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Randomized Trial

A Randomized, Double-Blind Controlled Trial of Lumbar Interlaminar Epidural Injections in Central Spinal Stenosis: 2-Year Follow-Up

Laxmaiah Manchikanti, MD[1,2], Kimberly A. Cash, RT[1], Carla D. McManus, RN, BSN[1], Kim S. Damron, RN[1], Vidyasagar Pampati, MSc[1], and Frank J.E. Falco, MD[3]

From: [1]Pain Management Center of Paducah, Paducah, KY, and [2]University of Louisville, Louisville, KY, and [3]Mid Atlantic Spine & Pain Physicians of Newark, Newark, DE

Additional Author Affiliatoni Information is on P. 89.

Address Correspondence:
Laxmaiah Manchikanti, MD
2831 Lone Oak Road
Paducah, Kentucky 42003
E-mail: drlm@thepainmd.com

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Background: While low back pain is the number one cause of disability in the United States, lumbar spinal stenosis along with intervertebral disc herniation and degenerative spondylolisthesis is one of the 3 most common diagnosis of low back and leg pain for which surgery is performed. Numerous modalities of treatments including drug therapy and complex surgical fusions have been recommended for treatment of central spinal stenosis. Epidural injections are one of the commonly performed nonsurgical interventions in managing central spinal stenosis; however, there has been paucity of literature in reference to efficacy of epidural injections in managing central spinal stenosis with lumbar interlaminar epidural injections.

Study Design: A randomized, double-blind, active controlled trial.

Setting: Private interventional pain management practice and specialty referral center in the United States.

Objective: To assess the effectiveness of lumbar interlaminar epidural injections with or without steroids in providing effective and long-lasting pain relief with improvement in functional status for the management of chronic low back and lower extremity pain related to lumbar central spinal stenosis.

Methods: A randomized, double-blind, active-control trial was designed with the inclusion of 120 patients assigned to 2 groups. Group I patients received lumbar interlaminar epidural injections of local anesthetic (lidocaine 0.5%) 6 mL, whereas Group II received lumbar interlaminar epidural injections with local anesthetic (lidocaine 0.5%) 5 mL mixed with 1 mL of steroids and 6 mg of betamethasone.

Outcomes Assessment: Outcomes were assessed utilizing the numeric pain rating scale (NRS) and Oswestry Disability Index (ODI) at 3, 6, 12, 18, and 24 months post treatment. The primary outcome measure was significant improvement, defined as 50% improvement in pain and disability scores.

Results: Significant relief and functional status improvement was seen in 72% and 73% of patients in Groups I and II at the end of 2 years considering all participants; however, this was 84% and 85% in the successful group. Overall significant improvement was achieved for 65.7 ± 37.3 weeks in Group 1 and 68.9 ± 37.7 weeks in Group II at the end of 2 years when all participants were considered; whereas, this was 77 ± 27.8 weeks and 77.9 ± 30.2 weeks when they were separated into successful categories. The average number of procedures per patient was 5 to 6 in both groups.

Limitations: Limitations of this trial include lack of placebo control group and treatment of patients with multiple procedures over a period of 2 years.

Conclusion: Lumbar interlaminar epidural injections of local anesthetic with or without steroids provide relief in a significant proportion of patients with lumbar central spinal stenosis.

Key words: Chronic low back pain, lower extremity pain, central spinal stenosis, interlaminar epidural injections, caudal epidural injections, steroids, local anesthetics, placebo, active control

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Low back pain is the number one cause of disability in the United States (1). In addition to intervertebral disc herniation and degenerative spondylolisthesis, lumbar spinal stenosis is one of the 3 most common diagnoses of low back and leg pain for which surgery is performed (2). In fact, Bae et al (3) showed that between 2004 and 2009 national estimates for the rate of decompressions increased 45%, simple fusions increased 60%, and complete complex fusions increased 76%. Deyo et al (4) showed the rate of fusion for spinal stenosis increased by 15-fold from 1.3 to 19.9 per 100,000 Medicare beneficiaries between 2002 and 2007. Despite significant debate in the literature concerning the optimal management of lumbar spinal stenosis, it has been established in surgical literature that decompressive surgery, with or without fusion, is effective in alleviating symptoms and improving quality of life (2,5). A review of current research demonstrates a lack of consensus and wide variability in surgical decision-making for patients with lumbar spinal stenosis (3). Complex fusions, however, continue to increase. Certain reports indicate heightened complications and costs, specifically with the use of recombinant human bone morphogenetic protein-2 for spinal fusion, bringing into question the desirability of surgical interventions (6-8). These complications include inflammatory reactions, back and leg pain, radiculitis, implant displacement, retrograde ejaculation, male sterility, cancer, infection, osteolysis, ectopic bone formation, and death (8). Consequently, new technologies have been developed including interspinous spacers and minimally invasive lumbar decompression (MILD) (9,10). In fact, Deyo et al (10) compared interspinous spacers with decompression or fusion for lumbar spinal stenosis, reaching the conclusions that there were fewer complications using interspinous spacers, but that there were higher rates of revision surgery.

