Randomized Trial

Thoracic Interlaminar Epidural Injections in Managing Chronic Thoracic Pain: A Randomized, Double-Blind, Controlled Trial with a 2-Year Follow-Up

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Background: Reports of prevalence of spinal pain indicate the prevalence of thoracic pain in approximately 13% of the general population compared to 32% of the population with neck pain and 43% of the population with low back pain during the past year. Even though, thoracic pain is less common than neck or low back pain, the degree of disability resulting from thoracic pain disorders seems to be similar to other painful conditions. Interventions in managing chronic thoracic pain are also less frequent, leading to the paucity of literature about various interventions in managing chronic thoracic pain.

Thoracic intervertebral discs and thoracic facet joints have been shown to be pain generators, even though thoracic radicular pain is very infrequent.

Thoracic epidural injections are one of the commonly performed procedures in managing thoracic pain. The efficacy of thoracic epidural injections has not been well studied.

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

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

Objective: The primary objective was to assess the effectiveness of thoracic interlaminar epidural injections in providing effective pain relief and improving function in patients with chronic mid and/or upper back pain.

Methods: One hundred and ten patients were randomly assigned into 2 groups with 55 patients in each group receiving either local anesthetic alone (Group I) or local anesthetic with steroids (Group II). Randomization was performed by computer-generated random allocation sequence by simple randomization.

Outcomes Assessment: Outcomes were assessed utilizing Numeric Rating Scale (NRS), the Oswestry Disability Index (ODI) 2.0, employment status, and opioid intake.

The patients experiencing greater than 3 weeks of significant improvement with the first 2 procedures were considered as successful. Others were considered as failed participants.

Significant improvement was defined as a decrease of greater than 50% NRS scores and ODI scores with measurements performed at baseline, 3, 6, 12, 18, and 24 months post treatment.

Results: Significant improvement was seen in 71% in Group I and 80% in Group II at the end of 2 years with all participants; however, improvement was seen in 80% and 86% when only successful patients were considered. Therapeutic procedural characteristics showed 5 to 6 procedures per 2 years with total average relief of 80 weeks in Group I and 78 weeks in Group II in the successful patient category; whereas, it was 71 and 72 weeks when all patients were considered.

Limitations: Limitations of this assessment include lack of a placebo group.

Conclusions: Based on the results of this trial, it is concluded that chronic thoracic pain of non-facet joint origin may be managed conservatively with thoracic interlaminar epidural injections with or without steroids.

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

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The reported prevalence of thoracic pain is approximately 13% of the general population compared to 43% of the low back pain population and 32% of the population with neck pain during the past year (1,2). In interventional pain management settings, thoracic pain has been reported at a highly variable proportion ranging from 3% to 33% of patients (3-7). Chronic pain in general and spinal pain in particular has been shown to be expensive and disabling (8-18). Similar to various other problems, a multitude of interventions are offered to manage chronic thoracic pain, including interventional techniques with facet joint interventions and epidural injections, which have been reported to be increasing at an uncontrollable pace (19-21). For all coding purposes, thoracic procedures are embedded with cervical procedures. Cervical and thoracic interlaminar epidural injections have shown an increase of 123% from 2000 to 2011 per 100,000 Medicare beneficiaries compared to 331% for sacroiliac joint interventions, 665% for lumbosacral transforaminal epidural injections, 359% for cervical/thoracic facet joint nerve blocks, and 836% for cervical/thoracic facet joint neurolysis (19). In addition, increases of surgical interventions are also smaller for the thoracic spine compared to the lumbar and cervical spine (22-28).

Epidural injections for managing chronic spinal pain, including thoracic spinal pain, are common interventions among multiple interventional techniques, surgery, physical therapy, and drug therapy (29-34). The effectiveness of thoracic interlaminar epidural injections has only been evaluated in a preliminary report of a randomized, double-blind, active-controlled trial (32) of 40 patients, which illustrated significant improvement defined as pain relief and reduction of disability by 50% from baseline. This improvement was reported in 80% of patients receiving local anesthetic only and 85% of those receiving local anesthetic with steroids.

This trial is designed to evaluate the role of thoracic interlaminar epidural injections of local anesthetics with or without steroids in patients with chronic, function-limiting, mid back and upper back pain with or without chest wall pain secondary to multiple abnormalities after excluding facet joint pain and intercostal neuritis. This report consists of the results of 110 patients at 2-year follow-up, which is a continuation of the preliminary report (32).

Methods

The study 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 randomized, double-blind, active-controlled trial of the effectiveness of thoracic interlaminar epidural injections has been conducted at a private interventional pain management practice and a specialty referral center in the United States. The trial is based on Consolidated Standards of Reporting Trials (CONSORT) guidelines (35,36).

There was no external funding used in conduct of this study.

Patients

The study patients were recruited from among new patients that presented to the interventional pain management practice. They were all provided with an IRB-approved protocol and informed consent.

Interventions

Of the 110 study patients, 55 were assigned into Group I receiving thoracic interlaminar epidural injections with local anesthetic only (lidocaine 0.5% preservative-free, 6 mL), and 55 were assigned into Group II receiving thoracic interlaminar epidural injections with 5 mL of 0.5% preservative-free lidocaine mixed with 1 mL or 6 mg of betamethasone for a total of 6 mL injectate in both groups.

