

## Randomized Trial

## A Randomized, Double-Blind, Active Control Trial of Fluoroscopic Cervical Interlaminar Epidural Injections in Chronic Pain of Cervical Disc Herniation: Results of a 2-Year Follow-Up

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**Background:** A recent evaluation of the state of U.S. health from 1990 to 2010 placed neck pain as the fourth condition leading to disability, with low back pain being the number one. Multiple treatment modalities have been described in managing neck and upper extremity pain secondary to cervical disc herniation after the failure of conservative management. The treatment modalities for chronic persistent pain of cervical disc herniation include surgery and epidural injections. The growth of interventional techniques in managing chronic spinal pain in recent years has been enormous. Evidence for the efficacy of cervical interlaminar epidural injections, however, continues to be debated, despite positive evidence derived from controlled randomized trials and systematic reviews.

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

**Setting:** A private, specialty referral, interventional pain management practice in the United States.

**Objectives:** To evaluate the effectiveness of epidural injections in managing chronic pain related to cervical disc herniation.

**Methods:** Patients were randomly assigned to one of 2 groups of 60, with a total of 120 patients. Group I patients received cervical epidural injections with lidocaine 0.5% preservative-free, 5 mL, whereas Group II patients received 0.5% preservative-free lidocaine mixed with 1 mL or 6 mg of non-particulate betamethasone.

**Outcome Assessment:** Multiple outcome measures included the numeric rating pain scale (NRS), the Neck Disability Index (NDI), employment status, opioid intake with assessment at 3, 6, 12, 18, and 24 months post treatment.

Significant improvement was described as pain relief with a 50% improvement in functional status.

**Results:** This evaluation showed significant improvement as 50% pain relief and improvement in functional status in 72% of the patients at 2 year follow-up in the local anesthetic group and 68% in those patients receiving local anesthetic and steroid. In the successful group of participants however, significant improvement was seen in 77% in Group I and 80% in Group II.

Overall, the average number of procedures was 5 to 6 in both groups per 2 years. The average total relief for 2 years was 75.9 ± 29.9 weeks in Group I and 72.7 ± 31.1 in Group II, the successful group of participants. Taking into consideration all of the participants, the average total relief for 2 years was 69.6 ± 35 weeks in Group I and 62.1 ± 38.4 weeks in Group II.

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

**Conclusion:** Cervical epidural injections with local anesthetic with or without steroids may offer significant benefit to patients suffering with chronic, persistent pain and disability related to cervical disc herniation.

**Key words:** Chronic neck pain, cervical disc herniation, upper extremity pain, cervical epidural injections, epidural steroids, local anesthetics  
Trial Registration: NCT01071369

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**C**hronic neck pain is common in the general adult population with persistent complaints seen in 22% of women and 16% of men (1,2). Moreover, the impact of chronic neck pain on general health showed 14% of patients reporting Grade II to IV neck pain with high pain intensity with disability (3-10). Furthermore, Grade III and IV pain with disability are seen in 5% of patients (3). In fact, a recent report describing the state of health in the U.S. from 1990 to 2010 showed that neck pain is the fourth condition leading to disability, with low back pain being the number one (11). In addition, Martin et al (12,13), in assessing the effect of chronic spinal pain on the U.S. economy, found that costs were 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. Furthermore, the Institute of Medicine (IOM) report on relieving pain in America (14), based on Gaskin and Richard (15), estimated the total economic cost of pain in the United States in 2010 to range from \$560 to \$635 billion. Of this, with the isolation of moderate and severe pain and eliminating other conditions, the costs appear to be approximately \$100 billion per year. Disability secondary to chronic pain also continues to increase (16).

Structures causing neck and upper extremity pain and headache include cervical intervertebral disc, cervical facet joints, ligaments, fascia, muscles, and nerve root dura, which are capable of transmitting pain (17-19). Cervical radicular pain is pain perceived in the upper extremity, shooting or electric in quality, caused by irritation and/or injury of cervical spinal nerves (19,20). Cervical radicular pain may be caused either by disc herniation or compression due to other ailments in the cervical spine, or chemical irritation (18-24).

Multiple treatment modalities have been described in managing neck and upper extremity pain secondary to cervical disc herniation after the failure of conservative management (25). The common treatment modalities for the chronic persistent pain of cervical disc herniation are related to surgery or epidural injections (17,18,20,26-36). Along with escalating growth of surgical interventions (26,27,32-36), cervical epidural injections also have shown intense growth, though less than in the lumbar spine (29-31). In an assessment of the growth of epidural injections in the fee-for-service Medicare population from 2000 to 2011 (31), it was shown that overall, epidural injections increased 130% per 100,000 Medicare beneficiaries with an annual increase of 7.5%. The increases per 100,000 Medicare

recipients were 123% for cervical/thoracic interlaminar epidural injections and 142% for cervical/thoracic transforaminal epidural injections. The increases were 665% for lumbosacral transforaminal epidural injections (31).

