	**3.6* ± 1.3**	**4.1 ± 1.02**
Average number of procedures for 2 years	6.0 ± 2.5	6.1 ± 2.3	2.0 ± 0.7	2.0	5.3 ± 2.7	6.1 ± 2.3
For initial 2 procedures in weeks	8.2* ± 7.7 (97)	6.3 ± 5.7 (116)	0.7 ± 0.8 (18)	0.0 (2)	7.1 ± 7.6 (115)	6.2 ± 5.7 (118)
After initial 2 procedures	12.7 ± 3.2 (97)	13.5 ± 6.9 (125)	0.5 ± 0.7 (2)	-	12.4 ± 3.6 (99)	13.5 ± 6.9 (125)
Average relief per procedure	12.2 ± 6.9	11.3 ± 7.6	0.7 ± 0.7	0	11.4 ± 7.2	11.2 ± 7.6
Average total relief for one year (weeks)	**40.1 ± 13.0**	**39.8 ± 11.2**	**1.32 ± 1.1**	**0**	**33.7 ± 18.1**	**39.1 ± 12.2**
Average total relief for 2 years (weeks)	71.8 ± 32.4	68.9 ± 27.9	1.3 ± 1.1	0.0	60.0 ± 39.7	67.8 ± 29.1

the groups, opioid intake decreased from baseline to one year and 2 years.

Changes in Weight

The results of characteristics of changes in weight are shown in Table 6. There were significant differences in weight at baseline with Group I patients weighing more than Group II patients, P 0.018; however, in both groups over 50% of patients showed weight reduction at the end of one year and 2 years. Weight gain was shown in 26% and 33% of Group I and II patients, respectively.

Adverse Events

A total of 682 lumbar interlaminar epidural procedures were performed. Adverse events included 11 dural punctures (1.6%). However, there were no headaches, nerve root irritations, or other adverse consequences.

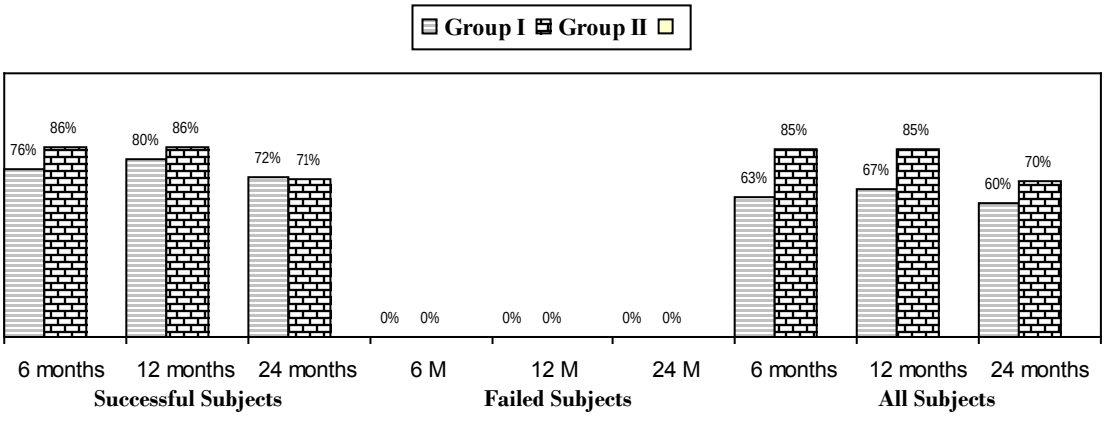

Fig. 2. *Results of significant improvement with reduction (at least 50%) in pain and Oswestry Disability Index from baseline.*

Table 4. *Employment characteristics.*

Employment Status	Group I			Group II		
	Baseline	12 months	24 months	Baseline	12 months	24 months
Employed part-time	2	1	1	5	4	4
Employed full-time	9	11	10	13	21	21
Unemployed (due to pain)	1	2	2	7	3	4
Not working	4	2	3	5	2	3
Eligible for employment at baseline	16	16	16	16	16	16
Total Employed	**11**	**12**	**11**	**18**	**25**	**25**
Housewife	5	5	5	5	4	3
Disabled	30	30	30	24	24	24
Retired/Over 65	9	9	9	1	1	1
Total Number of Patients	**60**	**60**	**60**	**60**	**60**	**60**