Pre-enrollment Evaluation

Pre-enrollment evaluation included patient demographic data, medical and surgical history with coexisting disease(s), radiologic investigations, physical

examination, pain rating scores using the Numeric Rating Scale (NRS), work status, opioid intake, and functional assessment by Oswestry Disability Index (ODI). Information on conservative management including other types of drug therapy and exercise programs was also collected.

Inclusion Criteria

Inclusion criteria were lack of diagnosis of thoracic facet joint pain with exclusion based on results of controlled, comparative local anesthetic blocks. In addition, patients must have been of at least 18 years of age with a history of chronic function-liming mid back or upper back pain of at least 6 months duration, and having failed physician directed conservative management with drug therapy, physical therapy, structured exercise program, and other modalities. Furthermore, it was essential that patients understood the study protocol and could provide voluntary written informed consent with participation in outcome measures.

Exclusion Criteria

Exclusion criteria included facet joint pain, uncontrollable or unstable opioid use, uncontrolled psychiatric disorders, uncontrolled medical illness (acute or chronic), any condition that could interfere with the interpretation of the outcome assessments, pregnancy and lactation, and history of adverse reactions to local anesthetics or steroids. Patients with large disc herniations with symptoms of spinal cord compression or any signs of infection were also excluded.

Description of Interventions

All patients with disc herniation, radiculitis, or spinal stenosis were included in the study without any further evaluations. Other patients were assessed on 2 separate occasions with controlled comparative local anesthetic blocks (3,30,37).

Interlaminar epidural injections were performed under appropriate monitoring and sedation with sterile preparation. All patients had intravenous infusion fluids and were also sedated with midazolam and fentanyl when medically necessary. The injections were all performed in a prone position by a single physician (LM). The epidural space was accessed with an 18 gauge Tuohy needle using the loss of resistance technique with confirmation of the location of the epidural space with injection of nonionic contrast, generally 5 mL. The location of the entry of the needle into the epidural space was based on the patients' pain complaints, as well as clinical and radiologic findings. The procedures were performed either between a space below or at the level indicated by the patients' complaints and findings.

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

Co-interventions

All patients continued drug therapy with either opioids or nonopioid analgesics, therapeutic exercise program, and normal activities, including work. No specific physical therapy, occupational therapy, or other interventions were offered other than the study interventions.

Objectives

The study was designed to evaluate the effectiveness of thoracic interlaminar epidural injections with or without steroids under fluoroscopy in managing chronic mid back and/or upper back pain with or without chest wall pain secondary to various causes except for the pain originating from facet joints.

Outcomes

This trial included a number of outcome measures to be recorded at baseline, 3, 6, 12, 18, and 24 months post treatment. The primary outcome measure was combined improvement in pain scores and functional status improvement. Significant improvement was defined as at least 50% pain relief and improvement in functional status measured by NRS and ODI, a robust measure compared to traditional 20% decrease in pain services (38-40). NRS has been validated in assessing chronic pain of various origins (41). Similarly, ODI has been validated for low back pain; however, it has not been validated for thoracic pain (42-44). The patients experiencing greater than 3 weeks of significant improvement with the first 2 procedures were considered as successful. Others were considered as failed patients.

Opioid intake measurements were carried out with conversion of opioid intake to morphine equivalence (45).

For consideration of the employment, enrollees were divided into multiple groups based on their employment or unemployment status.

Sample Size

The sample size calculations were based on significant pain relief. There have not been any studies in the thoracic spine to consider for sample size calculation. Thus, 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 required (46).

Randomization

Of the 110 patients assigned to participate, 55 patients were randomly assigned into either Group I or II.

Sequence Generation

Randomization was a simple randomization from a computer-generated random allocation sequence.

Allocation Concealment

Patients were randomized into 2 groups and the drugs were prepared by the same individual from one of the 3 coordinators, but not assisting with the procedure.

Blinding and Masking

The group assignment was blinded to all involved in the care including the physician and the patients. Both solutions were clear with nonparticulate Celestone so the group assignment was unidentifiable. In addition, all the study patients were mixed with other patients receiving routine treatments in all spinal regions, and the physician performing the procedure was not informed of the nature of the patients participating in this study.

Statistical Methods

Data analyses were carried out using the Statistical Package for Social Sciences version 9.01 (SPSS Inc., Chicago,IL). For categorical and continuous data comparison, Chi-square (Fisher test where necessary)and t-test were used respectively. Because the outcome measures of the patients were measured at 6 points in time, the repeated measures analysis of variance were performed with the post hoc analysis. Univariate analyses with gender, BMI as covariates were performed on reduction in average pain scores and Functional improvements between groups. A P value was less than 0.05 was considered as statistically significant.

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

Results

Patient Flow

Patient flow is illustrated in Fig. 1. The recruitment period spanned from January 2008 to September 2010.

Baseline Data

Baseline demographic and clinical characteristics are shown in Table 1. There were significant differences noted in relation to gender, body height, and body mass index among both groups. There were more women in Group I, they were shorter than patients in Group II, and had a higher body mass index.

Pain Relief and Functional Assessment

Table 2 shows NRS pain scores and ODI disability scores.

Fig. 2 illustrates the proportion of patients with a significant reduction in the NRS and ODI with greater than 50% reduction from baseline.

Therapeutic Procedural Characteristics

Therapeutic procedural characteristics are shown in Table 3. Epidural entry was at T9-10 and T10-11 in 30% and 31% of the patients respectively. Epidural entry was at T8-9 in 17% of the patients and T7-8 in 12% of the patients. All other levels were 6% or less.