Multiple other modalities of treatments have been advocated in managing lumbar central spinal stenosis, including interventional techniques and a multitude of conservative modalities (5,11-33). Despite intense debate in reference to surgical interventions for lumbar spinal stenosis¸ the literature describing the surgery, advantages, and indications continues to dominate, with surgical management with or without fusion being described as the gold standard. Variable results have been published in reference to the effectiveness of non-surgical management (5,11-34). Thus, optimal management of lumbar spinal stenosis has not been established, specifically in those without severe stenosis and patients who are not candidates for surgical interventions. Consequently, multiple factors have been described explaining the variation in outcomes and the influence of these outcomes on the prognosis of both surgery and epidural injections in lumbar spinal stenosis (35-42). Even then, interventions of all types are increasing exponentially in managing spinal pain, including spinal interventional pain management techniques in the management of spinal stenosis (43-51). The Institute of Medicine (IOM) report (48), based on the study of Gaskin and Richard (49), showed expenditures of $100 billion per year in managing chronic pain after the exclusion of other conditions included in this analysis. Martin et al (50,51) evaluated health care expenditures for the treatment of back and neck problems in the United States in 2005 and reported that these expenditures totaled approximately $86 billion, with an increase of 65% between 1997 and 2005 and a 49% increase in the number of patients seeking spine-related care.

A number of publications indicated significant improvement in central spinal stenosis with epidural injections, as well as percutaneous adhesiolysis (17-20,22-25,27,31), even though the results are disputed (5,11,12,16,18,28,32,52). In contrast, Radcliff et al (28), in an observational report of subgroup analysis, showed a lack of effectiveness of epidural injections at 5 years and inappropriately concluded that epidural injections increased the surgical rate. Both the analysis and conclusions have been questioned (52,53). In a recent systematic review (16) with an assessment of cost-effectiveness of epidural injections in spinal stenosis, the authors reached the conclusion that epidural injections were ineffective; however, the methodology of this assessment and the subsequent conclusions have been questioned (54). In fact, a design of the protocol used incomplete data to conclude that there were no studies showing the effectiveness of epidural injections in spinal stenosis (12). A recent study by Friedly et al [53] performed in multiple settings with enrollment of 400 patients, included a design which is not amenable to assess outcomes in central spinal stenosis with epidural injections [54]. Friedly et al [53] excluded available high quality randomized trials, yet they included low quality trials in their assessment of the literature. In addition, the follow-up by Friedly et al [53] was only 6 weeks, utilizing either interlaminar or transforaminal techniques with variable volumes of injection, with reports of an inordinate amount of adverse events [54]. Further, the interpretation of the results and outcomes were extremely poor utilizing a differential assessment for subgroup analysis, reducing the P value

from 0.5 to 0.25 resulting in inappropriate conclusions.

Despite, however, the negative surgical literature about epidural injections, epidural injections may be the only choice after the failure of conservative management in patients with mild and moderate stenosis – who are not candidates for surgical intervention and who may not respond well to surgery. Thus, next to surgery, epidural injections continue to be the most commonly performed interventions for managing chronic low back pain secondary to central spinal stenosis. However, in managing central spinal stenosis, only one well conducted randomized double-blind active-controlled trial with a 2-year follow-up has been published showing the effectiveness of caudal epidural injections (20), and for lumbar interlaminar epidural injections, there was only one randomized controlled trial publicizing preliminary results (19). The cost effectiveness of caudal epidural injections was also illustrated as being less than $2,200 per quality-adjusted life year (QALY) improvement (31). In contrast the cost effectiveness of surgical interventions has been shown to be $77,600 per QALY (55).

In the preliminary report (19) at 12 months of a total of 60 patients assessed with 30 patients in each group receiving either local anesthetic alone or local anesthetic and steroids, significant improvement was seen in the overall sample in 70% in Group I and 60% in Group II.

This trial was undertaken to evaluate the role of lumbar interlaminar epidural injections with local anesthetic with or without steroids to assess significant improvement with at least 50% improvement in pain and function in patients with chronic intractable pain secondary to lumbar central spinal stenosis. This 2-year follow-up report is an extension of a previously published preliminary report of one-year results (19).

Methods

This trial was conducted with a randomized, double-blind, active-control design based on Consolidated Standards of Reporting Trials (CONSORT) guidelines (56,57). The study was performed in a private interventional pain management practice, a specialty referral center in the United States. The study protocol was approved by the Institutional Review Board (IRB) and was registered with the U.S. Clinical Trial Registry with an assigned number of NCT00681447.

The study was conducted with the internal resources of the practice.

Patients

All patients were drawn from a single pain management practice. One hundred and twenty patients were recruited. All patients were provided with an IRB-approved protocol and informed consent describing in detail various aspects of the study including the withdrawal process.