Table 5. *Opioid intake (morphine equivalents in mg).*

Time	Group I (60)	Group II (60)
	Mean ± SD	Mean ± SD
Baseline	49.6 ± 39.3	47.1 ± 27.2
3 months	34.3# ± 25.2	42.4 ± 39.9
6 months	37.3# ± 43.3	36.5# ± 27.6
12 months	37.3# ± 43.3	36.5# ± 27.6
18 months	36.8# ± 43.4	36.6# ± 27.6
24 months	36.2# ± 43.7	36.6# ± 27.6
Group Difference	0.103	
Time Difference	0.002	
Group by Time Interaction	0.901	

# indicates significant difference from their baseline values ($P < 0.05$).

Table 6. *Characteristics of changes in weight.*

Weight (lbs)	Group I (60)	Group II (60)	*P* value
	Mean ± SD	Mean ± SD	
Weight at baseline	201.8 ± 49.4	181.8 ± 41.1	**0.018**
Weight at one year	197.1 ± 48.4	180.5 ± 41.3	**0.045**
Change	-4.7 ± 12.1	-1.4 ± 9.2	0.093
Lost weight	55% (33)	50% (30)	0.063
No change	20% (12)	8% (5)	
Gained weight	25% (15)	42% (25)	
Weight at 2 years	**195.4 ± 47.3**	**179.7 1 ± 42.4**	**0.057**
Change	-6.3 ± 17.3	0.98 ± 29.9	0.104
Lost weight	52% (31)	54% (32)	0.438
No change	22% (13)	13% (8)	
Gained weight	26% (16)	33% (20)	

Discussion

In chronic persistent low back and lower extremity pain secondary to disc herniation and radiculitis, this randomized, active-control, double-blind trial with 120 patients receiving lumbar interlaminar epidural injections with or without steroids as resulting in significant improvement in all parameters in 60% of patients with local anesthetic alone and 70% of patients with local anesthetic and steroid at the end of 2 years. However, when patients were separated into successful and failed categories, significant improvement with pain relief and functional status improvement of 50% or more was shown in 72% in the local anesthetic group and 71% in the local anesthetic with steroid group. Patients in the successful category were defined as those responding with at least 3 weeks of significant improvement with the first 2 procedures. Furthermore, patients with a successful response achieved 71.8 weeks of relief over a period of 2 years with 6 procedures per 2 years when only local anesthetic was administered and 68.9 weeks when local anesthetic with steroid were administered. Overall results showed some superiority of the steroid group at 6 months with pain relief and at 6 months and 12 months with functional status, and there was only one patient in the initialfailed category in the steroid group, compared to 10 in the local anesthetic group. Both groups showed significant improvement from baseline to 2 years. However, these results indicate that in clinical practice a failure with the first injection with local anesthetic in a patient may be improved with addition of steroid to the local anesthetic with the second injection. Consequently, this randomized trial provides evidence that in carefully selected patients with repeat injections in contemporary interventional pain management settings under fluoroscopy, patients respond to both local anesthetic alone and local anesthetic with steroids.

The results of this assessment are similar to the one-year results of this trial (7) and 2-year reports of randomized, double-blind, controlled trials of fluoroscopic caudal epidural injections (46). However, these results are vastly different from other interlaminar epidural trials published, specifically those without fluoroscopy (2-6). The results are also superior to previously published fluoroscopic interlaminar epidural injections(3,4,8-10). None of the previous assessments included 2 year follow up with robust outcome measures in contemporary interventional pain management settings with procedures performed under fluoroscopy, or repeated those procedures as required when pain and disability deteriorated. There have been numerous publications in the literature with multiple systematic reviews (1-11,46), mostly against lumbar interlaminar epidural injections with some in favor (3,4,7,8,46-48). However, various published studies and systematic reviews over the years have been criticized for their methods of evidence synthesis, design of the studies, and lack of utilization of fluoroscopy (3,4,12,47,48). Thus, the present trial is the largest (with 120 patients) performed under fluoroscopy in contemporary interventional pain management settings practicing judicious use of lumbar interlaminar epidural injections in properly selected patients with or without steroid with a long-term follow-up. Consequently, the implications of this randomized, double-blind, active-control trial are enormous in an era of evidence-based medicine and comparative effectiveness research using value-based interventional pain management as a means of controlling health care costs while providing quality cost-effective interventions (3,12,24,29,48). This trial, with a proper methodology in a practical setting, provides appropriate information and facilitates the proper application of interventions to reduce a patient's pain, improve function, reduce drug use, and potentially return them to the workforce. In contrast, inappropriate provision of any type of intervention, specifically those that are not cost effective, incurring substantial expenses, and systematic reviews without proper utilization of the criteria will harm the patient and the economy of health care.

