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Randomized Trial

A Preliminary Report of a Randomized Double-Blind, Active Controlled Trial of Fluoroscopic Thoracic Interlaminar Epidural Injections in Managing Chronic Thoracic Pain

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Background: The proportion of patients suffering from thoracic pain secondary to thoracic disorders is relatively small compared to low back and neck pain. Furthermore, thoracic interventions are not performed as often as in cervical and lumbar regions. In addition, there is a paucity of literature regarding thoracic intervertebral discs and thoracic disc herniation as causative structures of thoracic pain.

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

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

Objectives: To evaluate the effectiveness of thoracic interlaminar epidural injections in providing effective pain relief in managing chronic mid and upper back pain secondary to disc herniation or radiculitis and discogenic pain with local anesthetic alone or with steroids.

Methods: Inclusion criteria consisted of patients who either had disc herniation or radiculitis, or patients with discogenic pain proven by controlled comparative local anesthetic blocks not to be caused by facet joint pain. Patients were assigned to one of 2 groups. One group received injections containing local anesthetic only; the other group, local anesthetic mixed with non-particulate betamethasone. Randomization was performed by computer-generated random allocations sequence by simple randomization.

Outcomes Assessment: Participant outcomes were measured at baseline, 3, 6, and 12 months post-treatment with the Numeric Rating Scale (NRS), the Oswestry Disability Index 2.0 (ODI), employment status, and opioid intake. Decrease of ≥ 50% of NRS scores and Oswestry scores were considered significant.

Results: A total of 40 participants are included in this preliminary report with 20 participants in each group. Significant pain relief (≥ 50%) and reduction (by at least 50%) in ODI from baseline was seen at 12 months in 80% of patients in Group I and 85% in Group II.

Limitations: This is a preliminary report and there was no placebo group.

Conclusion: Overall, 80% of participants in Group I (who received injections without steroids) and 85% in Group II (who received injections with steroids) with thoracic pain secondary to disc herniation or radiculitis and discogenic pain might benefit from thoracic interlaminar epidural injections.

Key words: Chronic thoracic pain, chest wall pain, disc herniation, discogenic pain, radiculitis, thoracic interlaminar epidural injections, epidural steroids, local anesthetic

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The proportion of patients suffering from chronic upper or mid back pain secondary to thoracic disorders is relatively small compared to low back and neck pain. In interventional pain management settings, thoracic pain has been reported in 3% to 23% of patients (1-7). The prevalence of thoracic pain has been estimated as 13% of the general population in contrast to 43% in the low back and 32% in the neck during the past year (8). While the limited epidemiologic data in relation to thoracic pain support the view that the thoracic spine is less commonly implicated in chronic pain than the lumbar or cervical spine (8-10), the degree of disability resulting from thoracic pain disorders is similar to that of the other regions (9). Further, various interventional techniques are also less commonly performed in the thoracic spine compared to lumbar or cervical spine (11-14). The multiple structures which may be responsible for chronic thoracic pain include thoracic facet joints and intervertebral discs which can be evaluated by proven diagnostic techniques. Thoracic facet joints have been evaluated with controlled diagnostic techniques and also have been treated with therapeutic thoracic medial branch blocks effectively. Based on the systematic review by Atluri et al (15), which included controlled local anesthetic blocks, the prevalence was shown to be 34% to 48% with false-positive rates of 42% to 58% utilizing uncontrolled blocks (2,3,16,17).

In contrast to the facet joint pain and the treatment modalities (2,3,15-21), there is a paucity of literature on thoracic intervertebral discs and thoracic disc herniation. Degeneration of the thoracic disc along with endplate irregularities and changes due to osteophyte formation are common findings (22-27). Further, the contribution of the disc as a source of thoracic spinal pain has received only scant attention (21,24-33). Pain secondary to thoracic disc herniation is extremely rare and the treatments are associated with increased risk and not offered widely. However, imaging studies in the thoracic spine, including MRI, CT, myelography, and radiographs, are as incapable of identifying a degenerated disc as being painful in the thoracic spine as they are in the lumbar spine (2,3,15-19,21,24,25,32,33).