Evidence for the efficacy of cervical interlaminar epidural injections continues to be debated, even though evidence is derived from controlled randomized trials (17,18). Diwan et al (18), in a systematic review, identified 13 studies, utilizing 4 randomized trials assessing cervical disc herniation (37-41) meeting inclusion criteria for methodological quality assessment. Based on this review, they concluded that for cervical disc herniation, the evidence is good for cervical epidural with local anesthetic and steroids; whereas, it is fair with local anesthetic only. Among all the studies included in the evidence assessment for disc herniation, the study by Manchikanti et al (37,38) included 120 patients with an active control design and showed significant improvement with pain and function of 50% or more in 72% of the patients who received local anesthetic only and 68% who received local anesthetic and steroids. Furthermore, in the successful group of participants, significant improvement was illustrated in 77% of the local anesthetic group and 82% of the local anesthetic with steroid group.

The current study was undertaken to evaluate the role of cervical interlaminar epidural injections with local anesthetic or with local anesthetic and steroids in patients with disc herniation suffering with chronic function-limiting neck and upper extremity pain. The study was designed to be a randomized double-blind, active-control with 120 patients with 60 patients in each group. The preliminary report and one year follow-up of this study were published (37,38).

## **METHODS**

The design of the study was a randomized, double-blind, active control trial. The study was conducted based on the Consolidated Standards of Reporting Trials (CONSORT) guidelines (42,43). The study was performed in an interventional pain management practice, tertiary referral center in the United States. The protocol was approved by the Institutional Review Board (IRB) and was registered with the U.S. Clinical Trial Registry with an assigned number of (NCT01071369). This trial was conducted with internal resources of the practice without external funding.

## **Participants**

All study participants were derived from new

patients presenting to the interventional pain management practice. All the patients were provided with IRB approved protocol, as well as informed consent, which described in detail various aspects of the trial and withdrawal process.

### **Interventions**

Of the 120 patients included in the trial, 60 were assigned to each group. Thus, Group I patients received cervical interlaminar epidural injections of local anesthetic only with lidocaine 0.5%, 5 mL, preservative-free. In contrast, Group II patients received cervical interlaminar epidural injections with 0.5% lidocaine, 4 mL, mixed with 1 mL or 6 mg of non-particulate betamethasone with a total volume of 5 mL of injectate.

### **Pre-Enrollment Evaluation**

Prior to the enrollment in the trial, baseline demographic data were collected. This included demographics, medical and surgical history with co-existing disease(s), radiological investigations including magnetic resonance imaging and/or computed tomography, nerve conduction studies, physical assessment results, Numeric Rating Scale (NRS) pain scores, and functional status assessment scores utilizing Neck Disability Index (NDI). Additional information included work status, opioid intake, other drug therapy, and the details of conservative management.

### **Inclusion Criteria**

Only patients with cervical disc herniation with or without radiculitis were included. Patients of at least 18 years of age with chronic, function-limiting neck and upper extremity pain of at least 6 months duration were included. All patients must have been competent to understand the study protocol, provide voluntary informed consent, and participate in outcome measures. Additional criteria were that all patients have utilized conservative treatment modalities, including, but not limited to, physical therapy, a structured exercise program, and drug therapy.

However, any patient with cervical spine surgery, radiculitis secondary to spinal stenosis, discogenic pain without disc herniation, uncontrollable or unstable opioid use, uncontrolled psychiatric disorders, and uncontrolled medical illness were excluded. Additional exclusion criteria included any condition that could interfere with the interpretation of the outcome assessment, pregnancy and lactation or a history of adverse reactions to local anesthetic or steroids.

### **Description of Interventions**

Cervical interlaminar epidural injections were performed by one physician in an ambulatory surgery center, in a sterile operating room, under fluoroscopy. All patients were positioned in the prone position, appropriate monitors were applied, and intravenous access along with sedation with midazolam and fentanyl were utilized whenever indicated.

The epidural space was entered with the loss of resistance technique under fluoroscopic visualization between C7 and T1 to C5 and C6 with confirmation by injection of non-ionic contrast medium. After confirmation of the location of the needle in the epidural space with appropriate contrast spread, solutions were injected into the epidural space with a total of 5 mL mixture.

