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Randomized Trial

Cervical Epidural Injections in Chronic Discogenic Neck Pain Without Disc Herniation or Radiculitis: Preliminary Results of a Randomized, Double-Blind, Controlled Trial

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Background: Chronic neck pain is a common problem in the adult population with a typical 12-month prevalence of 30% to 50%. However, there is a lack of consensus regarding the causes and treatments of chronic neck pain.

Despite limited evidence, cervical epidural injections are one of the commonly performed non-surgical interventions in the management of chronic neck pain.

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

Setting: An interventional pain management practice, a specialty referral center, a private practice setting in the United States.

Objectives: To evaluate the effectiveness of cervical interlaminar epidural injections with local anesthetic with or without steroids in the management of chronic neck pain with or without upper extremity pain in patients without disc herniation or radiculitis or facet joint pain.

Methods: Patients without disc herniation or radiculitis and negative for facet joint pain by means of controlled diagnostic medial branch blocks were randomly assigned to one of 2 groups: injection of local anesthetic only or local anesthetic mixed with non-particulate betamethasone. Seventy patients were included in this analysis. Randomization was performed by computer-generated random allocation sequence by simple randomization.

Outcomes Assessment: Multiple outcome measures were utilized including the Numeric Rating Scale (NRS), the Neck Disability Index (NDI), employment status, and opioid intake with assessment at 3, 6, and 12 months post-treatment.

Significant pain relief or functional status was defined as a 50% or more reduction.

Results: Significant pain relief (≥ 50%) was demonstrated in 80% of patients in both groups and functional status improvement (> 50%) in 69% of Group I and 80% of Group II. The overall average procedures per year were 3.9 ± 1.01 in Group I and 3.9 ± 0.8 in Group II with an average total relief per year of 40.3 ± 14.1 weeks in Group I and 42.1 ± 9.9 weeks in Group II over a period of 52 weeks in the successful group.

Limitations: The results of this study are limited by the lack of a placebo group and that it is a preliminary report of 70 patients, with 35 patients in each group.

Conclusion: Cervical interlaminar epidural injections with local anesthetic with or without steroids may be effective in patients with chronic function-limiting discogenic.

Key words: Chronic neck pain, cervical disc herniation, cervical discogenic pain, cervical epidural injections, epidural steroids, local anesthetics

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Chronic recurrent neck pain is a common problem in the adult population with a typical 12-month prevalence of 30% to 50%, associated with high pain intensity and disability in 14% of the adult general population (1-6). However, there is a lack of consensus regarding the causes and treatments of chronic neck pain. The literature shows that cervical disc herniation and radiculopathy, cervical facet joint pain, and cervical discogenic pain are the common causes (7-11).

Pain emanating from a degenerative disc has been classified into 2 distinct types: a radicular pain secondary to stenosis and/or nerve root irritation and predominantly axial pain secondary to internal disc disruption (12-14). Thus, apart from disc herniation, radiculitis, and zygapophysial joint pain, discogenic pain is one of the most common causes of chronic neck, head, and upper extremity pain.

Epidural steroid injections are one of the most common interventions in the non-surgical management of disc herniation and radiculitis (1,15-24). However, cervical epidural injections are also commonly used to treat chronic neck pain secondary to spinal stenosis, post-cervical surgery syndrome, and chronic pain of discogenic origin (1,15-24).

The evidence for cervical interlaminar epidural injections has been a subject of debate and at best has only moderate success even in managing cervical radiculopathy. Benyamin et al (1) in a systematic review of cervical interlaminar epidural injections determined that the evidence was moderate in managing chronic neck and upper extremity pain. However, the evidence has been questioned and continues to be controversial similar to lumbar epidural injections due to the design of the study (fluoroscopic versus non-fluoroscopic), study size, outcome parameters, duration of follow-up; and bias exerted in review along with inappropriate methodology leading to inappropriate conclusions (1,22-33).

Benyamin et al (1) included 3 studies meeting inclusion criteria (34-36); however, none of them were performed under fluoroscopic visualization. The underlying mechanism of epidurally administered local anesthetic and steroids is not clear. While it is believed that the effects of a neural blockade are dependent on the anti-inflammatory properties of corticosteroids (37-44), the evidence also indicates that local anesthetics may be equally effective as steroids in managing spinal pain with or without disc herniation, secondary to post laminectomy syndrome, and of facet joint origin (33,45-60).

This study was undertaken to evaluate the role of cervical interlaminar epidural injections in patients with chronic, function-limiting, neck pain with or without upper extremity pain secondary to discogenic pain without disc herniation, radiculitis, or facet joint pain with local anesthetic with or without steroids. The study was designed to evaluate 120 patients. This preliminary report includes 70 patients completing one-year follow-up.

Methods

The study was conducted in an interventional pain management practice, a specialty referral center, in a private practice setting in the United States. The study was performed based on Consolidated Standards of Reporting Trials (CONSORT) guidelines (26,27,61,62). The study protocol was approved by the Institutional Review Board (IRB) and registered on the U.S. Clinical Trial Registry with an assigned number of NCT01071369.

Participants

Patients were recruited from new patients presenting for interventional pain management. They were assigned to one of the 2 groups with Group I patients receiving cervical interlaminar epidural injections with injection of local anesthetic (lidocaine 0.5%, 5 mL), whereas 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 for a total of 5 mL of injectate.

Interventions

All patients were provided with the IRB-approved protocol and the informed consent which described in detail all aspects of the study and withdrawal process.

Pre-Enrollment Evaluation

Controlled comparative local anesthetic blocks were performed during a pre-enrollment evaluation to exclude facet joint pain. Patient demographic data, medical and surgical history with co-existing disease(s), radiologic investigations, physical examination, pain rating scores using the Numeric Rating Scale (NRS), work status, opioid intake, and functional status assessment by Neck Disability Index (NDI) were also gathered.

Inclusion and Exclusion Criteria

Inclusion criteria used were negative diagnosis of cervical facet joint pain by means of controlled, comparative local anesthetic blocks and absence of cervical

disc herniation or radiculitis; at least 18 years of age; history of chronic function-limiting neck and upper extremity pain of at least 6 months duration; and patients who were competent to understand the study protocol and provide voluntary, written informed consent and participate in outcome measurements.

Exclusion criteria were cervical disc herniation, radiculitis secondary to spinal stenosis without disc herniation, uncontrollable or unstable opioid use, uncontrolled psychiatric disorders, uncontrolled medical illness either acute or chronic, any conditions that could interfere with the interpretation of the outcome assessments, pregnant or lactating women, and patients with a history or potential for adverse reaction(s) to local anesthetics or steroid.

Description of Interventions

Controlled comparative local anesthetic cervical facet joint nerve blocks were performed on all patients. First, diagnostic facet joint nerve blocks were conducted with 0.5 mL of 1% lidocaine then, on separate occasions, blockade of facet joint nerves was conducted with a 0.25% bupivacaine (63,64). A response was considered negative if pain relief lasted less than 2 hours following the lidocaine injection and lasted less than 3 hours or less than the duration of relief with lidocaine when bupivacaine was used.