The published cost utility analysis of caudal epidural injections (29) also is applicable to the results of this trial. It is expected that the cost effectiveness of lumbar interlaminar epidural injections in disc herniation would be similar to caudal epidural injections in disc herniation and other conditions at $2,200 per one QALY.

In reference to methodology, in the era of evidence-based medicine and comparative effectiveness research, practical clinical trials (3,24,29,47,48) with a pragmatic approach are considered to be clinically applicable and valid. This study meets the essential criteria for practical clinical trials with an active control group instead of a placebo group, and measures effectiveness, which is more appropriate than efficacy measured by explanatory trials, improving the applicability of the results in practical interventional pain management settings (49-52).

While this is considered the most appropriate available trial in the literature thus far, it also may be criticized for deficiencies, including the lack of a pla-

cebo and a larger proportion of patients with increased weight parameters in Group I compared to Group II. In reference to placebo design, most studies thus far have utilized inappropriate methodology in assessing epidural injections including caudal, interlaminar, and transforaminal approaches (1-6,11,12,53-55). Furthermore, all the placebo-controlled trials of the interlaminar approach were in blind epidural groups with significant variability (5,6,11). Thus, 2 of these trials utilized injections of sodium chloride solution into the interspinous ligament compared with epidural steroid injections (5,6). One study commonly cited in systematic reviews and health policies (11) utilized epidural saline versus a steroid. However, 2 studies using interspinous ligament injection of sodium chloride solution arrived at different conclusions from each other. One study was performed in 1973 (6) and the second one was performed in 2005 (5). Recently, proper placebo design has been lauded for its use in transforaminal epidural injections and percutaneous adhesiolysis (53,56). These properly conducted trials showed the appropriate effect of sodium chloride solution with its injection into an inactive structure(s). Thus, the majority of systematic reviews and opinions which equate local anesthetic with placebo are not only methodologically and conceptually inaccurate, but they also result in improper conclusions (1-3,12,47,48). The role of placebo and its interpretations have been extensively discussed (57-60). In addition, it has been well described that inactive substances, when injected into active structures, invariably result in various types of clinical effects (61-64). The injection of sodium chloride solution into an epidural space has been shown to be clinically effective in multiple studies (11,65,66). Furthermore, local anesthetics also show multiple effects along with long-term improvement or equal response to steroids in clinical and experimental settings (1-3,7,29-35,46,67-77). Consequently, it is essential to design a proper placebo study if one is contemplated. An additional weakness of the study includes differences in baseline demographic characteristics with respect to gender and weight, and the mode of onset of pain. We do not, however, expect any significant variations in outcomes attributable to these differences. If there are they will be minor without any significant effect on the final results.

Disc herniation and radiculitis are based on a pathophysiologic explanation of inflammatory pathology (1-4,78-89). Consequently, epidural steroids have been recommended to be effective in disc herniation and radiculitis secondary to their antiinflammatory profiles. Meanwhile, emerging evidence also shows that local anesthetics with or without steroids are equally effective as steroids in many settings (69-77), even though steroids have been shown to be somewhat superior in this trial initially and some others (3,46,90). In addition, emerging literature also shows the effectiveness of other applied antiinflammatory agents in managing disc herniation (78,86-89).

In summary, the results of this randomized, double-blind, active-control trial have significant implications for contemporary interventional pain management settings with comparative effectiveness research and cost utility analysis.

Conclusion

The results of the 2-year follow-up of this randomized double-blind controlled trial with 120 patients, with chronic persistent pain of disc herniation, receiving lumbar interlaminar epidural injections with local anesthetic alone or with local anesthetic and steroids are positive, with significant improvement in overall patients in 60% of patients with local anesthetic only and 70% of the patients with local anesthetic and steroids or 70% and 71% in the successful group.

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Disclosure: Dr. Falco is a consultant for St. Jude Medical Inc. and Joimax Inc. None of the remaining authors have any competing interest.

Ethical Approval: The study was approved by the IRB and was registered in the US Clinical Trial Registry. All ethical guidelines were followed.

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