Repeat cervical epidural injections were only provided based on the response to prior cervical epidural injections. The response was assessed by improvement in physical and functional status, with repeat procedures provided when increased levels of pain were reported with deterioration of functional status and pain relief to below 50%.

### **Co-interventions**

All patients received continued drug therapy with opioids or nonopioid analgesics, therapeutic exercise program, normal activities, and work. The total drug therapy was reduced in a majority of patients. In addition, there was no specific physical therapy, occupational therapy, or other interventions to any of the patients.

### **Objectives**

This assessment was designed to evaluate the effectiveness of cervical interlaminar epidural injections performed under fluoroscopy utilizing local anesthetic with or without steroids in managing chronic recalcitrant neck and upper extremity pain secondary to disc herniation.

### **Outcomes**

Multiple outcome measures were utilized. The primary outcome measure was combined improvement in pain scores and functional status improvement. Significant improvement was defined as at least 50% pain relief associated with at least 50% improvement in functional status as measured by NRS and NDI. This is a robust measure of improvement when compared to previous parameters of minimum clinically important

difference (MCID) (44-48). In addition, the NRS and NDI have been shown to be valid and reliable in patients with mechanical neck pain (49,50).

Opioid intake was measured in conversion units for morphine equivalency (51). The changes in intake were assessed based on these criteria in terms of morphine equivalence based on the dosage, frequency, and schedule of the drug.

Employment was also measured in both groups. Employment was based on patients who were employable and those who were not employable. Employable patients were selected based on their unemployment and employment status either on a part-time or a full-time basis. However, patients who chose not to work, were retired, or were homemakers without the necessity or desire to work outside the home, but not due to pain, were considered as not employable. Consequently, these were not included in the employment pool.

### **Sample Size**

The sample size was calculated based on significant pain relief. Consequently, a 0.05 two-sided significance level, a power of 80%, and an allocation ratio of 1:1, was utilized, yielding an estimated 55 patients in each group (52). Subsequently while allowing for a 10% attrition or non-compliance rate, it was estimated that 60 patients in each group were required.

### **Randomization**

Of the 120 patients, 60 patients were randomly assigned into Group I, whereas another 60 were assigned into Group II.

### **Sequence Generation**

A simple randomization formula was utilized with a computer-generated random allocation sequence.

### **Allocation Concealment**

The patients were randomized into 2 groups by one of the 3 trial coordinators. The drugs were appropriately prepared as to mask any identification of them.

### **Blinding (Masking)**

Various measures were undertaken to secure appropriate blinding and masking. The group assignment was blinded to all involved, including the physician and the patients. Furthermore, both solutions were clear, not allowing identification of the group assignment. As an extra measure, all study patients were mixed with the other patients receiving routine treatments. Neither

the physician performing the procedure nor the patient receiving the procedure were informed of group assignment or the nature of the study participation.

### **Statistical Methods**

Data analyses were carried out using SPSS version 9.01 (SPSS Inc, Chicago, IL). For categorical and continuous data comparison, Chi-squared statistic, Fisher's exact test, one-way analysis of variance, Student's t-test, and paired t-test were used. Because the outcome measures of the participants were measured at 6 time points, repeated measures analysis of variance were performed with post hoc analysis. A P value of less than 0.05 was considered significant.

A statistical significance was considered as a P value of 0.05.

### **Intent-to-Treat-Analysis**

An intent-to-treat analysis was performed utilizing either the last follow-up data or initial data for the patients withdrawn. In addition, sensitivity analysis utilizing best case, worst case, and last follow-up data was performed.

## **RESULTS**

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### **Patient Flow**

Figure 1 illustrates the patient flow. The recruitment period started in August 2007 and ended in June 2010.

### **Demographic Data**

Baseline demographic and clinical characteristics for Group I and II are illustrated in Table 1. While there were no significant differences in the majority of the parameters, Group I patients weighed significantly more than Group II patients.

### **Pain Relief and Functional Assessment**

Pain relief scores and functional assessment results are shown in Table 2.

The proportion of patients with a significant reduction in the NRS and NDI with greater than 50% reduction from baseline is illustrated in Figure 2. Successful patients, defined as those with the initial 2 procedures had at least 3 weeks of relief showed better results compared to all patients at 24 months, with an improvement of 72% in Group I and 68% in Group II for all patients compared to 77% and 80% in the successful groups.