All cervical interlaminar epidural procedures were performed by one physician in an ambulatory surgery setting, in a sterile operating room, under fluoroscopy, with patients in the prone position, under appropriate monitoring with intravenous access and sedation with midazolam and fentanyl. Access to the epidural space was obtained under sterile conditions with loss of resistance techniques under fluoroscopic visualization, entering the epidural space between C7 and T1 to C5 and C6 with confirmation by injection of non-ionic contrast. Following this, injection of 5 mL of lidocaine hydrochloride 0.5% preservative free, or 4 mL of lidocaine preservative free mixed with 6 mg of non-particulate betamethasone was carried out.

Additional Interventions

All patients underwent the treatments as assigned. A patient was unblinded on request or if an emergency situation existed. If a patient required additional cervical epidural injections, these were provided based on the patient's response, either after unblinding or without unblinding. Patients who were non-responsive and continued with conservative management were followed without further epidural injections with medical management, unless they requested unblinding.

Repeat cervical epidural injections were provided based on the response to prior cervical epidural injections evaluated by improvement in physical and functional status. Further, repeat cervical epidural injections were performed only when increased levels of pain were reported with deteriorating relief below 50%.

Co-Interventions

Most patients were receiving opioids and non-opioid analgesics, adjuvant analgesics, and some were involved in a therapeutic exercise program. If patients were improving significantly and the medical necessity for these drugs was lacking, medications were stopped or dosages were decreased. In addition, dosages were also increased, based on medical necessity. All patients continued previously directed exercise programs, as well as their work. Thus, in this study, there was no specific physical therapy, occupational therapy, bracing, or other interventions offered other than the study intervention.

Objectives

The study was designed to evaluate the effectiveness of cervical epidural injections with or without steroids in managing chronic neck and upper extremity pain secondary to discogenic pain without disc herniation, radiculitis, or facet join pain in providing effective pain relief.

Outcomes

Outcomes measured included NRS, NDI, work status, and opioid intake in terms of morphine equivalents, assessed at baseline, 3, 6, and 12 months post-treatment.

Significant improvement was defined as at least 50% pain relief associated with 50% improvement in NDI. The NDI has been shown to be valid and reliable in patients with mechanical neck pain (65-67).

Opioid intake was evaluated based on the dosage frequency and schedule of the drug, with conversion to morphine equivalents (68).

Patients unemployed or employed on a part-time basis with limited or no employment due to pain were classified as employable. Patients who chose not to work, were retired, or were homemakers (not working, but not due to pain) were not considered in the employment pool.

Sample Size

Sample size is calculated based on significant pain relief. Considering a 0.05 two-sided significance level, a power of 80%, and an allocation ratio of 1:1, 55 patients in each group were estimated (69) allowing for 10% attrition/ non-compliance rate, 60 subjects were required.

Previous studies of interventional techniques identified 50 to 60 patients as appropriate (53-57, 59,60,70-72).

Randomization

From a total of 120 patients, 60 patients were randomly assigned into each group.

Sequence Generation

Randomization was performed by computer-generated random allocations sequence by simple randomization.

Allocation Concealment

The operating room nurse assisting with the procedure randomized the patients and prepared the drugs appropriately.

Implementation

Participants were invited to enroll in the study if they met inclusion criteria. One of the 3 nurses assigned as coordinators of the study enrolled the participants and assigned participants to their respective groups.

Blinding (Masking)

Participants and those administering the interventions were blinded to group assignment. Both solutions were clear with inability to identify if the steroid was added or not. Further, the blinding was also assured by mixing the patients with other patients receiving routine treatment and not informing the physician performing the procedure of the inclusion of the patients in the study. All the patients for one-year follow-up were selected by the statistician not participating in provision of patient care. The unblinding results were not disclosed to either the treating physician or other participants or patients. Thus, the nature of blinding was not interrupted.

Statistical Methods

Statistical analysis included the chi-squared statistic, Fisher's exact test, t-test, and paired t-test. Results were considered statistically significant if the P value was less than 0.05.

Chi-squared statistic was used to test the differences in proportions. Fisher's exact test was used wherever the expected value was less than 5; a paired t-test was used to compare the pre- and post-treatment results of average pain scores and NDI measurements at baseline versus 3, 6, and 12 months. For comparison of mean scores between groups, t-test was performed.

Intent-to-Treat-Analysis

An intent-to-treat-analysis was performed. Either the last follow-up data or initial data were utilized in the patients who dropped out of the study and no other data were available.

Sensitivity analysis was performed utilizing best case, worst case, and last follow-up scores scenarios.

Results

Participant Flow

Figure 1 illustrates the participant flow.

Recruitment

The recruitment period lasted from August 2007 to April 2010.

Baseline Data

Baseline demographic and clinical characteristics of each group are illustrated in Table 1. There were significant differences noted in Group I with 77% females (P = 0.044); however, no other differences were noted.

Analysis of Data

Numbers Analyzed

A schematic illustration of patient flow is provided in Fig. 1. Seventy patients completed one-year follow-up of 70 patients with 35 patients in each group. The data were available in the majority of the included patients. Intent-to-treat analysis was performed due to non-available data on 2 occasions for one patient in Group I, and on 3 occasions for 2 patients in Group II. Based on the number of treatments provided, lack of follow-up was found in 2 of 105 occasions in Group I (2%) or one of 35 patients (3%); whereas it was 3 of 105 occasions (3%) in Group II with 2 of 35 patients (6%) at least one time.

Sensitivity Analysis

A sensitivity analysis with changes in the numeric pain scale was performed utilizing the last follow-up score, best case scenario, and worst case scenario. There