Patients experiencing at least 3 weeks of significant improvement with the first 2 procedures were considered as successful.

Average relief per year showed significant improvement with 13 weeks in Group I and Group II.

The average number of procedures for 2 years was 5 to 6; whereas they were 3 to 4 for one year. The total relief for 2 years was approximately 80 weeks in the successful patient group and 72 weeks in all patients out of 104 weeks.

Covariates of Gender and BMI

Univariate analyses with gender and BMI as a covariate revealed no significant differences in Average pain scores and ODI scores between Group I and Group II.

Employment Characteristics

The employment characteristics, showed nonsignificant improvement in both groups with number of employed increasing from 22 at baseline to 33 at 24 months among 35 eligible for employment.

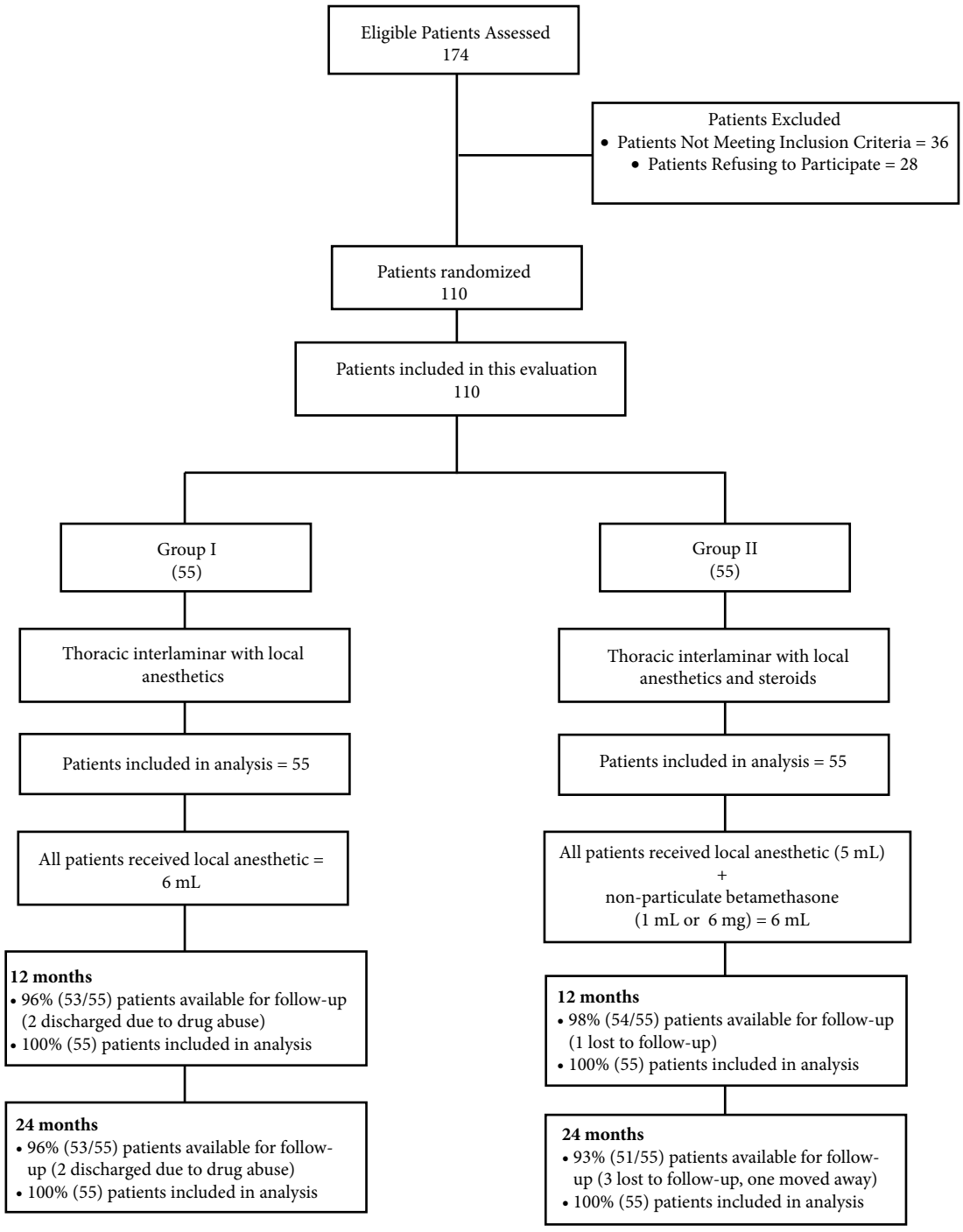

Fig. 1. *Schematic presentation of patient flow at 2-year follow-up.*

Table 1. *Baseline demographic characteristics.*

		Group 1 (55)	Group II (55)	*P* value
Gender	Men	14% (8)	44% (24)	0.001
	Women	86% (47)	56% (31)	
Age	Mean ± SD	42.8 ± 13.7	40.8 ± 13.1	0.432
Weight	Mean ± SD	174.9 ± 42.8	168.0 ± 39.1	0.380
Height	Mean ± SD	64.9 ± 3.1	66.9 ± 4.3	0.005
Body Mass Index	Mean ± SD	29.1 + 6.3	26.1 + 4.3	0.004
Duration of Pain (months)	Mean ± SD	103 ± 90.7	91 ± 85.7	0.464
Onset of the Pain	Gradual	62% (34)	67% (37)	0.690
	Injury	48% (21)	33% (18)	
Mid Back Pain Distribution	Bilateral	71% (39)	82% (45)	0.178
	Left or Right	29% (16)	18% (10)	
Numeric Rating Score (NRS)	Mean ± SD	7.9 ± 0.8	7.7 ± 0.6	0.367
Oswestry Disability Index (ODI)	Mean ± SD	29.5 ± 5.1	29.5 ± 8.0	0.989
Diagnosis				
Disc herniation		20% (11)	40% (22)	0.0378
Discogenic pain, stenosis, etc.		80% (44)	60% (33)	0.0378