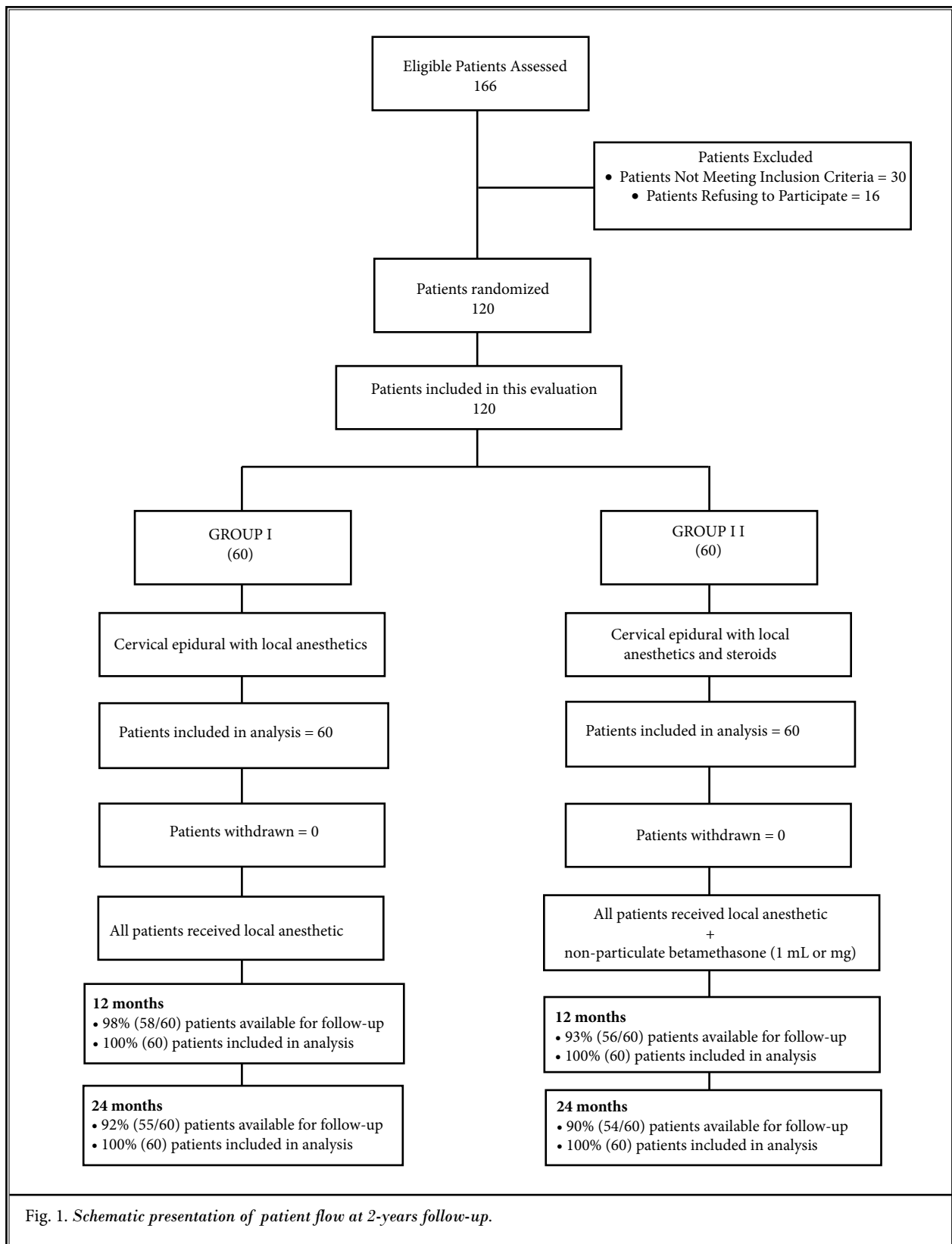


Fig. 1. Schematic presentation of patient flow at 2-years follow-up.

Table 1. *Baseline demographic characteristics.*

		<b>Group I (60)</b>	<b>Group II (60)</b>	<b>P value</b>
Gender	Male	47% (28)	42% (25)	0.581
	Female	53% (32)	58% (35)	
Age	Mean ± SD	46.2 ± 10.3	45.6 ± 10.4	0.738
Weight	Mean ± SD	208.9 ± 53.3	168.1 ± 35.2	0.000
Height	Mean ± SD	67.3 ± 4.4	66.3 ± 4.0	0.199
Duration of Pain (months)	Mean ± SD	118.3 ± 98.6	91.9 ± 94.5	0.137
Onset of the Pain	Gradual	53% (32)	52% (31)	0.855
	Injury	47% (28)	48% (29)	
Neck Pain Distribution	Neck pain only	15% (9)	17% (10)	0.975
	Neck pain worse than upper extremity	57% (34)	55% (33)	
	Upper extremity worse than neck pain	8% (5)	7% (4)	
	Both equal	20% (12)	21% (13)	
Disc Herniation Levels (at multiple levels)	C3/4	13% (8)	13% (8)	0.550
	C4/5	30% (18)	20% (12)	
	C5/6	50% (30)	60% (36)	
	C6/7	40% (24)	47% (28)	
	C7/T1	10% (6)	12% (7)	
Numeric Rating Score	Mean ± SD	7.9 ± 1.0	7.9 ± 0.9	1.000
Neck Disability Index	Mean ± SD	29.6 ± 5.3	29.2 ± 6.1	0.678