Epidural injections for managing chronic low back pain and neck pain, whether the pain is caused by disc herniation or not, are commonly performed interventions in the United States (11-14). However, the effectiveness of thoracic interlaminar epidural steroid injections has not been evaluated and there is a paucity of literature with controlled trials (21,34). Only 2 reports have described pain relief from thoracic epidural steroid injections in patients with disc disease (35,36).

The effectiveness of epidural injections has been demonstrated in the cervical and lumbar spine by means of various approaches with or without steroids. In general, evidence has been emerging for the efficacy of caudal, lumbar interlaminar, cervical interlaminar, and lumbar transforaminal epidural injections when appropriate technique and indications are utilized (21,34,37-52).

The mechanism of action that underlies local anesthetic and steroids that are administered neuraxially has been frequently described, albeit not completely understood (41-70). Emerging evidence suggests that steroids might have a role in patients with disc herniation. However, experimental evaluation in animals with nerve root infiltration with or without steroids showed no significant difference (64).

Due to a lack of available literature evaluating the effectiveness of thoracic interlaminar epidural injections, this study was undertaken to evaluate the role of thoracic interlaminar epidural injections in patients with chronic mid back, upper back, or chest wall pain secondary to disc herniation or radiculitis and discogenic pain. The study was designed to evaluate 120 participants. This preliminary report includes 40 participants who completed a one year follow-up.

Methods

This study took place at a private interventional pain management practice and specialty referral center in the United States. Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed (71-73). The Institutional Review Board (IRB) approved the study protocol. The study is registered with the U.S. Clinical Trial Registry: NCT01071369.

Participants

Recruitment took place from among new patients that presented at the center. After agreeing to be a part of the study, participants were assigned to either Group I receiving thoracic interlaminar epidural injections containing 6 mL of local anesthetic (lidocaine 0.5%), or Group II receiving 5 mL of local anesthetic (lidocaine 0.5%) mixed with 6 mg (1 mL) of nonparticulate betamethasone.

Interventions

The IRB-approved protocol as well as informed consent was given to each participant. These docu-

ments thoroughly explained the study as well as the withdrawal process.

Pre-Enrollment Evaluation

Facet joint pain was excluded during the pre-enrollment evaluation by performing controlled comparative local anesthetic blocks. In addition, the following participant information was collected: work status, demographic data, opioid intake, pain rating scores using the Numeric Rating Scale (NRS), functional assessment using the Oswestry Disability Index 2.0 (ODI), physical examination, radiologic investigations, and medical and surgical history with co-existing disease(s).

Inclusion Criteria

Inclusion criteria included a positive diagnosis of disc herniation or radiculitis by MRI or CT or a negative diagnosis of thoracic facet joint pain by means of controlled comparative local anesthetic blocks; older than 18; 6 months or more of chronic, function-limiting thoracic pain; and the ability to understand not only the study protocol but also able to provide voluntary, written informed consent and participate in outcome measurements; finally, conservative management must have failed to show improvement, including but not limited to bed rest, exercise and physical therapy, drug therapy, and chiropractic manipulation.

Criteria used for exclusion included: thoracic facet joint pain; unstable or uncontrollable opioid use; uncontrolled psychiatric disorders; uncontrolled acute or chronic medical illness; any conditions that could interfere with the interpretation of outcome assessments; pregnant or lactating women; adverse reaction(s) to local anesthetics or steroids in a patient's history or the potential for such a reaction.

Description of Interventions

All patients with disc herniation or radiculitis were included in the study without any further evaluations.

Diagnostic, controlled, comparative, local anesthetic, thoracic facet joint nerve blocks were used to evaluate all other patients. On separate occasions, facet joint nerve blocks were performed with 0.5 mL of 1% lidocaine, followed by another block with 0.25% bupivacaine. The response to each had to be at least 80% pain relief with appropriate duration.