Pre-enrollment Evaluation

All patients were assessed for various baseline parameters. This evaluation included the assessment of demographic data, medical and surgical history with co-existing disease(s), radiologic investigations, physical examination, pain rating scores using Numeric Rating Scale (NRS), work status, opioid intake, and functional status assessment by Oswestry Disability Index (ODI) 2.0.

Inclusion Criteria

Only patients with central spinal stenosis with radicular pain of at least 6 months duration were included. In addition, patients must have been at least 30 years of age with a history of chronic function-limiting low back and lower extremity pain of at least 6 months duration with demonstrated competency to understand the study protocol and provide voluntary, written informed consent with the ability to participate in outcome measures. In addition, all patients must have undergone conservative management with insufficient improvement.

Exclusion criteria were foraminal stenosis without central spinal stenosis, previous history of surgery, and uncontrollable or unstable psychiatric disorders, medical disorders, or opioid use. In addition, any conditions that could interfere with the interpretation of the outcome assessments, pregnancy or lactating women, and history of adverse reaction(s) to local anesthetic or steroids were also considered as exclusion criteria.

Interventions

From a total of 120 patients enrolled into the study, 60 patients were assigned to Group I receiving lumbar interlaminar epidural injections of local anesthetic, preservative-free lidocaine 0.5%, 6 mL. The 60 patients assigned to Group II received lumbar interlaminar epidural injections of 0.5% preservative-free lidocaine, 5 mL, mixed with 1 mL or 6 mg of betamethasone, with a total volume of 6 mL. Preservative free betamethasone was utilized through September 2012; due to meningitis issues developed as a result of tainted compounding of betamethasone from New England pharmacy (58), commercial betamethasone, which is particulate, was utilized from October 2012 to June 2013.

Description of Interventions

All procedures were performed under fluoroscopy by a single physician (LM). Patients were positioned in a prone position in an ambulatory surgery center in a sterile operating room. All patients received appropriate monitoring and those desiring sedation were provided with midazolam and fentanyl as medically indicated. With sterile preparation, the lumbar interlaminar epidural space was identified with the loss of resistance technique, under intermittent fluoroscopy, confirmed by an injection of nonionic contrast medium. Entry into the epidural space was made at L5/S1, or one space below the stenosis level. All attempts were made to direct the flow towards the involved segment. Once the needle placement and contrast flow patterns were confirmed, injections were performed with 6 mL of injectate in each group.

Additional Interventions

All patients received the assigned treatments with appropriate assessment and follow-up. Repeat procedures were performed in patients with deterioration of pain relief and/or functional status below 50%. Nonresponsive patients desiring to continue with conservative and medical management were followed without additional epidural injections.

Cointerventions

All patients received a structured therapeutic exercise program along with medical therapy, and continued employment. The majority of the study participants were taking opioids, nonopioid analgesics, and adjuvant analgesics when enrolled (59). No specific treatments, including physical therapy, occupational therapy, or other interventions, were provided to the study participants separately in either group.

Objectives

This study was designed to determine the effectiveness of lumbar interlaminar epidural injections with or without steroids in providing significant improvement in patients with chronic low back and lower extremity pain secondary to central lumbar spinal stenosis and also to assess the differences between the use of local anesthetic alone or local anesthetics with steroids.

Outcomes

Multiple outcome measures were utilized. These included NRS (0 to 10 scale) pain scale, ODI (0 to 50 scale) for functional abilities, employment status, and opioid intake in terms of morphine equivalence. Progress was assessed through follow-up in all patients at 3, 6, 12, 18, and 24 months post treatment. The NRS represents no pain with a 0 and the worst pain imaginable with a 10 (60,61). The ODI was utilized for functional assessment on a scale of 0 to 50. The ODI represents disability as 0% - 20%: minimal disability; 20% - 40%: moderate disability; 40% - 60%: severe disability; 60% - 80%: crippled; 80% - 100%: bed-bound or exaggerating their symptoms (62,63).

The primary outcome measure was significant improvement of at least 50% based on NRS and ODI scores. This is a robust measure compared to previous measures of minimum clinically important difference (MCID) of 20% to 30% (64). Patients experiencing at least 3 weeks of consistent improvement with 2 initial injections were considered as successful and categorized as such. All others were considered as failures.

Opioid intake was determined based on morphine equivalency with conversion into morphine equivalent of opioids consumed (65).

Employment was assessed based on multiple categories of patients. In contrast to previous studies categorizing all participants to be employable in this study, employability was determined based on their work status and desire to be employed. Patients who were unemployed due to pain, or employed but on sick leave, or laid off but actively pursuing employment opportunities, were considered as employable. However, patients who were not employable were those with no desire to work outside the home, including housewives, the retired, or those over the age of 65.

Sample Size

The sample size was based on significant pain relief with consideration of a 0.05, 2-sided significance level, a power of 80%, with an allocation ratio of 1:1. This estimation yielded 18 patients in each group (66). With a 10% attrition/non-compliance rate, it was estimated that 40 patients were required for the study.