Table 2. *Comparison of Numeric Pain Rating Scale and Oswestry Disability Index score for 2 years.*

Time Points	Numeric Pain Rating scale		Oswestry Disability Index	
	Group I (55)	Group II (55)	Group I (55)	Group II (55)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Baseline	7.9 ± 0.8	7.7 ± 0.6	29.5 ± 5.1	29.5 ± 8.0
3 months	3.4* ± 1.4 (78%)	3.4* ± 1.3 (87%)	14.0* ± 5.6 (80%)	14.8* ± 7.7 (82%)
6 months	3.5* ± 1.4 (76%)	3.4* ± 1.1 (86%)	14.3* ± 6.2 (75%)	14.1* ± 6.3 (86%)
12 months	3.5* ± 1.3 (73%)	3.3* ± 1.1 (84%)	14.0* ± 5.9 (73%)	13.2* ± 5.8 (86%)
18 months	3.3* ± 1.1 (80%)	3.2* ± 1.1 (87%)	13.5* ± 5.9 (82%)	12.7* ± 5.8 (87%)
24 months	3.6* ± 1.3 (73%)	3.3* ± 1.3 (80%)	13.8* ± 5.7 (76%)	12.5* ± 5.9 (85%)
Group Difference	0.804		0.203	
Time Difference	0.001		0.001	
Group by Time Interaction	0.440		0.716	

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

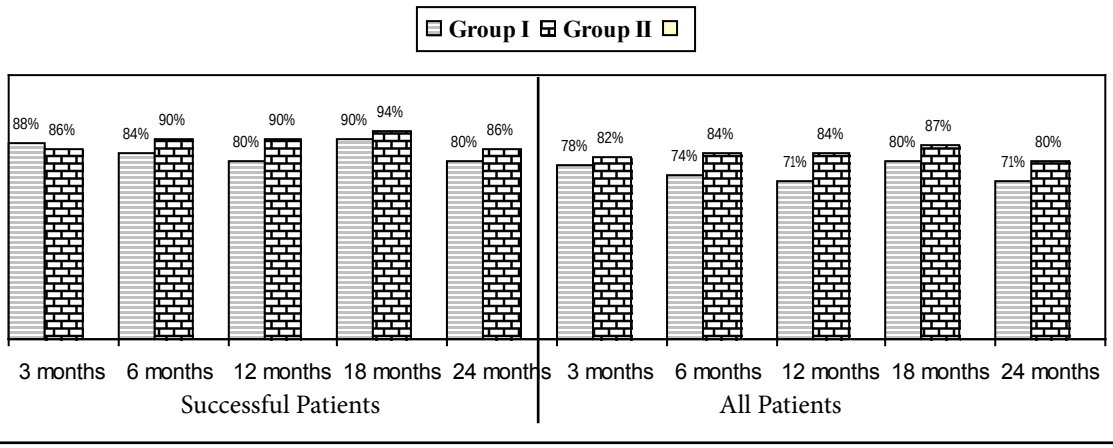

Fig. 2. *Illustration of reduction (at least 50%) in pain and Oswestry Disability Index from baseline.*

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

	Successful Patients		Failed Patients		All Patients	
	Group I (49)	Group II (51)	Group I (6)	Group II (4)	Group I (55)	Group II (55)
At one year						
Average number of procedures per one year	3.5 ± 1.0	3.7 ± 1.1	1.8 ± 0.4	2.3 ± 1.3	3.3 ± 1.1	3.6 ± 1.2
Total number of procedures in one year	171	189	11	9	182	198
Total relief per one year (weeks)	41.2 ± 11.6	43.6 ± 12.3	1.5 ± 1.8	2.3 ± 2.6	36.9 ± 16.6	40.6 ± 16.1
At 2 years						
Average number of procedures per 2 years	6.0 ± 2.2	5.8 ± 2.4	1.8 ± 0.4	2.3 ± 1.3	5.5 ± 2.5	5.5 ± 2.5
Total number of injections in 2 years	292	294	11	9	303	303
Total relief per 2 years (weeks)	79.9 ± 25.0	77.8 ± 26.4	1.5 ± 1.8	2.3 ± 2.6	71.3 ± 34.1	72.3 ± 32.2
Average relief per procedure						
For initial 2 procedures in weeks	10.9 ± 10.7	12.0 ± 15.5	0.8 ± 1.2	1.0 ± 1.2	9.9 ± 10.6	11.3 ± 15.2
After initial 2 procedures	15.0 ± 9.2	14.4 ± 6.3	-	1.0 ± 0.0	15.0 ± 9.2	14.2 ± 6.4
All procedures	13.6 ± 9.9	13.6 ± 10.5	0.8 ± 1.2	1.0 ± 1.0	13.2 ± 10.0	13.2 ± 10.5

Successful patients: At least 3 weeks of significant improvement with first 2 injections

Opioid Intake

Opioid intake is shown in Table 4. There was a significant decrease from baseline to all follow-up periods and at 2 years. There were also significant differences between Group I and II at 18 month follow-up.