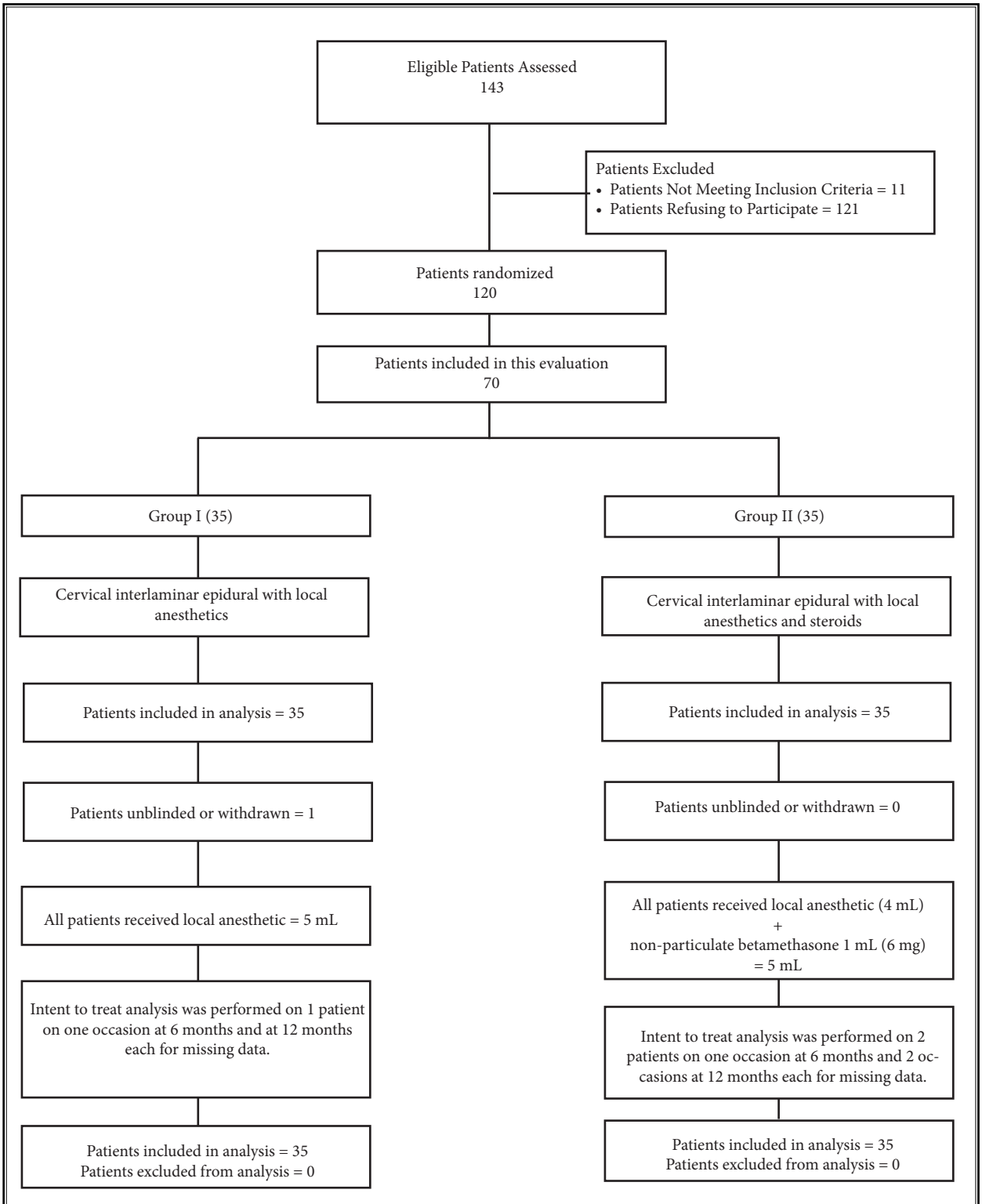

Fig. 1. Schematic presentation of patient flow at 1-year follow-up.

Table 1. *Baseline demographic characteristics.*

		Group 1 (35)	Group II (35)	P value
Gender	Male	23% (8)	46% (16)	0.044
	Female	77% (27)	54% (19)	
Age	Mean ± SD	43.7 ± 13.0	45.2 ± 11.0	0.607
Weight	Mean ± SD	174.2 ± 50.6	179.6 ± 40.9	0.627
Height	Mean ± SD	64.9 ± 3.1	67.3 ± 3.6	0.004
Duration of pain (months)	Mean ± SD	86.7 ± 81.8	86.6 ± 93.7	0.995
Onset of the pain	Gradual	57% (20)	40% (14)	0.151
	Injury	43% (15)	60% (21)	
Neck pain distribution	Neck pain only	34% (12)	40% (14)	0.492
	Neck pain worse than Upper extremity	60% (21)	43% (15)	
	Both equal	6% (2)	17% (6)	
Pain Distribution	Unilateral	31% (11)	31% (11)	1.00
	Bilateral	69% (24)	69% (24	
Numeric rating score	Mean ± SD	7.8 ± 0.8	7.4 ± 0.9	0.059
Neck Disability Index	Mean ± SD	30.0 ± 4.8	28.5 ± 7.0	0.302

Table 2. *Pain relief characteristics.*

Numeric Rating Score	Group I (35) Mean ± SD	Group II (35) Mean ± SD	*P* value
Baseline	7.8 ± 0.8	7.4 ± 0.9	0.059
3 months	3.4* ± 1.4	3.1* ± 1.0	0.313
6 months	3.5* ± 1.5	3.2* ± 1.0	0.457
12 months	3.5* ± 1.3	3.2* ± 1.1	0.372

* indicates significant difference with baseline values ($P < 0.001$)

were no significant differences; therefore, the intention-to-treat analysis with last follow-up visit was used.

Outcomes

Pain Relief

Table 2 illustrates the NRS scores. Pain scores changed significantly from baseline, at 3, 6, and 12 months in all groups, with no significant differences between the groups or follow-up periods.

The proportion of patients with significant pain relief of 50% or greater are illustrated in Fig. 2 with 80%

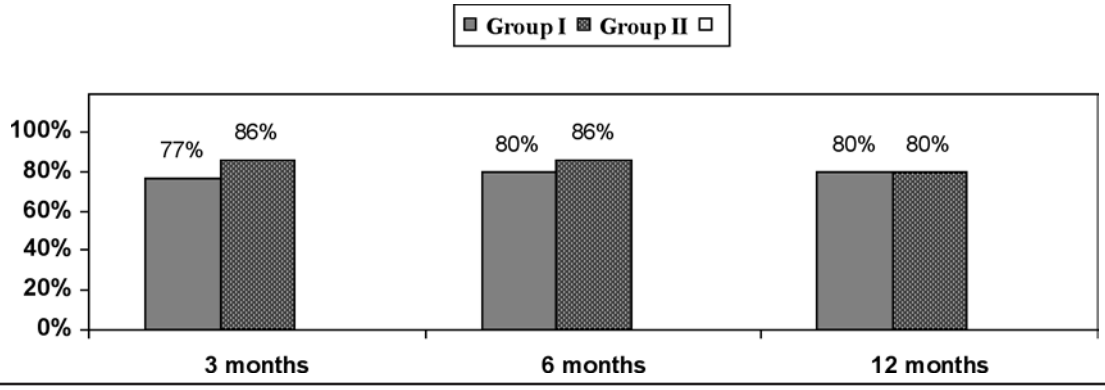

Fig. 2. *Proportion of patients with significant pain relief (≥ 50%).*

in Group I and Group II at 12 months.

Functional Assessment

Functional assessment results assessed by the NDI are illustrated in Table 3. Significant improvement was seen in the functional status in both groups from baseline to one year. Reduction of NDI scores of at least 50% was seen in 69% (Group I) and 80% (Group II) of the patients at 12-months as shown in Fig. 3. There were no significant differences between the groups or during follow-up periods.

Employment Characteristics

Table 4 demonstrates employment characteristics in both groups.