Randomization

Of the 120 patients, 60 patients were randomized to each group.

Sequence Generation

Sequence generation was achieved by a computer-generated simple random allocation sequence.

Allocation Concealment

Patients were randomized to one of the 2 groups

by one of the 3 study coordinators. Physician, patient, and all other personnel were blinded to the allocation. The study coordinators also prepared all the drugs.

Implementation

All eligible patients with central spinal stenosis were invited to participate. Those willing to participate were enrolled and assigned to a group by one of the 3 study coordinators.

Blinding/Masking

Blinding or masking was established by multiple means. No one was aware of the group assignment except for the study coordinator. In addition, study patients were mixed with routine treatment patients. Both solutions were clear and unidentifiable with nonparticulate Celestone, until September 2012. However, due to the meningitis issues related to nonparticulate solutions from compounding pharmacies (58), commercial betamethasone was utilized with solutions concealed or masked by one of the study coordinators from October 2012 to June 2013.

Statistical Methods

Data analyses were carried out using the Statistical Package for Social Sciences version 9.01 (SPSS Inc, Chicago,IL). For categorical and continuous data comparison, Chi-square (Fisher test where necessary) and t-test were used respectively. Because the outcome measures of the participants were measured at 6 points in time, the repeated measures analysis of variance were performed with the post hoc analysis. A P value of less than 0.05 was considered significant.

Intent-to-Treat Analysis

An intent-to-treat analysis was performed after sensitivity analysis. The sensitivity analysis was conducted using changes in the numeric pain scale utilizing the last follow-up score, best case scenario, and worst case scenario. Following the sensitivity analysis, if there were no differences, the last follow-up visit was used for intention-to-treat analysis. In those patients without any follow-ups, the initial data was used when no other data were available.

Results

Participant Flow

The participant flow of the 120 patients selected is shown in Fig. 1. The enrollment period lasted from January 2008 through July 2011. Among the 120 patients included, 2 patients died due to unrelated conditions, one patient was lost to follow-up, and one patient moved away in Group I; whereas in Group II, 2 patients were lost to follow-up, 2 patients failed to respond and were withdrawn, and one patient was discharged due to drug abuse at 12 months. At 24 months in Group I, one additional patient was lost to follow-up due to development of a cerebral tumor, one patient underwent surgery which also failed, and one patient stopped procedures due to the lack of a response; whereas, in Group II, one patient was withdrawn and one patient was discharged due to drug abuse.

Baseline Demographic and Clinical Characteristics

Demographic and clinical characteristics are shown in Table 1. There were significant differences noted in gender between Group I and Group II with a larger proportion of female patients than male patients in Group I, and mean weight which was higher in Group I compared to Group II patients.

Table 2 shows severity and levels of stenosis. The majority of patients presented with primary stenosis at L4/5 level with a total of 17 patients with severe stenosis, 30 patients with moderate stenosis, and 39 patients with mild stenosis. The severity was graded based on a radiologic analysis of MRI findings as interpreted by a radiologist not associated with the trial.

Pain and Function Outcomes

Table 3 shows the pain scores and disability index score summaries for 2 years with the proportion of patients with improvement of greater than 50% in each category. Figure 2 shows the proportion of patients with significant pain relief based on NRS and ODI with greater than 50% improvement.

Overall significant improvement was seen in 72% of patients in Group I and 73% of patients in Group II at the end of 24 months; whereas this was 84% and 85% in Groups I and II in successful participants.

Therapeutic Procedural Characteristics

Therapeutic procedural characteristics are shown in Table 4.

Patients receiving at least 3 weeks of relief from the initial 2 epidural procedures were included in the successful category. Any other result was considered as being in the failed category.