One physician performed all the thoracic interlaminar epidural procedures. They were performed using fluoroscopy in a sterile operating room located in an ambulatory surgery center. Participants had an intravenous access, were sedated with midazolam and fentanyl, were prone, and were monitored appropriately. After sterile preparation, the epidural space was accessed and then confirmed with non-ionic contrast. Based on the participant's pain complaints, as well as clinical and radiological findings, the procedures were performed either between a space below or at the level indicated by the participant's complaints and findings.

Additional Interventions

Each participant received the treatment assigned to his or her group. Participants were unblinded if an emergency arose, or upon request. Participants received additional thoracic interlaminar injections if their response to the first injection deteriorated to below 50% after successful relief. Non-responsive participants continued with conservative management and did not receive further injections unless they requested unblinding.

Co-Interventions

Participants were encouraged to take part in a therapeutic exercise program, increase functional status, return to work if eligible, and continue their work, if working. There was no physical or occupational therapy, or bracing offered. In addition, most participants were on drug therapy, including opioid and nonopioid analgesics as well as adjuvant analgesics.

Objectives

This study seeks to assess whether thoracic interlaminar epidural injections using local anesthetic or local anesthetic and steroids can provide effective pain relief for those who have chronic thoracic pain.

Outcomes

A number of outcome measures were recorded at baseline, 3 months, 6 months, and 12 months post-treatment. For pain, the NRS on a scale of 0-10 where 0 is no pain and 10 is the worst pain was used. The ODI on a 0-50 scale was used to assess function since there is no specific measurement for the thoracic spine. The NRS's and ODI's value and validity are well established (72-76). From a total score of 50, thresholds for the minimum clinically important ODI difference varied from 4 to 15 points (74). These thresholds have been questioned recently (77,78). For pain relief or improvement of function to be considered significant, there must be a 50% reduction in the NRS or ODI. Other outcome measures recorded were employment status

and opioid intake expressed as morphine equivalents (79).

Employability at enrollment inception was used to determine employment and work status, including employable, housewife not desiring to work outside the home, retired, or over 65. Participants unemployed due to pain, employed but on sick leave, or laid off were considered employable.

Sample Size

The sample size was calculated based on significant pain relief. Considering a 0.05 2-sided significance level, a power of 80%, and an allocation ratio of 1:1, 55 participants in each group were estimated (80). Allowing for a 10% attrition/non-compliance rate, 60 participants were required.

Previous studies of interventional techniques have identified 50 to 60 participants as acceptable (19,45-52,65-68,81,82).

Randomization

Sixty participants will eventually be randomly assigned into each group from a pool of 120 participants.

Sequence Generation

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

Allocation Concealment

Participants were randomized and the injectates appropriately prepared by an operating room nurse assisting with the procedure.

Implementation

If they met the inclusion criteria, patients were invited to enroll in the study. One of the 3 nurses assigned as study coordinators handled enrollment and group assignment.

Blinding (Masking)

Group assignment was blinded to both the participants and the physician administering the intervention. Participants were mixed with patients receiving routine treatment at the center. A statistician not involved with the participants' care chose the participants for this one-year follow-up. In addition, any unblinding was not disclosed to the doctor or other participants. Therefore, blinding was not interrupted. Overall assignment was approximately equal to both groups (33 versus 37).

Statistical Methods

Three statistical analysis methods were used. They included: Fisher's exact test, which was used wherever the expected value was less than 5; t-test, for comparing mean scores between the groups; and paired t-test, which was used to compare the pre- and post-treatment results of average pain scores and ODI measurements at baseline compared with 3 months, 6 months, and 12 months. If the *P* value was less than 0.05, then the results were considered statistically significant.

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, average value and last follow-up scores scenarios.

Results

Participant Flow

Figure 1 illustrates the participant flow.

Recruitment

The recruitment period started in January 2008 with continued enrollment.

Baseline Data

Table 1 illustrates the baseline demographic and clinical characteristics of each group.

Analysis of Data

Numbers Analyzed

A schematic illustration of patient flow is provided in Fig. 1. The data were available in all of the included patients.