Table 3. *Functional assessment evaluated by Neck Disability Index.*

Neck Disability Index	Group I (35)	Group II (35)	P value
	Mean ± SD	Mean ± SD	
Baseline	30.0 ± 4.8	28.5 ± 7.0	0.302
3 months	15.1* ± 5.9	13.1* ± 4.9	0.134
6 months	14.5* ± 5.8	13.1* ± 5.2	0.266
12 months	14.4* ± 5.6	12.7* ± 4.9	0.185

* indicates significant difference with baseline values ($P < 0.001$)

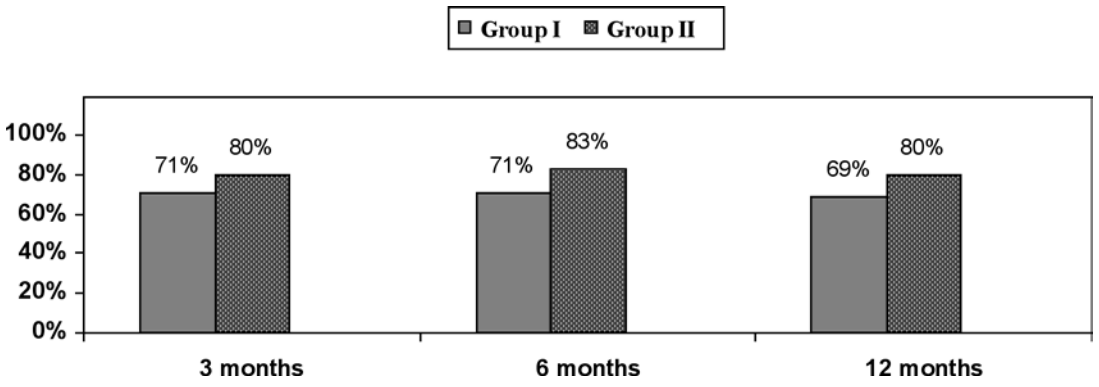

Fig. 3. *Proportion of patients with significant (> 50% decrease in NDI) functional status improvement.*

Table 4. *Employment characteristics.*

Employment status	Group I		Group II	
	Baseline	12 months	Baseline	12 months
Employed part-time	4	0	3	3
Employed full-time	1	9	7	8
Unemployed (due to pain)	3	1	3	2
Not working	4	2	1	1
Eligible for employment	12	12	14	14
Total Employed	5	9	10	11
Housewife	22	22	18	18
Disabled	2	1	2	2
Retired	0	0	1	1
Total Number of Patients	35	35	35	35

Opioid Intake

Table 5 illustrates opioid intake characteristics.

Therapeutic Procedural Characteristics

Therapeutic procedural characteristics are illustrated in Table 6. Epidural entry was as follows: 27% between C7 and T1, 64% between C6 and C7, and 9% between C5 and C6 vertebral interspaces.

Average relief per year was 37.6 ± 16.2 weeks in Group I and 39.7 ± 13.6 weeks in Group II with no significant differences. The total number of injections per year were 3.9 ± 1.1 in Group I and 3.8 ± 0.9 in Group II. However, when patients were separated into successful and failed groups, the total number of injections per year was 3.9 ± 1.01 in Group I and 3.9 ± 0.8 in Group II in the successful group, with total relief of 40.3 ± 14.1 weeks in Group I and 42.1 ± 9.9 weeks in Group II. In contrast, the relief was 9.3 ± 9.3 and 1.0 ± 1.4 weeks in failed group.

Epidurals were considered to be successful if a patient obtained consistent relief with 2 initial injections of at least 3 weeks. All others were considered as failures.

Changes in Weight

There were no differences in change (gain or loss) in body weight from baseline in both groups (Table 7).

Adverse Events

Of the 262 cervical epidural procedures performed, no subarachnoid punctures were reported. Nerve root irritation was observed in 3 patients without long-term

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

Opioid Intake (morphine equivalence mg)	**Group I (35)**	**Group II (35)**	***P* value**
	Mean ± SD	**Mean ± SD**	
Baseline	60.7 ± 59.8	47.6 ± 40.9	0.290
3 months	51.1 ± 53.7	36.1 ± 23.9	0.138
6 months	50.5 ± 53.7	36.1 ± 23.9	0.151
12 months	50.5 ± 53.7	36.4 ± 23.9	0.531

Table 6. *Therapeutic procedural characteristics with procedural frequency, average relief per procedure, and average total relief in weeks over a period of one year.*

	Successful Subjects		**Failed Subjects**		**Combined**	
	Group I (32)	**Group II (33)**	**Group I (3)**	**Group II (2)**	**Group I (35)**	**Group II (35)**
1st procedure relief	6.5 ± 5.3 (32)	8.5 ± 7.9 (33)	2.2 ± 1.0 (3)	0.2 ± 0.1 (2)	6.1 ± 5.2 (35)	8.0 ± 7.9 (35)
2nd procedure relief	11.0 ± 5.8 (32)	10.8 ± 6.4 (33)	1.3 ± 1.2 (3)	1.00 (1)	10.2 ± 6.2 (35)	10.5 ± 6.6 (34)
3rd procedure relief	12.3 ± 6.4 (29)	11.6 ± 3.8 (31)	2.6 ± 3.3 (2)	1.00 (1)	11.7 ± 6.7 (31)	11.3 ± 4.1 (32)
4th procedure relief	12.8 ± 2.9 (22)	12.2 ± 2.7 (27)	13.00 (1)	-	12.8 ± 2.8 (23)	12.2 ± 2.6 (27)
5th procedure relief	11.1 ± 4.1 (10)	13.2 ± 0.42 (6)	0.00 (1)	-	10.1 ± 5.2 (11)	13.2 ± 0.4 (6)
Number of procedures per year	3.9 ± 1.01 (32)	3.9 ± 0.8 (33)	3.3 ± 1.5 (3)	2.0 ± 1.4 (2)	3.9 ± 1.1 (35)	3.8 ± 0.9 (35)
Average relief per procedure	10.3 ± 3.9 (32)	11.2 ± 4.4 (33)	2.5 ± 1.5 (3)	0.3 ± 0.5 (2)	9.7 ± 4.3 (35)	10.6 ± 4.9 (35)
Average relief per procedure 3rd procedure and after	11.8 ± 4.5 (28)	12.1 ± 4.1 (28)	4.6 ± 6.1 (2)	10.3 (1)	11.3 ± 4.9 (30)	12.0 ± 4.0 (29)
Total relief per year (weeks)	40.3 ± 14.1 (32)	42.1 ± 9.9 (33)	9.3 ± 9.3 (3)	1.0 ± 1.4 (2)	37.6 ± 16.2 (35)	39.7 ± 13.6 (35)

Table 7. *Characteristics of changes in weight.*

Weight (lbs)	Group I (35)	Group II (35)	P value
	Mean ± SD	Mean ± SD	
Weight at beginning	174.2 ± 50.6	179.6 ± 40.9	0.627
Weight at one year	173.3 ± 53.8	177.9 ± 43.1	0.694
Change	-0.9 ± 12.7	-1.6 ± 11.5	0.791
Lost weight	43% (15)	46% (16)	0.645
No change	23% (8)	14% (5)	
Gained weight	34% (12)	40% (14)	

sequelae. All patients experiencing nerve root irritation, even though transient, were given 8 mg of Decadron intravenously.