Overall 9 patients in Group I and 7 patients in

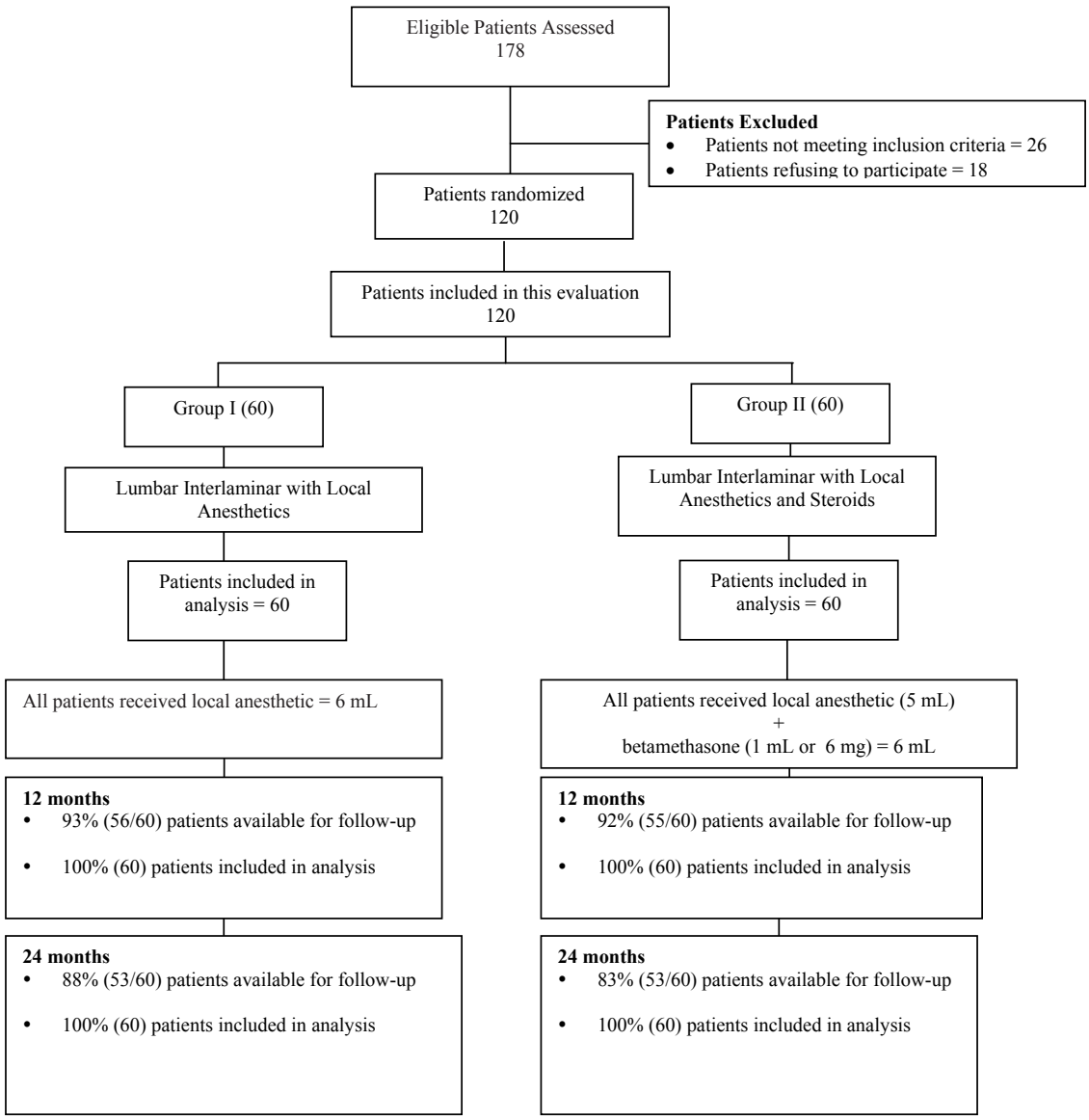

Fig 1. *Schematic presentation of participant flow at 2-year follow-up of lumbar interlaminar epidural injections in lumbar central spinal stenosis.*

Group II were categorized as failed. The average number of injections per year was 3 to 4 after one year in both groups, whereas these were 5 to 6 in both groups at the end of 2 years. Average relief for the first 2 procedures in the successful category was approximately 10 weeks in Group I and 9 weeks in Group II; whereas it was 9 weeks in Group I and 8 weeks in Group II when all patients were combined. Overall relief per procedure at the end of the 2 years was approximately 13 weeks in both groups. At the end of 2 years, total relief achieved was 65.7± 37.3 weeks in Group I and 68.9 ± 37.7 in Group II when all participants were considered; however, in the successful category it was 77.0 ± 27.8 in Group I, and 77.9 ± 30.2 weeks out of 104 weeks in Group II. Overall 84% and 85% of the patients in Group I and II showed significant improvement in the success-

Table 1. *Baseline demographic and clinical characteristics.*

		Group 1 (60)	Group II (60)	*P* value
Gender	Male	32% (19)	55% (33)	0.016
	Female	68% (41)	45% (27)	
Age	Mean ± SD	54.6 ± 13.5	50.0 ± 15.3	0.084
Weight	Mean ± SD	217.4 ± 44.5	170.78 ± 39.8	0.001
Height	Mean ± SD	66.7 ± 3.8	67.2 ± 3.7	0.487
Duration of Pain (months)	Mean ± SD	125 ± 120.3	105 ± 87.7	0.252
Onset of Pain	Gradual	80% (48)	80% (48)	1.000
	Injury	20% (12)	20% (12)	
Back Pain Distribution	Back pain only	12% (7)	17% (10)	0.465
	Back pain worse than leg pain	48% (29)	48% (29)	
	Leg pain worse than back pain	10% (6)	3% (2)	
	Both equal	30% (18)	32% (19)	
Numeric Rating Score	Mean ± SD	8.0 ± 0.7	8.0 ± 1.0	1.000
Oswestry Disability Index	Mean ± SD	31.0 ± 6.3	30.5 ± 8.4	0.676

Table 2. *Lumbar central spinal stenosis: Severity and involved level(s) as classified by radiologist(s) (MRI or CT scan).*

	Group	Severe				Moderate				Mild			
		L2/3	L3/4	L4/5	L5/S1	L2/3	L3/4	L4/5	L5/S1	L2/3	L3/4	L4/5	L5/S1
Primary*	I	0	0	11	1	1	4	15	3	0	5	17	3
	II	0	3	6	0	1	2	15	3	0	2	22	6
	Total	0	3	17	1	2	6	30	6	0	7	39	9
Secondary	I	0	0	0	0	0	5	1	2	0	1	1	3
	II	0	0	0	0	0	0	4	1	0	1	2	3
	Total						5	5	3		2	3	6

*Primary: Indicates worst level of stenosis or same type stenosis at multiple levels in participants with multiple level stenosis and all participants with single level stenosis.