Changes in Weight

There was no significant weight gain at one year or 2 years with 42% in Group I and 33% in Group II gaining weight at the end of 2 years.

Adverse Events

Of the 606 thoracic interlaminar epidural procedures performed, there were 2 subarachnoid punctures. No postoperative headache was reported. One patient developed immediate postoperative pain and spasms, lasting for 3 hours, with no technical difficulties. Another patient experienced transient pain in the lower extremity, returning after 6 hours, lasting for 3 months.

Table 4. *Opioid intake (morphine equivalents in mg).*

Time	Group I (55)	Group II (55)
	Mean ± SD	Mean ± SD
Baseline	105.7 ± 145.9	103.4 ± 153.3
3 months	63.4* ± 66.7	57.0* ± 101.5
6 months	59.6* ± 64.6	45.8* ± 36.7
12 months	59.1* ± 64.7	40.4* ± 29.9
18 months	59.3* ± 65.2	38.9*#± 29.0
24 months	55.7* ± 62.7	38.2* ± 29.5
Group Difference	0.809	
Time Difference	0.001	
Group by Time Interaction	0.276	

* indicates significant difference from their baseline values ($P < 0.05$).
\# indicates significant difference with Group I at 18 months ($P < 0.05$).

Discussion

This trial of thoracic interlaminar epidural injections with 110 patients with 55 patients in each group with local anesthetic with or without steroids is the first of its nature in the literature with a randomized, double-blind, active control design. The procedures were performed under fluoroscopy. The results showed significant improvement in 71% of the patients in the local anesthetic group and 80% of the patients in the local anesthetic with steroids group. Significant improvement was defined with robust outcome measures utilizing at least 50% pain relief and 50% improvement in functional status as measured by NRS and ODI, in contrast to previous measures of 30% improvement. Furthermore, in patients who were defined as successful, based on the response to the first 2 initial procedures with at least 3 weeks of improvement, significant improvement was seen in 80% in Group I and 86% in Group II at 2-year follow-up. This trial is the first performed appropriately in a contemporary interventional pain management setting with fluoroscopy with long-term follow-up of 2 years. In addition, this trial also showed overall average procedures per 2 years of 5 – 6, with an average total relief per 2 years of 71.3 ± 34.1 weeks for Group I patients and 72.3 ± 32.2 weeks for Group II patients from a total of 104 weeks. As expected, the average total relief was higher in the successful group compared to assessment of all the patients (79.9 ± 25.0 versus 77.8 ± 26.4 weeks). Opioid intake was also significantly reduced in both groups from baseline.

The results of this assessment are similar to previous evaluations assessing cervical and lumbar epidural injections with similar protocols and utilizing either interlaminar or caudal approaches in disc herniation, spinal stenosis, discogenic pain without facet joint pain, and post surgery syndrome (47-59). However, overall, there has been significant debate in reference to the effectiveness of epidural injections in managing spinal pain (30,60-67). The results of this trial may assist in managing thoracic pain considering that it is difficult to manage thoracic pain with surgical interventions. Further, despite extensive use of epidural injections in managing various types of spinal pain, the underlying mechanism of action of epidural administered local anesthetics and steroids continues to be unclear (68-77). Multiple hypotheses have been developed to explain the various mechanisms of local anesthetics and steroids (68-77). The recent synthesis of literature shows that nonsteroidal solutions may be as effective as steroids (63).

The strengths of this trial include its comparative evaluation which has become pivotal in modern evidence-based medicine (78-81). The study provided insight into not only the effectiveness of local anesthetic with or without steroids, but also into successful and failed groups based on the first 2 procedures. Overall the study has shown no significant difference whether steroids were used or not. The trial was conducted in a contemporary interventional pain management setting utilizing fluoroscopy and repeating the procedures when the improvement deteriorated below 50%. 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 clinical and practical outcomes.

Limitations

The limitations include the lack of a placebo group. However, the design of the study with an appropriate placebo has been discussed widely with enormous placebo effects, specifically when impure placebos are utilized, or inactive solutions are injected into active structures (30,82-89). Consequently, even local anesthetic injection has been interpreted as placebo in the past (61,62). The effects of placebo, nocebo, Hawthorne effect, natural course of the disease, (even though not applicable to these chronic pain patients), and regression to mean have been extensively discussed in reference to placebo, nocebo, and pure, impure, and fake placebos (82-84). While appropriate placebo design is difficult in interventional pain management settings, 2 such studies have been performed with proper placebo

design by Ghahreman et al (90) and Gerdesmeyer et al (91). These trials essentially showed when proper placebo design is achieved with injection of an inactive solution into inactive structure, it is not only considered as true placebo, but the results are strikingly effective in the treatment groups.

Another limitation of this assessment is the time invested in recruiting the patients due to thoracic pain and combination of a multitude of thoracic conditions except for facet joint pain into one group, rather than studying only disc herniation, discogenic pain, spinal stenosis, or post surgery syndrome. Finally, the differences in baseline characteristics with height and body mass index may not be significant in outcomes assessment. Despite appropriate randomization, the significant differences were noted. Thus, randomization may not be a foolproof process to have similar baseline characteristics in both groups (6). Further analysis showed lack of influce of BMI, age and gender on outcomes.