Discussion

This preliminary report of the one-year follow-up of a randomized trial of 70 patients demonstrates no significant differences in outcomes whether patients received injections of anesthetic alone or anesthetic with steroids. In terms of pain relief, 80% of the patients in both groups experienced significant pain relief (≥ 50%), whereas a significant improvement in functional status (≥ 50% reduction in NDI scores) was seen in 69% in Group I and 80% of the patients in Group II. In the successful group, the overall average procedures per year were 3.9 ± 1.01 in Group I and 3.9 ± 0.8 in Group II, with an average total relief per year of 40.3 ± 14.1 weeks in Group I and 42.1 ± 9.9 weeks in Group II, over a period of 52 weeks. Opioid intake was significantly reduced in both groups.

Despite significant use of epidural injections in the cervical spine there have been only 2 systematic reviews (1,73), and a Cochrane review of medicinal and injection therapies for mechanical neck disorders (74). Of the randomized evaluations included in the evidence synthesis (34-36), Benyamin et al (1) concluded that all 3 studies showed positive results for short-term relief, whereas 2 were positive for long-term relief, and the results of long-term relief were not available for one study (36), defining short-term relief as 6 months, and long-term relief as greater than 6 months. As illustrated in the present study, cervical interlaminar epidural injections with local anesthetic with or without steroids do not provide long-term relief, even though long-term relief can be achieved by appropriate patient evaluation and judicious use of repeat injection therapy. The study has illustrated an average of 11.8 to 12.1 weeks of relief in the therapeutic phase after 2 initial injections in the successful group. These results are similar to patients receiving cervical epidural injections with steroids with disc herniation utilizing the same methodology (33). These results are also similar to the results obtained with caudal and lumbar interlaminar epidural injections with disc herniation and discogenic pain without disc herniation (54,55,59,60).

Further, this study also provided insight into successful or failed groups based on the first 2 procedures. The patients in the successful group with good pain relief with the first and second procedures showed an overall average relief from 40.3 to 42.1 weeks of 52 weeks with an average number of procedures per year of 3.9. In contrast, in the failed group, the average relief per procedure was 0.3 to 2.5 weeks, with overall 1.0 to 9.3 weeks of relief in one year.

An advantage of this evaluation is its generalizability to interventional pain management settings. This is the first study performed under fluoroscopic visualization in the United States in a private practice setting. Overall, pragmatic or practical clinical trials (with an active control) measuring effectiveness are considered more appropriate than explanatory trials measuring efficacy (25-29,73-79). The present design with an active control shows not only the existence of effect, but also compares 2 commonly used therapies (80), instead of existence of effect or absolute effect size. This study is also different from other studies as we have utilized repeat cervical interlaminar epidural injections based on the requirement that there be an increase in pain and deterioration in functional status rather than routinely providing 3 injections or limiting to 1-3 procedures.

The limitation of this evaluation includes the lack of a placebo group and the fact that it is a preliminary analysis. However, conducting clinical trials with a placebo group is extremely difficult in the United States with interventional techniques. Further, even though placebo control trials have been known to provide internal validity, they lack external validity. The internal validity is provided in an active control trial with a treatment response accounting for the total difference between 2 treatments including both treatment as well as associated placebo effects. Further, external validity, also known as applicability, is the extent to which the results of the study can be generalized to other circumstances and the general population, and is best provided with pragmatic or active control trials. This preliminary report may also resolve to some extent the issue of local anesthetics with or without steroids in managing chronic function-limiting neck pain of discogenic origin. These results describe a pattern of practice

in the United States in an interventional pain management setting. The results may not be applicable in the general population unless the same methodology is utilized under fluoroscopy. In addition, generalizability of the findings of any study may only be feasible utilizing larger populations in multiple settings.

Placebo-controlled neural blockade is not only unrealistic, but it has been frequently misinterpreted (81,82). Some have inappropriately reported that any local anesthetic injection which yields similar results as steroids is considered a placebo, due to a lack of understanding of clinical aspects. Even the injections of sodium chloride solution and dextrose have been shown to be different (83).

The experimental and clinical findings from the investigation of the electrophysiological effects of 0.9% sodium chloride and dextrose 5% in water solution have illustrated multiple aspects of neural stimulation used in regional anesthesia. The potential inaccuracy created by 0.9% sodium chloride solution versus 5% dextrose has been described (84,85). In fact, injection of sodium chloride solution either into the disc, facet joint, or paraspinal muscles is also different (85,86).

The mechanism of the action of steroids and local anesthetic has been described (36-48,87-93). There is also emerging evidence that local anesthetics may be equally as effective as steroids in managing low back and neck pain without disc herniation and also pain of facet joint origin (49-60). It has been reported that local anesthetics will influence multiple pathophysiologic mechanisms involved in chronic pain including noxious peripheral stimulation, excess nociception resulting in the sensitization of the pain pathways at several neuronal levels, and excess release of neurotransmitters causing complex central responses including hyperalgesia or wind-up (36), resulting in an increase in nociceptive sensitization of the nervous system (93,94), and phenotype changes which are also considered as part of the neuronal plasticity (93-95). Thus, there is evidence for the long-term effect of either local anesthetics or steroids in managing radicular pain. Corticosteroid anti-inflammatory properties have been associated with the inhibition of prostaglandin synthesis and decreases in regional levels or inflammatory mediators such as interleukin-1, tumor necrosis factor, and phospholipase A2 (36-48,96-103). The results of this preliminary report show no significant improvement with corticosteroids in managing chronic neck pain with or without upper extremity pain. In addition, corticosteroids are also known to possess direct neurotoxic effects on peripheral nerve tissue unlike local anesthetics (85,104-106).

Conclusion

Assessment of the preliminary results of this randomized, double-blind, controlled trial of cervical interlaminar epidural injections in chronic function-limiting neck pain and upper extremity pain with discogenic pain without disc herniation, radiculitis, or facet joint pain demonstrated significant pain relieving effectiveness in 80% of the patients with improvement in functional status as well.