Table 3. *Comparison of Numeric Pain Rating Scale and Oswestry Disability Index score 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	8.0 ± 0.7	8.0 ± 1.0	31.0 ± 6.3	30.5 ± 8.4
3 months	3.7* ± 1.3 (77%)	3.7* ± 1.5 (83%)	15.3* ± 5.3 (78%)	15.2* ± 6.2 (77%)
6 months	3.6* ± 1.5 (75%)	3.8* ± 1.7 (80%)	15.1* ± 5.9 (73%)	14.8* ± 6.4 (78%)
12 months	3.7* ± 1.6 (73%)	3.7* ± 1.8 (77%)	15.0* ± 6.4 (75%)	14.4* ± 6.4 (75%)
18 months	3.7* ± 1.8 (75%)	3.8* ± 1.7 (75%)	15.0* ± 7.2 (78%)	14.4* ± 6.5 (77%)
24 months	3.8* ± 1.8 (72%)	3.6* ± 1.7 (73%)	15.1* ± 7.2 (75%)	13.7* ± 6.4 (75%)
Group Difference	0.841		0.781	
Time Difference	0.001		0.001	
Group by Time Interaction	0.954		0.569	

Lower the value indicates better condition
* significant difference with baseline values within the group (P < 0.001)
(____) illustrates proportion with significant pain relief (≥ 50%) from baseline

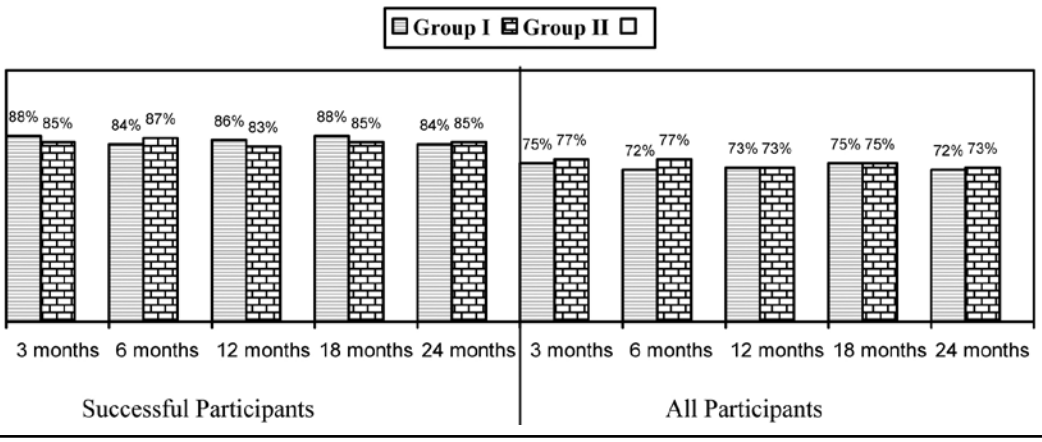

Fig. 2. *Illustration of reduction (at least 50%) in pain and Oswestry Disability Index from baseline.*

Table 4. *Therapeutic procedural characteristics with average relief per procedure and average total relief in weeks over a period of 2 years.*

	Successful Participants		Failed Participants		All Participants	
	Group I (51)	Group II (53)	Group I (9)	Group II (7)	Group I (60)	Group II (60)
At one year						
Average number of injections per one year	3.6 ± 0.9	3.8 ± 1.1	2.0 ± 0.5	1.9 ± 0.5	3.4 ± 1.1	3.6 ± 1.2
Total number of injections in one year	186	203	18	13	204	216
Total relief per one year (weeks)	40.6 ± 11.5	40.2 ± 12.7	1.5 ± 1.4	1.2 ± 1.3	34.7 ± 17.6	35.6 ± 17.4
At 2 years						
Average number of injections per 2 years	5.7 ± 2.3	6.1 ± 2.4	2.0 ± 0.5	1. 9 ± 0.9	5.1 ± 2.5	5.6 ± 2.7
Total number of injections in 2 years	291	322	18	13	309	335
Total relief per 2 years (weeks)	77.0 ± 27.8	77.9 ± 30.2	1.5 ± 1.4	1.2 ± 1.3	65.7 ± 37.3	68.9 ± 37.7
Average relief per procedure						
For initial 2 procedures in weeks	10.1 ± 13.9	8.6 ± 13.6	0.8 ± 1.1	0.7 ± 0.9	8.7 ± 13.2	7.9 ± 13.1
After initial 2 procedures	15.6 ± 12.4	15.5 ± 12.7	1.0	0.2 ± 0.0	15.6 ± 12.4	15.3 ± 12.7
All procedures	13.7 ± 13.2	13.2 ± 13.3	0.8 ± 1.0	0.6 ± 0.8	12.9 ± 13.1	12.8 ± 13.3

Successful subject - At least 3 weeks relief from first 2 injections

ful participant category; whereas, in the category of all participants significant improvement was seen in 72% and 73% of the patients in Groups I and II consecutively.