Table 2. *Comparison of Numeric Rating Scale for pain and Neck Disability Index score summaries.*

Time Points	Numeric Pain Rating Score Mean ± SD		Neck Disability Index Mean ± SD	
	Group I (N=60)	Group II (N=60)	Group I (N=60)	Group II (N=60)
Baseline	7.9 ± 1.0	7.9 ± 0.9	29.6 ± 5.3	29.2 ± 6.1
3 months	3.7* ± 1.4 (85%)	3.8* ± 1.4 (75%)	14.7* ± 5.5 (85%)	15.6* ± 6.3 (70%)
6 months	3.5* ± 1.4 (83%)	3.9* ± 1.5 (73%)	13.8* ± 5.4 (83%)	15.3* ± 6.9 (73%)
12 months	3.7* ± 1.5 (72%)	3.9* ± 1.5 (72%)	13.8* ± 5.7 (75%)	15.1* ± 7.0 (68%)
18 months	3.6* ± 1.6 (75%)	3.6* ± 1.5 (72%)	13.7* ± 5.5 (77%)	14.7* ± 6.8 (72%)
24 months	3.8* ± 1.6 (72%)	3.8* ± 1.7 (68%)	13.7* ± 5.7 (73%)	14.3* ± 6.9 (70%)
Group Difference	0.645		0.466	
Baseline vs follow-up points	0.001		0.001	
Group by Time Interaction#	0.350		0.416	

Percentages in parenthesis illustrates proportion with significant pain relief (≥ 50%) from baseline

\* indicates significant difference with baseline values (P < 0.01) within the group

# Group by Time Interaction - There was no significant difference between groups at 3 months, 6 months, 12 months, 18 months, and 24 months

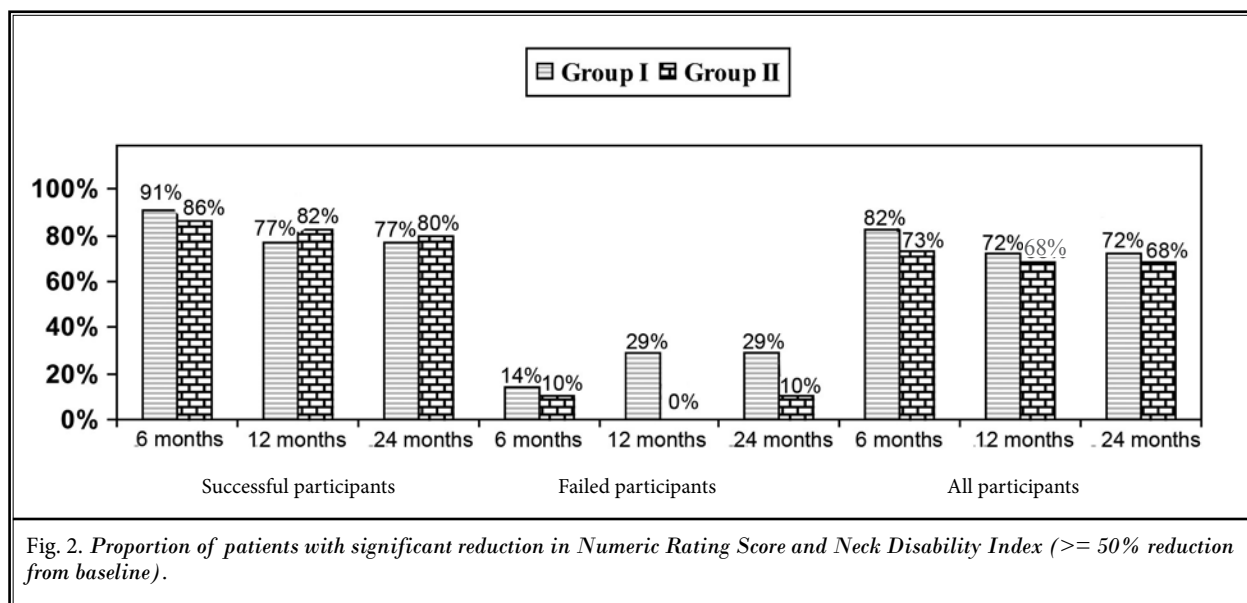


Fig. 2. Proportion of patients with significant reduction in Numeric Rating Score and Neck Disability Index (>= 50% reduction from baseline).