Based on previous cost utility analysis, thoracic epidural injections may be cost effective at less than $3,000 per quality-adjusted life year (92).

In summary, this randomized active controlled trial has shown the effectiveness of thoracic epidural injections with or without steroids which was sustained for 2 years with repeat injection therapy administered as medically necessary.

Conclusions

In conclusion, this large randomized, double-blind, active-control trial of the effectiveness of thoracic epidural injections with local anesthetic with or without steroids for chronic thoracic pain secondary to various ailments, except for facet joint pain, showed effectiveness in 80% of patients in the local anesthetic group and 86% in the steroid group, with improvement in pain and functional status in the successful groups, requiring an average of 5 to 6 procedures providing approximately 80 weeks of relief over a 2 year period.

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References

1. Leboeuf-Yde C, Fejer R, Nielsen J, Kyvik KO, Hartvigsen J. Pain in the three spinal regions: The same disorder? Data from a population-based sample of 34,902 Danish adults. *Chiropr Man Therap* 2012; 20:11.
2. Leboeuf-Yde C, Nielsen J, Kyvik KO, Fejer R, Hartvigsen J. Pain in the lumbar, thoracic or cervical regions: Do age or gender matter? A population-based study of 34,902 Danish twins 20–71 years of age. *BMC Musculoskeletal Disorders* 2009; 10:39.
3. 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.
4. Manchikanti L, Cash KA, Malla Y, Pampati V, Fellows B. A prospective evaluation of psychotherapeutic and illicit drug use in patients presenting with chronic pain at the time of initial evaluation. *Pain Physician* 2013; 16:E1-E13.
5. Manchikanti L, Pampati V, Fellows B, Beyer CD, Damron KS, Barnhill RC, Burks T. Characteristics of chronic low back pain in patients in an interventional pain management setting: A prospective evaluation. *Pain Physician* 2001; 4:131-142.
6. Manchikanti L, Pampati VS. Research designs in interventional pain management: Is randomization superior, desirable or essential? *Pain Physician* 2002; 5:275-284.
7. Stolker RJ, Vervest AC, Groen GJ. Percutaneous facet denervation in chronic thoracic spinal pain. *Acta Neurochir* 1993; 122:82-90.
8. Martin BI, Deyo RA, Mirza SK, Turner JA, Comstock BA, Hollingworth W, Sullivan SD. Expenditures and health status among adults with back and neck problems. *JAMA* 2008; 299:656-664. Erratum in: *JAMA* 2008; 299:2630.
9. Martin BI, Turner JA, Mirza SK, Lee MJ, Comstock BA, Deyo RA. Trends in health care expenditures, utilization, and health status among US adults with spine problems, 1997-2006. *Spine (Phila Pa 1976)* 2009; 34:2077-2084.
10. US Burden of Disease Collaborators. The state of US health, 1999-2010: Burden of diseases, injuries, and risk factors. *JAMA* 2013; 310:591-608.
11. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724.
12. Institute of Medicine (IOM). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. The National Academies Press, Washington, DC, June 29, 2011.
13. Hoy DG, Bain C, Williams G, March L, Brooks P, Blyth F, Woolf A, Vos T, Buchbinder R. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012; 64:2028-2037.
14. Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. *Best Pract Res Clin Rheumatol* 2010; 24:769-781.
15. Hoy DG, Protani M, De R, Buchbinder R. The epidemiology of neck pain. *Best Pract Res Clin Rheumatol* 2010; 24:783-792.
16. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.
17. Bressler HB, Keyes WJ, Rochon PA, Badley E. The prevalence of low back pain in the elderly. A systematic review of the literature. *Spine (Phila Pa 1976)* 1999; 24:1813-1819.