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References

1. Benyamin RM, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician* 2009; 12:137-157.
2. Manchikanti L. Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician* 2009; 12:E35-E70.
3. Hogg-Johnson S, van der Velde G, Carroll LJ, Holm LW, Cassidy JD, Guzman J, Côté P, Haldeman S, Ammendolia C, Carragee E, Hurwitz E, Nordin M, Peloso P, Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. The burden and determinants of neck pain in the general population: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine (Phila Pa 1976)* 2008; 33:S39-S51.
4. Côté P, Cassidy JD, Carroll L. The Saskatchewan Health and Back Pain Survey. The prevalence of neck pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1689-1698.
5. Côté P, Cassidy JD, Carroll LJ, Kristman V. The annual incidence and course of neck pain in the general population: A population-based cohort study. *Pain* 2004; 112:267-273.
6. Côté P, Kristman V, Vidmar M, Van Eerd D, Hogg-Johnson S, Beaton D, Smith PM. The prevalence and incidence of work absenteeism involving neck pain: A cohort of Ontario lost-time claimants. *Spine (Phila Pa 1976)* 2008; 33:S192-S198.
7. Carette S, Fehlings MG. Clinical practice. Cervical radiculopathy. *N Engl J Med* 2005; 353:392-399.
8. Radhakrishnan K, Litchy WJ, O'Fallon

WM, Kurland LT. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. *Brain* 1994;117:325-335.

9. Falco FJE, Erhart S, Wargo BW, Bryce DA, Atluri S, Datta S, Hayek SM. Systematic review of diagnostic utility and therapeutic effectiveness of cervical facet joint interventions. *Pain Physician* 2009; 12:323-344.
10. Manchikanti L, Dunbar EE, Wargo BW, Shah RV, Derby R, Cohen SP. Systematic review of cervical discography as a diagnostic test for chronic spinal pain. *Pain Physician* 2009; 12:305-321.
11. Yin W, Bogduk N. The nature of neck pain in a private pain clinic in the United States. *Pain Medicine* 2008; 9:196-203.
12. Lotz JC, Ulrich JA. Innervation, inflammation, and hypermobility may characterize pathologic disc degeneration: Review of animal model data. *J Bone Joint Surg Am* 2006; 88:76-82.
13. Cloward RB. Cervical discography. *Acta Radiol Diagn (Stockh)* 1963; 1:675-688.
14. Cloward RB. Cervical diskography. A contribution to the etiology and mechanism of neck, shoulder and arm pain. *Ann Surg* 1959; 150:1052-1064.
15. Manchikanti L. Medicare in interventional pain management: A critical analysis. *Pain Physician* 2008; 11:13-42.
16. Manchikanti L, Pampati V, Boswell MV, Smith HS, Hirsch JA. Analysis of the growth of epidural injections and costs in the Medicare population: A comparative evaluation of 1997, 2002, and 2006 data. *Pain Physician* 2010; 13:199-212.
17. Manchikanti L, Singh V, Pampati V, Smith HS, Hirsch JA. Analysis of growth of interventional techniques in managing chronic pain in Medicare population: A 10-year evaluation from 1997 to 2006. *Pain Physician* 2009; 12:9-34.
18. Manchikanti L, Singh V, Derby R, Schultz DM, Benyamin RM, Prager JP, Hirsch JA. Reassessment of evidence synthesis of occupational medicine practice guidelines for interventional pain management. *Pain Physician* 2008; 11:393-482.
19. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, Buenaventura RM, Conn A, Datta S, Derby R, Falco FJE, Erhart S, Diwan S, Hayek SM, Helm S, Parr AT, Schultz DM, Smith HS, Wolfer LR, Hirsch JA. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:699-802.
20. Manchikanti L, Pampati V, Singh V, Boswell MV, Smith HS, Hirsch JA. Explosive growth of facet joint interventions in the Medicare population in the United States: A comparative evaluation of 1997, 2002, and 2006 data. *BMC Health Serv Res* 2010; 10:84.
21. Manchikanti L, Boswell MV, Datta S, Fellows B, Abdi S, Singh V, Benyamin RM, Falco FJE, Helm S, Hayek S, Smith HS. Comprehensive review of therapeutic interventions in managing chronic spinal pain. *Pain Physician* 2009: 12:E123-E198.
22. Manchikanti L, Singh V, Derby R, Helm S, Trescot AM, Staats PS, Prager JP, Hirsch JA. Review of occupational medicine practice guidelines for interventional pain management and potential implications. *Pain Physician* 2008; 11:271-289.
23. Manchikanti L, Singh V, Helm S, Trescot AM, Hirsch JA. A critical appraisal of 2007 American College of Occupational and Environmental Medicine (ACOEM) practice guidelines for interventional pain management: An independent review utilizing AGREE, AMA, IOM, and other criteria. *Pain Physician* 2008; 11:291-310.
24. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, Benyamin RM, Sharma ML, Helm II S, Fellows B, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 2. Therapeutic interventions. *Pain Physician* 2010; 13:E215-E265.
25. Manchikanti L. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 1: Introduction and general considerations. *Pain Physician* 2008; 11:161-186.
26. Manchikanti L, Hirsch JA, Smith HS. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 2: Randomized controlled trials. *Pain Physician* 2008; 11:717-773.
27. Manchikanti L, Benyamin RM, Helm S, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 3: Systematic reviews and meta-analysis of randomized trials. *Pain Physician* 2009; 12:35-72.
28. Manchikanti L, Singh V, Smith HS, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 4: Observational studies. *Pain Physician* 2009; 12:73-108.
29. Manchikanti L, Datta S, Smith HS, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 6. Systematic reviews and meta-analyses of observational studies. *Pain Physician* 2009; 12:819-850.
30. Conn A, Buenaventura R, Datta S, Abdi S, Diwan S. Systematic review of caudal epidural injections in the management of chronic low back pain. *Pain Physician* 2009; 12:109-135.
31. Parr AT, Diwan S, Abdi S. Lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain: A systematic review. *Pain Physician* 2009; 12:163-188.
32. Buenaventura RM, Datta S, Abdi S, Smith HS. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. *Pain Physician* 2009; 12:233-251.
33. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. The effectiveness of fluoroscopic cervical interlaminar epidural injections in managing chronic cervical disc herniation and radiculitis: Preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:223-236.
34. Stav A, Ovadia L, Sternberg A, Kaadan M, Weksler N. Cervical epidural steroid injection for cervicobrachialgia. *Acta Anaesthesiol Scand* 1993; 37:562-566.
35. Castagnera L, Maurette P, Pointillart V, Vital JM, Erny P, Senegas J. Long term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. *Pain* 1994; 58:239-243.
36. Pasqualucci A, Varrassi G, Braschi A, Peduto VA, Brunelli A, Marinangeli F, Gori F, Colò F, Paladini A, Mojoli F. Epidural local anesthetic plus corticosteroid for the treatment of cervical brachial radicular pain: Single injection versus continuous infusion. *Clin J Pain* 2007; 23:551-557.
37. Byrod G, Otani K, Brisby H, Rydevik B, Olmarker K. Methylprednisolone reduces the early vascular permeability increase in spinal nerve roots induced

by epidural nucleus pulposus application. *J Orthop Res* 2000; 18:983-987.