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 Participants		Failed Participants		All Participants	
	Group I (53)	Group II (50)	Group I (7)	Group II (10)	Group I (60)	Group II (60)
Average number of procedures for one year	3.7 ± 1.1	3.7 ± 1.2	2.7 ± 1.5	2.0 ± 1.2	3.6 ± 1.2	3.4 ± 1.3
Average number of procedures for 2 years	5.8 ± 2.5	5.9 ± 2.4	3.7 ± 3.1	2.4 ± 2.4	5.6 ± 2.7	5.3 ± 2.7
Average relief per procedure for initial 2 procedures in weeks	9.8# ± 7.9	7.8 ± 8.1	0.8 ± 1.1	0.5 ± 0.6	8.8 ± 8.0	6.8 ± 7.9
Average relief per procedure after initial 2 procedures	13.5 ± 6.5	12.5 ± 3.4	7.7 ± 5.5	8.8 ± 5.3	13.1 ± 6.6	12.3 ± 3.5
Average relief per procedure	13.2 ± 11.0	12.5 ± 10.7	5.9 ± 5.9	3.9 ± 5.4	12.6 ± 10.9	11.8 ± 10.6
Average total relief for one year (weeks)	41.4 ± 12.7	36.3 ± 14.6	9.0 ± 13.4	4.2 ± 10.9	37.6# ± 16.4	31.0 ± 18.5
Average total relief for 2 years (weeks)	75.9 ± 29.9	72.7 ± 31.1	21.9 ± 35.6	9.2 ± 26.6	69.6 ± 35.0	62.1 ± 38.4

# indicates significant difference with Group II ( $P < 0.05$ )

### Therapeutic Procedural Characteristics

Epidural entry was performed between C7 and T1 in 28% of patients, between C6 and C7 in 60% of patients, and between C5 and C6 in 12% of patients as shown in Table 1. Therapeutic procedural characteristics are illustrated in Table 3.

Average relief per 2 years showed no significant differences: 69.6 ± 35.0 weeks in Group I and 62.1 ± 38.4 weeks in Group II. The total number of injections per 2 years was 5.6 ± 2.7 in Group I and 5.3 ± 2.7 in Group II. However, when patients were separated into successful and failed groups, the total number of injections per 2

years was 5.8 ± 2.5 in Group I and 5.9 ± 2.4 in Group II in the successful groups, and 3.7 ± 3.1 for Group I and 2.4 ± 2.4 for Group II in the failed groups. Total relief for 2 years of 75.9 weeks was obtained in the successful group in Group I; in Group II it was 72.7 weeks. In contrast, the relief was 21.9 weeks in Group I and 9.2 weeks in Group II for the failed groups.

The initial therapy was considered to be successful if a patient obtained consistent relief with 2 initial injections lasting at least 3 weeks. All others were considered failures.

Table 4. *Employment characteristics.*

Employment status	Group I			Group II		
	Baseline	12 months	24 months	Baseline	12 months	24 months
Employed part-time	2	2	3	2	3	2
Employed full-time	9	9	9	13	14	17
Unemployed (due to pain)	0	0	0	2	1	0
Not working	2	2	2	5	4	4
Eligible for employment at Baseline	13	13	13	22	22	22
<b>Total Employed</b>	11	11	12	15	17	19
Housewife	3	3	3	1	1	1
Disabled	37	37	36	33	33	32
Retired	7	7	7	4	4	4
<b>Total Number of Patients</b>	60	60	60	60	60	60

Table 5. *Opioid intake (morphine equivalence mg).*

Opioid intake (Morphine Equivalence mg)	Group I (60)	Group II (60)
	Mean $\pm$ SD	Mean $\pm$ SD
Baseline	57.0 $\pm$ 46.1	53.8 $\pm$ 36.1
3 months	34.4* $\pm$ 21.7	35.2* $\pm$ 16.3
6 months	33.0* $\pm$ 22.3	35.5* $\pm$ 16.3
12 months	34.7* $\pm$ 23.5	35.5* $\pm$ 16.3
18 months	35.8* $\pm$ 24.9	32.0* $\pm$ 18.9
24 months	35.8* $\pm$ 24.9	31.3* $\pm$ 19.1
Group difference	0.614	
Baseline vs follow-up points	0.001	
Group by time interaction#	0.623	