Outcomes

Pain Relief and Functional Assessment

Table 2 illustrates the NRS scores. Table 3 illustrates functional assessment results. The proportion of patients with significant pain relief of 50% or greater and reduction of ODI scores by at least 50% is illustrated in

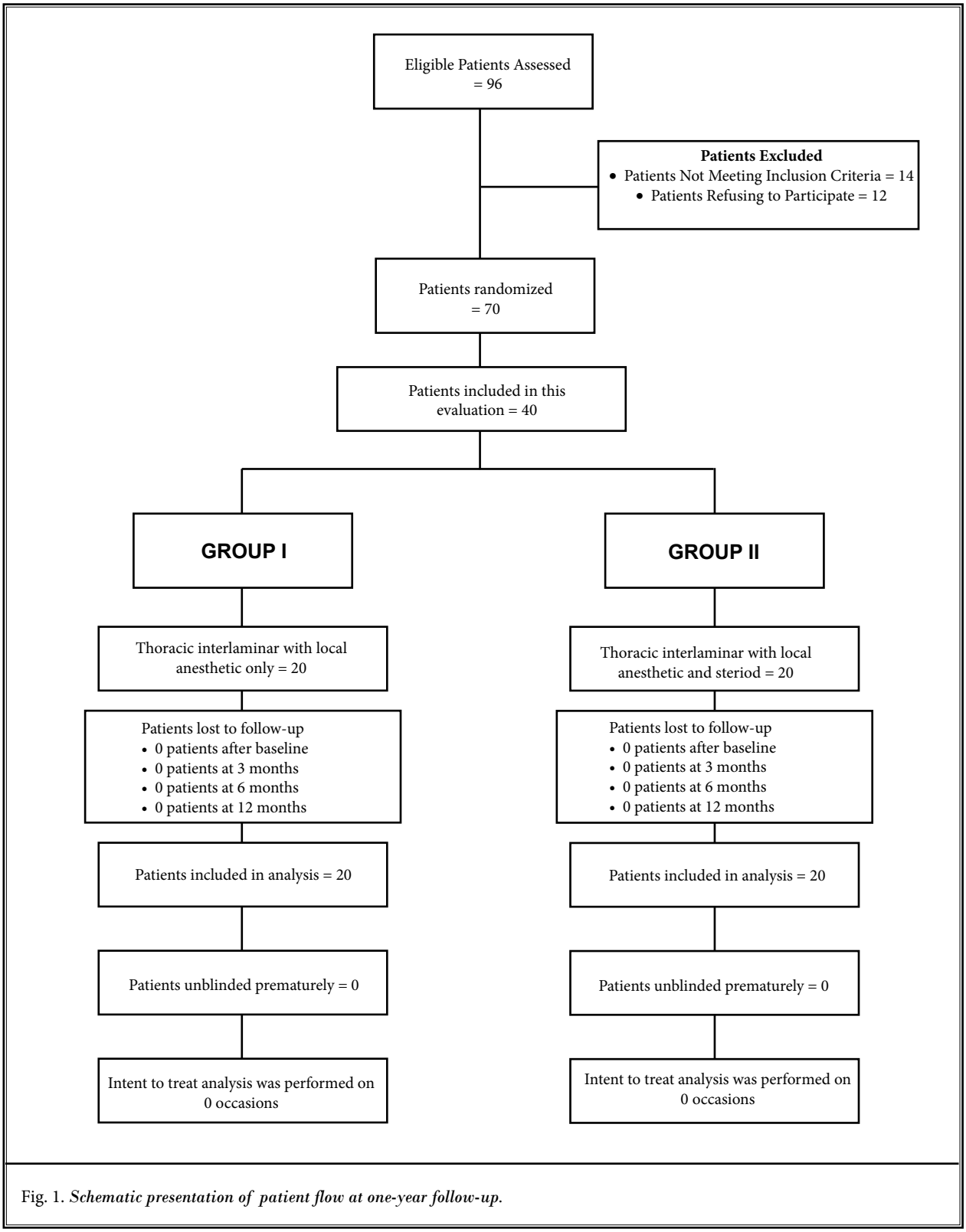

Fig. 1. *Schematic presentation of patient flow at one-year follow-up.*

Table 1. *Demographic characteristics.*

		Group I (N=20)	Group II (N=20)	*P* value
Gender	Male	30% (6)	40% (8)	0.503
	Female	70% (14)	60% (12)	
Age	Mean ± SD	40.5 ± 11.9	44.1 ± 15.3	0.405
Height (inches)	Mean ± SD	65.4 ± 3.9	67.1 ± 4.3	0.189
Weight (lbs.)	Mean ± SD	177.3 ± 37.5	172.3 ± 36.6	0.672
BMI	Mean ± SD	28.9 ± 4.7	26.8 ± 4.5	0.135
Duration of Pain (months)	Mean ± SD	113.9 ± 102.0	106.1 ± 84.1	0.793
Mode of onset of Pain	Non-Traumatic	50% (10)	65% (13)	0.337
	Traumatic	50% (10)	35% (7)	
Disc herniation		25% (5)	30% (6)	0.723
Discogenic pain		75% (15)	70% (14)	0.723

Table 2. *Pain relief characteristics.*

		Group I (N=20)	Group II (N=20)	*P* value
Average Pain Scores (Mean ± SD)	Baseline	7.9 ± 1.0	7.5 ± 0.7	0.201
	3 months	2.9* ± 1.3	3.0* ± 0.7	0.882