Employment Characteristics

Employment characteristics are described in Table 5. There were 12 patients eligible for employment at baseline with 9 of them employed in Group I with 12 of 12 employed at the end of one year and 11 of 12 employed at the end of 2 years. In Group II there were 18 patients eligible for employment at baseline, 11 of whom were employed which increased to total employment of 17 out of 18 at 12 months and 24 months.

Opioid Intake

Opioid intake is shown in Table 6. Opioid intake showed significant reductions from baseline to all follow-up periods.

Characteristics of Weight Monitoring

Characteristics of weight monitoring are shown in Table 7. There were no significant changes in weight apart from the baseline differences which carried on to 2 years among the groups or between the groups. A reduction in weight was noted in approximately 6% of the patients in Group I; whereas a reduction was noted in 1.5% of the patients in Group II.

Table 5. *Employment characteristics.*

Employment status	Group I			Group II		
	Baseline	12 months	24 months	Baseline	12 months	24 months
Employed part-time	3	2	1	1	1	1
Employed full-time	6	10	10	10	16	16
Unemployed (due to pain)	3	0	1	7	1	1
Eligible for employment at baseline	12	12	12	18	18	18
Total Employed	9	12	11	11	17	17
Housewife	2	2	2	10	8	8
Disabled	33	32	32	24	24	24
Retired/Over 65	13	13	13	8	8	8
Total Number of Patients	60	60	60	60	60	60

Adverse Events

Of the 644 lumbar interlaminar epidural procedures performed on 120 participants, there were 14 subarachnoid entries, one episode of nerve root irritation, and one episode of pain and swelling at the site of injection. There were no major adverse events noted.

Table 6. *Opioid intake (morphine equivalents in mg).*

Time	Group I (60) Mean ± SD	Group II (60) Mean ± SD
Baseline	60.5 ± 56.6	71.0 ± 92.3
3 months	44.0# ± 40.4	42.8# ± 40.8
6 months	40.2# ± 40.6	40.2# ± 36.2
12 months	39.4# ± 40.9	38.2# ± 30.4
18 months	37.9# ± 38.3	33.4# ± 29.5
24 months	37.9# ± 38.3	33.4# ± 29.5
Group Difference	0.833	
Time Difference	0.091	
Group by Time Interaction	0.970	

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

Table 7. *Characteristics of changes in weight.*

Weight (lbs)	Group I (60) Mean ± SD	Group II (60) Mean ± SD	*P* value
Weight at beginning	217.4 ± 44.6	170.7 ± 39.8	0.001
Weight at one year	215.4 ± 44.2	169.8 ± 39.1	0.001
Change	-2.0 ± 8.3	-0.9 ± 8.9	0.498
Lost weight	47% (28)	42% (25)	0.835
No change	18% (11)	22% (13)	
Gained weight	35% (21)	37% (22)	
Weight at 2 years	211.3 ± 44.0	169.1 ± 38.7	0.001
Change	-6.1 ± 11.9	-1.5 ± 10.8	0.031
Lost weight	57% (34)	52% (31)	0.821
No change	17% (10)	17% (10)	
Gained weight	26% (16)	32% (19)	

Discussion

This randomized, double-blind, active-control trial of local anesthetic with or without steroids in managing central spinal stenosis in 120 patients showed the effectiveness of epidural injections at the end of one year and 2 years. This study, performed in a contemporary interventional pain management setting providing the interventions as medically necessary for patients suffering with persistent, severe, chronic low back and lower extremity pain showed significant improvement with lumbar interlaminar epidural injections with 72% in Group I with local anesthetic only and 73% with local anesthetic and steroids in Group II at the end of 2 years. Overall, the response was superior when patients were separated into successful and failed categories with at least 3 weeks of significant improvement with the first 2 procedures. In the successful category, 84% of patients in Group I and 85% of patients in Group II showed significant improvement at the end of 2 years. The average number of procedures for 2 years was 5 to 6, with average total relief for 2 years of 65.7 ± 37.3 weeks in Group I and 68.9 ± 37.7 weeks in Group II. In contrast, the overall total relief in the successful participant category was 77 ± 27.8 weeks in Group I and 77.9 ± 30.2 weeks in Group II at the end of 2 years. Even though unsuccessful participants showed an extremely low response rate, there were no significant differences between the patients receiving either local anesthetic alone or local anesthetic with steroids. Consequently, the results of this study showed that if the response is poor with the first 2 procedures, future treatments might be represented with a poor or no response.