\* indicates significant difference with baseline values ( $P < 0.01$ )

# Group by Time Interaction - There was no significant difference between groups at 3, 6, 12, 18 and 24 months

Table 6. *Characteristics of changes in weight.*

Weight (lbs)	Group I (60)	Group II (60)	P value
	Mean $\pm$ SD	Mean $\pm$ SD	
Weight at Beginning	208.9 $\pm$ 53.3	168.1 $\pm$ 35.2	0.000
<b>Weight at one year</b>	205.4 $\pm$ 53.6	166.9 $\pm$ 32.7	0.000
Change	-3.5 $\pm$ 9.9	-1.1 $\pm$ 7.4	0.139
Lost weight	57% (34)	43% (26)	0.311
No change	20% (13)	25% (15)	
Gained weight	22% (13)	32% (19)	
<b>Weight at 2 years</b>	205.5 $\pm$ 53.9	167.7 $\pm$ 33.26	0.000
Change	-3.4 $\pm$ 11.8	-0.35 $\pm$ 10.89	0.000
Lost weight	53% (32)	35% (21)	0.123
No change	15% (9)	23% (25)	
Gained weight	32% (19)	42% (25)	

## Employment Characteristics

Table 4 shows the employment characteristics in both groups.

## Opioid Intake

The results of opioid intake and changes in opioid intake are shown in Table 5.

## Changes in Weight

Table 6 shows changes in weight, either with gain or loss.

## Adverse Events

Of the 654 procedures performed, there were 2 subarachnoid punctures, 4 intravascular penetrations, 5 nerve root irritations, and one report of soreness

lasting one week. No postoperative headache was reported after subarachnoid punctures.

## DISCUSSION

The present randomized, double-blind, controlled trial of 120 patients with cervical disc herniation showed significant improvement with local anesthetics with or without steroids performed under fluoroscopic guidance. In this active control design 72% of patients in the local anesthetic group and 68% of patients in the local anesthetic with steroids group showed significant improvement with at least 50% improvement in pain and disability at 2-year follow-up. Significant improvement utilized here is a robust outcome measure compared to previous measures of 20% or 30% improvement in one or both parameters (44-46). In addition, in selected



patients, defined as successful participants, with those responding to the first 2 initial procedures with at least 3 weeks of improvement, significant improvement was seen in 77% in Group I and 88% in Group II at 2-year follow-up. Thus, the long-term follow-up of a large proportion of patients administered with cervical interlaminar epidural injections under fluoroscopy in a contemporary interventional pain management setting confirms that the treatment of cervical disc herniation and radiculitis shows a significant clinical effect. This study also showed overall average procedures per 2 years of 5.6 in Group I and 5.3 in Group II, with an average total relief per 2 years of 69.6 weeks for Group I patients and 62.1 weeks for Group II patients from a total of 104 weeks. The average total relief was higher in the successful group compared to overall patients. In addition, opioid intake was significantly reduced in both groups from the baseline.

The common causes of radicular pain and radiculopathy are disc protrusion, cervical spondylosis, or cervical spinal stenosis. Other causes include facet joint pathology, vertebral body pathology, meningeal pathology, and pathology from the involvement of blood vessels, nerve sheaths, and nerves (17,19,20,22). Multiple mechanisms other than mechanical compressions have been described which included unique properties of spinal nerves and inflammatory mechanisms (17,19,22-24,53,54). Furthermore, herniated cervical intervertebral discs have been shown to produce multiple potential irritants of spinal nerves causing inflammation (20,22,24,53,54). Even though a large number of treatments have been described in managing the pain of cervical disc herniation, once the disc and resultant pain becomes recalcitrant and long lasting resulting in long-term disability, apart from surgical interventions, interventional pain management is the choice of treatment (17).

The primary goals of surgical interventions are to relieve radiating arm pain in the case of radiculopathy and to prevent progression of neurological deficit in case of myelopathy (27). Cervical epidural injections have been used to treat radicular pain from herniated discs, spinal stenosis, chronic pain secondary to post cervical surgery syndrome, and chronic neck pain of discogenic origin without disc herniation (17,18,37-41,55-63).