	6 months	3.0* ± 1.2	3.2* ± 0.8	0.640
	12 months	3.2* ± 1.0	3.3* ± 0.8	0.730

* indicates significant difference with baseline values

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

		Group I (N=20)	Group II (N=20)	*P* value
Disability Scores (Mean ± SD)	Baseline	29.0 ± 5.6	27.1 ± 5.7	0.294
	3 months	11.7* ± 4.6	12.4* ± 3.7	0.576
	6 months	12.2* ± 5.2	12.3* ± 3.8	0.945
	12 months	11.4* ± 4.1	11.9* ± 3.0	0.692

* indicates significant difference with baseline

Fig. 2 with 80% in Group I and 85% in Group II at the end of one year.

Employment Characteristics

Table 4 demonstrates employment characteristics for both groups.

Opioid Intake

Table 5 illustrates opioid intake.

Therapeutic Procedural Characteristics

Table 6 illustrates therapeutic procedural characteristics. The procedures being studied were performed at T9/10 and T10/11 50% of the time; the remaining 50% at other levels. When comparing the 2 groups, no significant difference in average overall relief per year was seen: in Group I it was 39.8 ± 8.7 weeks; in Group II it was 43.6 ± 16.3 weeks. The total number of procedures per year was 3.4 ± 0.9 in Group I and 3.5 ± 1.0 in Group II.