The results of this assessment are superior to results of an evaluation with caudal epidural injection with a 2 year publication (20). Consequently, based on the cost effectiveness of caudal epidural injections, the results of this trial show that with appropriate patient selection and prudent use of repeat injections, long-term relief can be achieved – albeit modest. While these results are in contrast to other publications (16,28), these publications were based on inappropriately performed studies that reached conclusions not based on the evidence. Thus, the present trial is significant for interventional pain management practices as it is the only pragmatic or practical clinical trial for the lumbar interlaminar approach. Trials with an active-control that measure effectiveness may be considered practical compared to explanatory trials that measure efficacy (67,68). The results of this trial complement the caudal epidural injection study in central spinal stenosis with similar results in a large scale trial with a long-term follow-up of 2 years (20). However, the results of this trial are in contradiction to the trial by Friedly et al [53]. Considering the multiple design flaws and extremely short-term follow-up with inappropriate statistical analysis by Friedly et al (53), the results of this trial appear to be practical in line with practice patterns of interventional pain management in the United States.

As with multiple other studies, the study incorporates both strengths and weaknesses. The study may face criticism with or without appropriate understanding of the design and the results (12). In addition, the study may be criticized for the lack of a placebo group. Design of a placebo group is difficult in the United States. Also, there continues to be misunderstandings of what constitutes true placebo and the role of true placebo in in interventional techniques (69-76). While lack of understanding or inappropriate interpretation of true placebo involves injecting inactive substances into active structures and considering local anesthetics as placebo, a true placebo essentially means injection of an inactive substance into an inactive structure, namely away from nerves and closed spaces. A true placebo design has been shown under fluoroscopy in recent years by 2 groups (77,78). Both of these groups used proper placebo in contrast to a multitude of others who have used impure placebo (79,80). Even though multiple reviews have considered local anesthetics as placebos, the experimental and clinical evidence shows an active response, which may yield to inaccuracies, even with sodium chloride solution, along with local anesthetic injection or other substances (81-83). In addition, epidural saline has been shown to be active and therapeutic (79,80). The numerous interactions with placebo and nocebo effects are misunderstood and inappropriately applied (69-72). It is also inconceivable for a placebo effect to last for 2 years in over 60% of patients, with repeat interventions (18-20,84-91). Other arguments in response to placebo effect include the Hawthorne Effect, as well as natural process. Both of these can be ruled out in this trial as these patients have been suffering with chronic intractable pain and already have undergone multiple interventions. Furthermore, such a culmination of opinions considering local anesthetics and steroid injections as being divergent and local anesthetic as placebo is inaccurate since a wealth of clinical and experimental evidence illustrates similar effects of local anesthetics with or without steroids (18-20,33,84-93).

Furthermore, the results of this trial also show that the effectiveness in central spinal stenosis are similar to those of post surgery syndrome with caudal epidural injections and similar or somewhat inferior results to epidural injections in managing disc herniation and discogenic pain (87-91) utilizing the same protocols.

The mechanism of action of epidural injections in relieving radicular or other low back pain continues to be based on hypothesis. Some of the postulated mechanisms of action of steroids and local anesthetics are based on anti-inflammatory effects (18-20,32,33,84-100). Both local anesthetics and steroids are expected to suppress multiple pathophysiologic mechanisms of chronic pain including noxious peripheral stimulation and excess nociception resulting in the sensitization of the pain pathways at several neuronal levels, and an excess release of neurotransmitters causing a complex central response including hyperalgesia windup (18).

The results of this study once again illustrate that a prudent use of lumbar interlaminar epidural injections in managing pain of central spinal stenosis is reasonable and probably cost effective based on caudal injections.

Conclusion

This study shows that lumbar interlaminar epidural injections, with or without steroids, are an effective modality of treatment in the management of chronic function-limiting low back pain and lower extremity pain secondary to central lumbar spinal stenosis.

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Author Affiliations

Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Associate Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY. Kimberly A. Cash is a Research Coordinator at the Pain Management Center of Paducah, Paducah, KY. Carla D. McManus is a Nursing Administrator at the Pain Management Center of Paducah, Paducah, KY. Kim S. Damron is a Nursing Administrator at the Pain Management Center of Paducah, Paducah, KY. Vidyasagar Pampati is a Statistician at the Pain Management Center of Paducah, Paducah, KY. Dr. Falco is Medical Director of Mid Atlantic Spine & Pain Physicians, Newark, DE; Director, Pain Medicine Fellowship Program, Temple University Hospital, Philadelphia, PA; and Adjunct Associate Professor, Department of PM&R, Temple University Medical School, Philadelphia, PA.

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Conflict of Interest

Dr. Falco is a consultant for St. Jude Medical Inc. and Joimax Inc.

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