Epidural injections in the cervical spine are performed either by the interlaminar or transforaminal routes; however, cervical transforaminal epidural injections are associated with high risk and are subject to intense debate (64-69). However, the interlaminar

epidural injections are also associated with significant risk, though substantially less than that associated with transforaminal epidural injections (70-75). Despite these complications, cervical transforaminal epidural injections have increased 142% from 2000 to 2011 per 100,000 Medicare fee-for-service population (31). In contrast, cervical interlaminar epidural injections increased 123% over the same period (31); however, these increases are significantly less than cervical facet joint interventions, which showed increases of 359% for cervical facet joint nerve blocks and 836% for neurolytic procedures (76). Consequently, all these increases are exponential and uncontrollable compared to lumbar interlaminar epidural injections which have shown a 25% increase over the same period (31). The majority of the literature describes cervical interlaminar epidural injections performed without fluoroscopy. In fact, surveys conducted in the past in reference to the technical aspects of epidural steroid injections showed only 39% of interlaminar epidural injections being performed under fluoroscopy in academic settings compared to 73% in private practice settings (77). Other studies have shown a significant proportion of procedures without entry into the epidural space without fluoroscopy (78). The major risk of cervical interlaminar epidural injection is the narrow epidural space leading to a higher incidence of discontinuity in the ligamentum flavum resulting in a higher rate of dural punctures (71,79,80).

The results of this randomized trial are similar to the previous assessments as shown by Diwan et al (18) based on the preliminary assessment of this trial: There was good evidence in managing cervical disc herniation. The same was echoed in the comprehensive evidence-based spinal interventional techniques guidelines (17); however, results may not correlate with non-fluoroscopically performed cervical interlaminar epidural injections. There is no study with a large population of patients of 120, as in this study with 60 patients in each group with appropriate follow-up of clinical parameters for 2 years. Essentially the multiple studies in the past have been criticized for their design and inability to confirm the location as the majority of them were performed without fluoroscopy. Systematic reviews also have been criticized for their methodology by evaluating the studies inappropriately, reaching inaccurate conclusions (81,82).

Even though epidural injections are extensively used in managing various types of spinal pain, the underlying mechanism of action of epidurally administered local anesthetics and steroids continues to be

unclear. It has been hypothesized that the effects of neural blockade are dependent on various mechanisms for both local anesthetics and steroids, including anti-inflammatory properties (83-87). The wide array of literature assessing the clinical and experimental nature of these drugs indicates that local anesthetic injections may provide relief similar to corticosteroids (88-93).

The strengths of this trial include its comparative evaluation which has become pivotal in modern evidence-based medicine (94-96). This study provided insight into not only the effectiveness of local anesthetic with or without steroids, but also successful and failed groups based on the first 2 procedures. The patients in the successful group, those who had good pain relief with first and second procedures, constituting over 80% of the enrolled patients, showed average relief from 72.7 to 75.6 weeks out of 104 weeks. In contrast, in the failed group, the average relief per procedure was 9.2 to 21.9 weeks, with overall relief of 62.1 to 69.6 weeks over a period of 2 years. Further, this study also revealed that there were no significant differences noted whether a steroid was utilized or not in the proportion of failed patients as well as the duration of relief. The same results carried on for all the patients over 2 year period. This is in contrast to lumbar disc herniation, which demonstrated a superiority of improvement in the steroid group with lumbar disc herniation both with caudal and lumbar interlaminar approaches at least in short term (97,98). Further, in contemporary interventional pain management the procedures were repeated when the relief started deteriorating below 50% as per published guidelines (17,18). Thus, this study embodies the practical nature of interventional pain management with an active control group instead of placebo group measuring the effectiveness and clinical importance which provides meaningful outcomes.

Nevertheless, limitations do include the lack of a placebo group. Having a placebo group designed with appropriate inclusion (99,100) of injection of a placebo

solution into a nonactive structure has been continuously debated (17,18,81,82,100-106). Placebo interventions have been misinterpreted based on the solution injected and the location of the injection, with some even interpreting local anesthetic injection as placebo, not realizing the inactive substances injected into active structures invariably result in a multitude of effects, with the majority of them being therapeutic (82,101-109). The effects of placebo, nocebo, Hawthorne effect, natural course of the disease, which is not applicable in these chronic patients, and regression to the mean have been extensively discussed in reference to placebo, nocebo, and pure, impure, and fake placebo's (107-109). The only appropriate placebo designs reported in interventional pain management were those of Ghahreman et al (104) and Gerdesmeyer et al (110). These trials showed when proper placebo design is achieved, with injection of an inactive solution into inactive structure, it is not only considered to be a true placebo, but the results are striking in the treatment groups.

## **CONCLUSION**

Fluoroscopically guided cervical interlaminar epidural injections of local anesthetic with or without steroids for chronic neck and upper extremity pain secondary to disc herniation and radiculitis illustrated effectiveness in 72% of patients in the local anesthetic group and 68% in the steroid group, with improvement in pain and functional status in the successful groups, requiring an average of 5.5 procedures over a 2-year period.

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