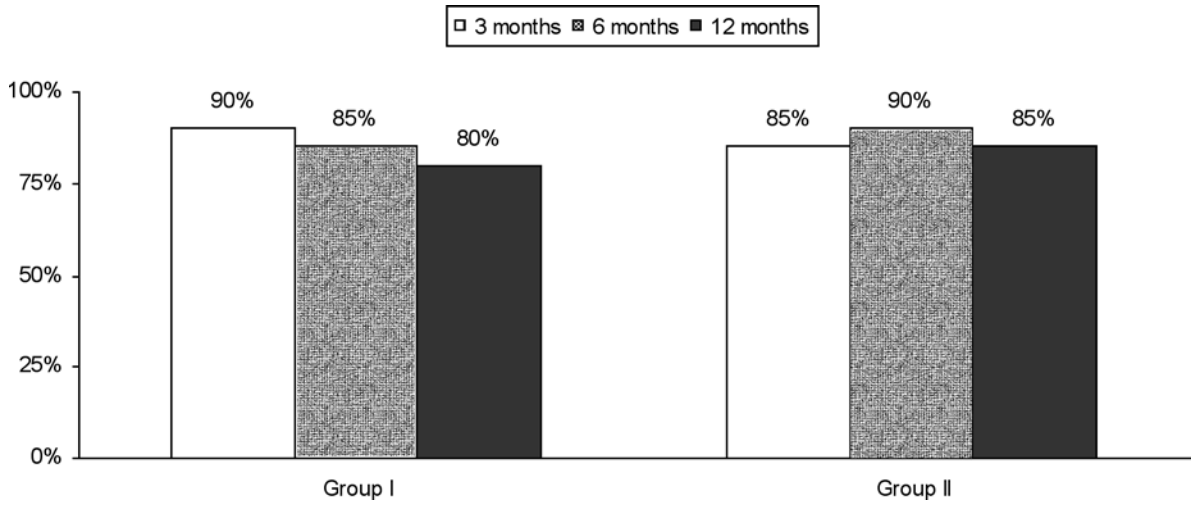

Fig. 2. *Illustration of significant pain relief (≥ 50%) and reduction (at least 50%) in Oswestry Disability Index from baseline.*

Table 4. *Employment characteristics.*

Employment status	**Group I**		**Group II**	
	Baseline	**12 months**	**Baseline**	**12 months**
Employed part-time	2	0	3	1
Employed full-time	2	6	4	7
Unemployed (due to pain)	3	3	1	0
Not working	1	1	0	0
Eligible for employment	8	8	8	8
Total Employed	4	9	7	8
Housewife	3	1	0	0
Disabled	9	9	10	10
Retired	0	0	2	2
Total Number of Patients	20	20	20	20

Table 5. *Opioid Intake (Morphine Equivalence mg)*

Opioid intake (Morphine Equivalence mg)	**Group I (20)**	**Group II (20)**	***P* value**
	Mean ± SD	**Mean ± SD**	
Baseline	60.7 ±52.8	42.2 ± 31.1	0.185
3 months	40.8# ± 39.9	33.0 ± 27.3	0.475
6 months	40.8# ± 39.9	39.0 ± 32.4	0.876
12 months	40.8# ± 39.9	40.0 ± 32.5	0.945

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

Table 6. *Therapeutic procedural characteristics with procedural frequency, average relief per procedure, and average total relief in weeks over a period of 1-year.*

	Group I (N=20)		Group II (N=20)	
Number of Procedures	**Average Relief in Weeks per Procedure**	**Average in Weeks Total Relief**	**Average Relief in Weeks per Procedure**	**Average Total Relief**
One	43 (1)	43 (1)	—	—
Two	23.5 ± 3.5 (2)	47.0 ± 7.1 (2)	21.9 ± 15.0 (5)	43.8 ± 30.0 (5)
Three	12.5 ± 3.5 (7)	37.4 ± 10.5 (7)	9.3 ± 1.7 (3)	28.0 ± 5.2 (3)
Four	9.9 ± 2.1 (9)	39.7 ± 8.5 (9)	11.5 ± 2.1 (7)	45.9 ± 8.4 (7)
Five	7.8 (1)	39 (1)	9.9 ± 0.6 (5)	49.6 ± 2.9 (5)
Average per Procedure/Total per 1 Year	13.7 ± 8.4 (20)	39.8 ± 8.7 (20)	13.4 ± 8.7 (20)	43.6 ± 16.3 (20)

Table 7. *Characteristics of changes in weight.*

Weight (lbs)	**Group I (20)**	**Group II (20)**	***P* value**
	Mean ± SD	**Mean ± SD**	
Weight at beginning	177.3 ± 37.45	172.3 ± 36.6	0.672
Weight at one year	173.7 ± 36.8	171.7 ± 37.6	0.869
Change	-3.6 ± 9.8	-0.6 ± 8.4	0.296
Lost weight	5% (1)	10% (2)	0.748
No change	60% (12)	50% (10)	
Gained weight	35% (7)	40% (8)	

Changes in Weight

Body weight changes in both groups (gain or loss) were not significant (Table 7).

Adverse Events

Of the thoracic epidural procedures performed, there were 2 subarachnoid punctures. No postoperative headache was reported. A third patient developed immediate postoperative pain and spasms, lasting for 3 hours, with no technical difficulties. A fourth patient experienced instant pain in lower extremity, resolving immediately, but returning after 6 hours, lasting for 3 months. This patient was treated with immediate intravenous Decadron (dexamethasone) 8 mg, postoperative opioids, and antiepileptics.