38. Hayashi N, Weinstein JN, Meller ST, Lee HM, Spratt KF, Gebhart GF. The effect of epidural injection of betamethasone or bupivacaine in a rat model of lumbar radiculopathy. *Spine (Phila Pa 1976)* 1998; 23:877-885.
39. Lee HM, Weinstein JN, Meller ST, Hayashi N, Spratt KF, Gebhart GF. The role of steroids and their effects on phospholipase A2: An animal model of radiculopathy. *Spine (Phila Pa 1976)* 1998; 23:1191-1196.
40. Minamide A, Tamaki T, Hashizume H, Yoshida M, Kawakami M, Hayashi N. Effects of steroids and lipopolysaccharide on spontaneous resorption of herniated intervertebral discs: An experimental study in the rabbit. *Spine (Phila Pa 1976)* 1998; 23:870-876.
41. Tachihara H, Sekiguchi M, Kikuchi S, Konno S. Do corticosteroids produce additional benefit in nerve root infiltration for lumbar disc herniation. *Spine (Phila Pa 1976)* 2008; 33:743-747.
42. Hua SY, Chen YZ. Membrane receptor-mediated electrophysiological effects of glucocorticoid on mammalian neurons. *Endocrinology* 1989; 124:687-691.
43. Flower RJ, Blackwell GJ. Anti-inflammatory steroid induced biosynthesis of a phospholipase A2 inhibitor which prevents prostaglandin generation. *Nature* 1979; 278:456-459.
44. Lundin A, Magnuson A, Axelsson K, Nilsson O, Samuelsson L. Corticosteroids preoperatively diminishes damage to the C-fibers in microscopic lumbar disc surgery. *Spine (Phila Pa 1976)* 2005; 30:2362-2367.
45. Pasqualucci A. Experimental and clinical studies about the preemptive analgesia with local anesthetics. Possible reasons of the failure. *Minerva Anestesiol* 1998; 64:445-457.
46. Arner S, Lindblom U, Meyerson BA, Molander C. Prolonged relief of neuralgia after regional anesthetic block. A call for further experimental and systematic clinical studies. *Pain* 1990; 43:287-297.
47. Sato C, Sakai A, Ikeda Y, Suzuki H, Sakamoto A. The prolonged analgesic effect of epidural ropivacaine in a rat model of neuropathic pain. *Anesth Analg* 2008; 106:313-320.
48. Wertheim HM, Rovenstine EA. Suprascapular nerve block. *Anesthesiology* 1941; 2:541.
49. Manchikanti L, Singh V, Falco FJ, Cash KA, Pampati V. Lumbar facet joint nerve blocks in managing chronic facet joint pain: One-year follow-up of a randomized, double-blind controlled trial: Clinical Trial NCT00355914. *Pain Physician* 2008; 11:121-132.
50. Manchikanti L, Singh V, Falco FJ, Cash KA, Fellows B. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2008; 33:1813-1820.
51. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Effectiveness of thoracic medial branch blocks in managing chronic pain: A preliminary report of a randomized, double-blind controlled trial. Clinical Trial NCT00355706. *Pain Physician* 2008; 11:491-504.
52. Manchikanti L, Damron KS, Cash KA, Manchukonda R, Pampati V. Therapeutic cervical medial branch blocks in managing chronic neck pain: A preliminary report of a randomized, double-blind, controlled trial: Clinical Trial NCT00033272. *Pain Physician* 2006; 9:333-346.
53. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of lumbar facet joint nerve blocks in managing chronic low back pain: A randomized, double-blind, controlled trial with a 2-year follow-up. *Int J Med Sci* 2010; 7:124-135.
54. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 1. Discogenic pain without disc herniation or radiculitis. *Pain Physician* 2008; 11:785-800.
55. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 2. Disc herniation and radiculitis. *Pain Physician* 2008; 11:801-815.
56. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 3. Post surgery syndrome. *Pain Physician* 2008; 11:817-831.
57. Manchikanti L, Cash KA, McManus CD, Pampati V, Abdi S. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 4. Spinal stenosis. *Pain Physician* 2008; 11:833-848.
58. Riew KD, Park JB, Cho YS, Gilula L, Patel A, Lente LG, Bridwell KH. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006; 88:1722-1725.
59. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of the effectiveness of lumbar interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:343-355.
60. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin R. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.
61. Moher D, Schulz KF, Altman D, for the CONSORT Group. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; 285:1987-1991.
62. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med* 2001; 134:663-694.
63. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. One-year results of a randomized double-blind, controlled trial of fluoroscopic caudal epidural injections with or without steroids in managing chronic discogenic low back pain without disc herniation or radiculitis: NCT00370799. 2010; in press.
64. Manchukonda R, Manchikanti KN, Cash KA, Pampati V, Manchikanti L. Facet joint pain in chronic spinal pain: An evaluation of prevalence and false-positive rate of diagnostic blocks. *J Spinal Disord Tech* 2007; 20:539-545.
65. Cleland JA, Childs JD, Whitman JM. Psychometric properties of the Neck Disability Index and Numeric Pain Rating

Scale in patients with mechanical neck pain. *Arch Phys Med Rehabil* 2008; 89:69-74.

66. Pietrobon R, Coeytaux RR, Carey TS, Richardson WJ, DeVellis RF. Standard scales for measurement of functional outcome for cervical pain or dysfunction: A systematic review. *Spine (Phila Pa 1976)* 2002; 27:515-522.
67. Vernon H, Mior S. The Neck Disability Index: A study of reliability and validity. *J Manipulative Physiol Ther* 1991; 14:409-415.
68. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. A critical review and proposals for long-term dosing. *J Pain Symptom Manage* 2001; 22:672-687. Narcotic analgesic converter, GlobalRPh Inc. www.globalrph.com/narcotic.cgi
69. Browner WS, Newman TB, Cummings SR, Hulley SB. Estimating sample size and power. In: Hulley SB, Cummings SR, Browner WS, Grady D, Hearst N, Newman TB (eds). *Designing Clinical Research: An Epidemiologic Approach*, 2nd ed. Lippincott, Williams & Wilkins, Philadelphia, 2001, pp 65-84.
70. Koes BW, Scholten RJ, Mens JMA, Bouter LM. Epidural steroid injections for low back pain and sciatica. An updated systematic review of randomized clinical trials. *Pain Digest* 1999; 9:241-247.
71. Manchikanti L, Cash KA, McManus CD, Pampati V, Singh V, Benyamin RM. The preliminary results of a comparative effectiveness evaluation of adhesiolysis and caudal epidural injections in managing chronic low back pain secondary to spinal stenosis: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E341-E354.
72. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing lumbar post surgery syndrome: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E355-E368.
73. Abdi S, Datta S, Trescot AM, Schultz DM, Adlaka R, Atluri SL, Smith HS, Manchikanti L. Epidural steroids in the management of chronic spinal pain: A systematic review. *Pain Physician* 2007; 10:185-212.
74. Peloso PMJ, Gross A, Haines T, Trinh K, Goldsmith CH, Burnie SJ, Cervical Overview Group. Medicinal and injection therapies for mechanical neck disorders. *Cochrane Database Syst Rev* 2007; 3:CD000319.
75. Manchikanti L, Falco FJE, Boswell MV, Hirsch JA. Facts, fallacies, and politics of comparative effectiveness research: Part I. Basic considerations. *Pain Physician* 2010; 13:E23-E54.
76. Manchikanti L, Falco FJE, Boswell MV, Hirsch JA. Facts, fallacies, and politics of comparative effectiveness research: Part 2. Implications for interventional pain management. *Pain Physician* 2010; 13:E55-E79.
77. Hotopf M, Churchill R, Lewis G. Pragmatic randomized controlled trials in psychiatry. *Br J Psychiatry* 1999; 175:217-223.
78. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials. Increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003; 290:1624-1632.
79. Roland M, Torgerson DJ. What are pragmatic trials? *BMJ* 1998; 316:285.
80. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Choice of Control Group and Related Issues in Clinical Trials E10. July 20, 2000.
81. Smuck M, Levin JH. RE: Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2008; 33:1813-20. *Spine (Phila PA 1976)* 2009; 34:1116-1117.
82. Manchikanti L, Singh V, Falco FJE. In response to Smuck M, Levin JH. RE: Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2009; 34:1116-1117.
83. Pham Dang C, Lelong A, Guilley J, Nguyen JM, Volteau C, Venet G, Perrier C, Lejus C, Blanloeil Y. Effect on neurostimulation of injectates used for perineural space expansion before placement of a stimulating catheter: Normal saline versus dextrose 5% in water. *Reg Anesth Pain Med* 2009; 34:398-403.
84. Tsui BC, Kropelin B, Ganapathy S, Finucane B. Dextrose 5% in water: Fluid medium maintaining electrical stimulation of peripheral nerve during stimulating catheter placement. *Acta Anaesthesiol Scand* 2005; 49:1562-1565.
85. Indahl A, Kaigle AM, Reikeräs O, Holm SH. Interaction between the porcine lumbar intervertebral disc, zygapophysial joints, and paraspinal muscles. *Spine (Phila Pa 1976)* 1997; 22:2834-2840.
86. Indahl A, Kaigle A, Reikerås O, Holm S. Electromyographic response of the porcine multifidus musculature after nerve stimulation. *Spine (Phila Pa 1976)* 1995; 20:2652-2658.
87. Manchikanti L. Pharmacology of neuraxial steroids. In: Manchikanti L, Singh V (eds). *Interventional Techniques in Chronic Spinal Pain*. ASIPP Publishing, Paducah, KY, 2007; pp 167-184.
88. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain* 2000; 87:7-17.
89. Ferrante FM, Paggioli J, Cherukuri S, Arthru GR. The analgesic response to intravenous lidocaine in the treatment of neuropathic pain. *Anesth Analg* 1996; 82:91-97.
90. Lavoie PA, Khazen T, Filion PR. Mechanisms of the inhibition of fast axonal transport by local anesthetics. *Neuropharmacology* 1989; 28:175-181.
91. Bisby MA. Inhibition of axonal transport in nerves chronically treated with local anesthetics. *Exp Neurol* 1975; 47:481-489.
92. Manchikanti L. Interventional pain management: Past, present, and future. The Prithvi Raj lecture: Presented at the 4th World Congress-World Institute of Pain, Budapest, 2007. *Pain Pract* 2007; 7:357-371.
93. Kawakami M, Weinstein JN, Chatani K, Spratt KF, Meller ST, Gebhart GF. Experimental lumbar radiculopathy. Behavioral and histologic changes in a model of radicular pain after spinal nerve root irritation with chromic gut ligatures in the rat. *Spine (Phila Pa 1976)* 1994; 19:1795-1802.
94. Decosterd I, Woolf CJ. Spared nerve injury: An animal model of persistent peripheral neuropathic pain. *Pain* 2000; 87:149-158.
95. Pennypacker KR, Hong JS, McMillian MK. Implications of prolonged expression of Fos-related antigens. *Trends Pharmacol Sci* 1995; 16:317-321.
96. Aoki Y, Rydevik B, Kikuchi S. Local application of disc-related cytokines on spinal nerve roots. *Spine (Phila Pa*

1976) 2002; 27:1614-1617.

97. Norimoto M, Ohtori S, Yamashita M, Inoue G, Yamauchi K, Koshi T, Suzuki M, Orita S, Eguchi Y, Sugiura A, Ochiai N, Takaso M, Takahashi K. Direct application of the TNF-alpha inhibitor, etanercept, does not affect CGRP expression and phenotypic change of DRG neurons following application of nucleus pulposus onto injured sciatic nerves in rats. *Spine (Phila Pa 1976)* 2008; 33:2403-2408.
98. Genevay S, Finckh A, Payer M, Mezin F, Tessitore E, Gabay C, Guerne PA. Elevated levels of tumor necrosis factor-alpha in periradicular fat tissue in patients with radiculopathy from herniated disc. *Spine (Phila Pa 1976)* 2008; 33:2041-2046.
99. Sugiura A, Ohtori S, Yamashita M, Inoue G, Yamauchi K, Koshi T, Suzuki M, Norimoto M, Orita S, Eguchi Y, Takahashi Y, Watanabe TS, Ochiai N, Takaso M, Takahashi K. Existence of nerve growth factor receptors, tyrosine kinase a and p75 neurotrophin receptors in intervertebral discs and on dorsal root ganglion neurons innervating intervertebral discs in rats. *Spine (Phila Pa 1976)* 2008; 33:2047-2051.
100. Yamashita M, Ohtori S, Koshi T, Inoue G, Yamauchi K, Suzuki M, Takahashi K. Tumor necrosis factor-alpha in the nucleus pulposus mediates radicular pain, but not increase of inflammatory peptide, associated with nerve damage in mice. *Spine (Phila Pa 1976)* 2008; 33:1836-1842.
101. Igarashi T, Kikuchi S, Myers RR. Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology. Molecular, histologic, and behavioral comparisons in rats. *Spine (Phila Pa 1976)* 2000; 25:2975-2980.
102. McCarron RF, Wimpee MW, Hudkins PG, Laros GS. The inflammatory effect of nucleus pulposus: A possible element in the pathogenesis of low-back pain. *Spine (Phila Pa 1976)* 1987; 12:760-764.
103. Olmarker K, Blomquist J, Stromberg J. Inflammatogenic properties of nucleus pulposus. *Spine (Phila Pa 1976)* 1995; 20:665-669.
104. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. *Acta Anaesthesiol Scand* 1990; 34:335-338.
105. Mackinnon SE, Hudson AR, Gentili F, Kline DG, Hunter D. Peripheral nerve injection injury with steroid agents. *Plast Reconstr Surg* 1982; 69:482-489.
106. Shishido H, Kikuchi S, Heckman H, Myers RR. Dexamethasone decreases blood flow in normal nerves and dorsal root ganglia. *Spine (Phila Pa 1976)* 2002; 27:581-586.