Discussion

This preliminary report of 40 participants shows that 80% of Group I (who received injections with local anesthetic only) and 85% of Group II (who received injections with local anesthetics and steroids) showed significant functional status improvement and pain relief ≥ 50%. In addition, no significant differences were noted over a one year period. The average procedures per year were 3-4 with an average total relief per year of 39.8 ± 8.7 weeks in Group I and 43.6 ± 16.3 weeks in Group II. Average relief per procedure was 13-14 weeks. There were changes in opioid use, only in Group I from baseline, whereas no changes were observed in opioid use in Group II, nor in employment in either group.

Significant debate exists concerning medical necessity and indications for thoracic epidural injections.

However, as shown in this preliminary report, they could provide long-term relief if patients are screened and evaluated appropriately and their application is judicious.

Of interest to clinicians is that the results of the present evaluation could be generalizable to other interventional pain management settings if the clinician uses appropriate diagnostic techniques and fluoroscopic visualization. Pragmatic or practical clinical trials that measure effectiveness, rather than explanatory trials that measure efficacy, are considered more appropriate, especially in light of today's era of evidence-based medicine (72,73,75,76,83-85). Providing results of a treatment's benefit as will be seen in routine clinical practice is the best design for practical trials (85). An active control trial such as the present one, is practical over a placebo-controlled trial because placebo-controlled trials measure absolute effect size and show the existence of effect; instead, active control trials not only show the existence of effect, they also compare therapies (86).

The present study is not immune from criticism. The lack of a placebo group and preliminary analysis with 20 patients in each group, and other variables are points to criticize. However, the current analysis of these results is justifiable since no controlled studies are available.

Even though unrealistic, the current emphasis on the necessity of placebo-controlled neural blockade is the result of misinterpretation (87,88). It has been mistakenly reported that any local anesthetic injection which yields similar results to steroids is a placebo. These interpretations are inaccurate. The difference between injections of sodium chloride solution and dextrose has been shown (89,90). The potential inaccuracy created by 0.9% sodium chloride solution versus 5% dextrose has been described (89,90). Differing effects of sodium chloride solution when injected into either the disc, the facet joint, or paraspinal muscles has been shown(91,92). Finally, multiple studies have shown the clinical effectiveness of epidural injection of sodium chloride solution (93-95).

Explanations for the effectiveness of neural blockade include the hypothesis that there is an alteration or interruption of nociceptive input such as a reflex mechanism of the afferent fibers, a self-sustaining activity of the neurons or the pattern of central neuronal activities. By inhibiting either the synthesis or release of a number of pro-inflammatory mediators and by causing a reversible local anesthetic effect, corticosteroids have been shown to reduce inflammation (53-58). On the other hand, short- to long-term symptomatic relief from local anesthetics have been described based on various mechanisms (59-64,96-98). Several studies have reported that local anesthetics might alter multiple pathophysiologic mechanisms involved in chronic pain. These include noxious peripheral stimulation, excess nociceptive process resulting in the sensitization of the pain pathways at several neuronal levels, and excess release of neurotransmitters (59-64,96-98). The effect of local anesthetics in epidural injections and facet joint nerve blocks without steroids has been demonstrated in a host of studies (19,45-52,65-70,96-98). Epidural bupivicaine's prolonged analgesic effect in neuropathic pain in a rat model was evaluated by Sato et al (63). They concluded that bupivicaine's repeated injection into the epidural space in rats exerts an analgesic effect, possibly by inducing a plastic change in nociceptive input. Nerve root infiltration in rats was shown by Tachihara et al (64) to prevent mechanical allodynia; however, using corticosteroid showed no additional benefit, suggesting that corticosteroid might be unnecessary for nerve root blocks.

Conclusion

This study, assessing the preliminary results of a randomized, double-blind, controlled trial of thoracic interlaminar epidural injections in chronic function-limiting thoracic pain, demonstrated the effectiveness in 80% of the patients receiving local anesthetic only and 85% of patients receiving local anesthetic and steroids utilizing an average of 3-4 procedures per year.

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