18. Cassidy JD, Carroll LJ, Côté P. The Saskatchewan Health and Back Pain Survey. The prevalence of low back pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1860-1867.
19. Manchikanti L, Helm II S, Singh V, Hirsch JA. Accountable interventional pain management: A collaboration among practitioners, patients, payers, and government. *Pain Physician* 2013; 16:E635-E670.
20. Manchikanti L, Pampati V, Falco FJE, Hirsch JA. Growth of spinal interventional pain management techniques: Analysis of utilization trends and Medicare expenditures 2000 to 2008. *Spine (Phila Pa 1976)* 2013; 38:157-168.
21. Abbott ZI, Nair KV, Allen RR, Akuthota VR. Utilization characteristics of spinal interventions. *Spine J* 2012; 1:35-43.
22. Oppenlander ME, Clark JC, Kalyvas J, Dickman CA. Surgical management and clinical outcomes of multiple-level symptomatic herniated thoracic discs. *J Neurosurg Spine* 2013; 19:774-783.
23. Patil PG, Turner DA, Pietrobon R. National trends in surgical procedures for degenerative cervical spine disease: 1990-2000. *Neurosurgery* 2005; 57:753-758.
24. Nacar OA, Ulu MO, Pekmezci M, Deviren V. Surgical treatment of thoracic disc disease via minimally invasive lateral transthoracic trans/retropleural approach: analysis of 33 patients. *Neurosurg Rev* 2013; 36:455-465.
25. Yoshihara H. Surgical Treatment for Thoracic Disc Herniation: An Update. Spine (Phila Pa 1976). 2013 Dec 20. [Epub ahead of print]
26. Nandyala SV, Marquez-Lara A, Fineberg SJ, Singh K. Epidemiological Trends in the Utilization of Bone Morphogenetic Protein in Spinal Fusions From 2002-2011. Spine (Phila Pa 1976). 2013 Dec 20. [Epub ahead of print]
27. Zhang, HQ, Lin MZ, Shen KY, Ge L, Li JS, Tang MX, Wu JH, Liu JY. Surgical management for multilevel noncontiguous thoracic spinal tuberculosis by single-stage posterior transforaminal thoracic debridement, limited decompression, interbody fusion, and posterior instrumentation (modified TTIF). *Arch Orthop Trauma Surg* 2012; 132:751-757.
28. Zhang P, Shen Y, Ding WY, Zhang W, Shang Z. The role of surgical timing in the treatment of thoracic and lumbar spinal tuberculosis. *Arch Orthop Trauma Surg* 2014; 134:167-172.
29. Benyamin RM, Wang VC, Vallejo R, Singh V, Helm II S. A systematic evaluation of thoracic interlaminar epidural injections. *Pain Physician* 2012; 15:E497-E514.
30. Manchikanti L, Abdi S, Atluri S, Benyamin RM, Boswell MV, Buenaventura RM, Bryce DA, Burks PA, Caraway DL, Calodney AK, Cash KA, Christo PJ, Cohen SP, Colson J, Conn A, Cordner HJ, Coubarous S, Datta S, Deer TR, Diwan SA, Falco FJE, Fellows B, Geffert SC, Grider JS, Gupta S, Hameed H, Hameed M, Hansen H, Helm II S, Janata JW, Justiz R, Kaye AD, Lee M, Manchikanti KN, McManus CD, Onyewu O, Parr AT, Patel VB, Racz GB, Sehgal N, Sharma M, Simopoulos TT, Singh V, Smith HS, Snook LT, Swicegood J, Vallejo R, Ward SP, Wargo BW, Zhu J, Hirsch JA. An update of comprehensive evidence-based guidelines for interventional techniques of chronic spinal pain: Part II: Guidance and recommendations. *Pain Physician* 2013; 16:S49-S283.
31. Manchikanti L, Benyamin RM, Swicegood JR, Falco FJE, Datta S, Pampati V, Fellows B, Hirsch JA. Assessment of practice patterns of perioperative management of antiplatelet and anticoagulant therapy in interventional pain management. *Pain Physician* 2012; 15:E955-E968.
32. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A preliminary report of a randomized double-blind, active controlled trial of fluoroscopic thoracic interlaminar epidural injections in managing chronic thoracic pain. *Pain Physician* 2010; 13:E357-E369.
33. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V, Fellows B. The role of thoracic medial branch blocks in managing chronic mid and upper back pain: A randomized, double-blind, active-control trial with a 2-year follow-up. *Anesthesiol Res Pract* 2012; 2012:585806.
34. Manchikanti L, Hirsch JA. Lessons learned in the abuse of pain relief medication: A focus on health care costs. *Expert Rev Neurother* 2013; 13:527-544.
35. 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.
36. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c869.
37. Atluri S, Singh V, Datta S, Geffert S, Sehgal N, Falco FJE. Diagnostic accuracy of thoracic facet joint nerve blocks: An update of the assessment of evidence. *Pain Physician* 2012; 15:E483-E496.
38. Gatchel RJ, Mayer TG, Choi Y, Chou R. Validation of a consensus-based minimal clinically important difference (MCID) threshold using an objective functional external anchor. *Spine J* 2013; 13:889-893.
39. Carragee EJ. The rise and fall of the "minimum clinically important difference." *Spine J* 2010; 10:283-284.
40. Carragee EJ, Chen I. Minimum acceptable outcomes after lumbar spinal fusion. *Spine J* 2010; 10:313-320.
41. National Institutes of Health. Warren Grant Magnuson Clinical Center. Pain Intensity Instruments, Numeric Rating Scale, July 2003. www.mvltca.net/Presentations/mvltca.pdf
42. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)* 2000; 25:2940- 2952.
43. Mousavi SJ, Parnianpour M, Mehdian H, Montazeri A, Mobini B. The Oswestry Disability Index, the Roland-Morris Disability Questionnaire, and the Quebec Back Pain Disability Scale: Translation and validation studies of the Iranian versions. *Spine (Phila Pa 1976)* 2006; 31:E454-E459.
44. Marin TJ, Furlan AD, Bombardier C, van Tulder M; Editorial Board of the Cochrane Back Review Group. Fifteen years of the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2013; 38:2057-2063.
45. 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, Global-RPh Inc. www.globalrph.com/narcotic.cgi
46. 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. *Designing Clinical Research: An Epidemiologic Approach*. 2nd ed. Lippincott, Williams & Wilkins, Philadelphia, 2001, pp 65-84.
47. Manchikanti L, Cash KA, McManus CD, Pampati V. Fluoroscopic caudal epidur-

al injections in managing chronic axial low back pain without disc herniation, radiculitis or facet joint pain. *J Pain Res* 2012;5:381-390.

48. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. Effect of fluoroscopically guided caudal epidural steroid or local anesthetic injections in the treatment of lumbar disc herniation and radiculitis: A randomized, controlled, double blind trial with a two-year follow-up. *Pain Physician* 2012; 15:273-286.
49. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. Results of 2-year follow-up of a randomized, double-blind, controlled trial of fluoroscopic caudal epidural injections in central spinal stenosis. *Pain Physician* 2012; 15:371-384.
50. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. A randomized, controlled, double-blind trial of fluoroscopic caudal epidural injections in the treatment of lumbar disc herniation and radiculitis. *Spine (Phila Pa 1976)* 2011; 36:1897-1905.
51. Manchikanti L, Cash RA, McManus CD, Pampati V, Fellows B. Fluoroscopic caudal epidural injections with or without steroids in managing pain of lumbar spinal stenosis: One year results of randomized, double-blind, active-controlled trial. *J Spinal Disord Tech* 2012; 25:226-234.
52. Manchikanti L, Cash KA, Pampati V, Malla Y. Fluoroscopic cervical epidural injections in chronic axial or disc-related neck pain without disc herniation, facet joint pain, or radiculitis. *J Pain Res* 2012; 5:227-236.
53. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. 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. *Pain Physician* 2013; 16:465-478.
54. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic epidural injections in cervical spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:E59-E70.
55. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical post-surgery syndrome: Preliminary results of a randomized, double-blind active control trial. *Pain Physician* 2012; 15:13-26.
56. Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJE. The role of fluoroscopic interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind trial. *Pain Pract* 2013; 13:547-558.
57. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A randomized, double-blind, active-controlled trial of fluoroscopic lumbar interlaminar epidural injections in chronic axial or discogenic low back pain: Results of a 2-year follow-up. *Pain Physician* 2013; 16:E491-504.
58. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJE. Lumbar interlaminar epidural injections in central spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:51-63.
59. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJE. A randomized, double-blind controlled trial of lumbar interlaminar epidural injections in central spinal stenosis: 2-year follow-up. *Int J Phys Med Rehab* 2014; in press.
60. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: A comprehensive, evidence-based review. *Reg Anesth Pain Med* 2013;38:175-200.
61. Pinto RZ, Maher CG, Ferreira ML, Hancock M, Oliveira VC, McLachlan AJ, Koes B, Ferreira PH. Epidural corticosteroid injections in the management of sciatica: A systematic review and meta-analysis. *Ann Intern Med* 2012; 157:865-877.
62. Chou R, Huffman L. *Guideline for the Evaluation and Management of Low Back Pain: Evidence Review*. American Pain Society, Glenview, IL, 2009.

    www.americanpainsociety.org/uploads/pdfs/LBPEvidRev.pdf
63. Bicket M, Gupta A, Brown CH, Cohen SP. Epidural injections for spinal pain: A systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. *Anesthesiology* 2013; 119:907-931.
64. Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low back pain: An updated Cochrane review. *Spine (Phila Pa 1976)* 2009; 34:49-59.
65. American College of Occupational and Environmental Medicine (ACOEM) Chronic Pain. In *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery of Workers*, Second Edition. American College of Occupational and Environmental Medicine Press, Elk Grove Village, 2008.
66. Dennison PL, Kennedy CW. *Official Disability Guidelines*. 16th ed. Work Loss Data Institute, Encinitas, 2011.
67. Manchikanti L, Benyamin RM, Falco FJ, Kaye AD, Hirsch JA. Do epidural injections provide short- and long-term relief for lumbar disc herniation? A systematic review. *Clin Orthop Relat Res* 2014 Feb 11. [Epub ahead of print].
68. 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.
69. 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.
70. 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.
71. 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.
72. He L, Uçeyler N, Krämer HH, Colaço MN, Lu B, Birklein F, Sommer C. Methylprednisolone prevents nerve injury-induced hyperalgesia in neprilysin knockout mice. *Pain* 2014; 155:574-580.
73. 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.
74. 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 experience study in the rabbit. *Spine (Phila Pa 1976)* 1998; 23:870-876.
75. Hollmann MW, Durieux M. Local anesthetics and the inflammatory response. *Anesthesiology* 2000; 93: 858-875.
76. Lavoie PA, Khazen T, Filion PR. Mecha-

nisms of the inhibition of fast axonal transport by local anesthetics. *Neuropharmacol* 1989; 28:175-181.

77. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiol Scand* 2006; 50:265-282.
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. 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.
80. Manchikanti L, Helm II S, Hirsch JA. The evolution of the Patient-Centered Outcome Research Institute. *J Neurointervent Surg* 2012; 4:157-162.
81. Hirsch JA, Turk AS, Mocco J, Fiorella DA, Jayaraman MV, Meyers PM, Yoo AJ, Manchikanti L. Evidence-based clinical practice for the neurointerventionalist. *J Neurointerv Surg* 2014 Feb 27. [Epub ahead of print]
82. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010; 1:CD003974.
83. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AJ. Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS One* 2010; 5:e15591.
84. Howick J, Bishop FL, Heneghan C, Wolstenholme J, Stevens S, Hobbs FD, Lewith G. Placebo use in the United Kingdom: Results from a national survey of primary care practitioners. *PLoS One* 2013; 8:e58247.
85. Carette S, Leclaire R, Marcoux S, Morin F, Blaise GA, St-Pierre A, Truchon R, Parent F, Levesque J, Bergeron V, Montminy P, Blanchette C. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997; 336:1634-1640.
86. Iversen T, Solberg TK, Romner B, Wilsgaard T, Twisk J, Anke A, Nygaard O, Hasvold T, Ingebrigtsen T. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: Multicentre, blinded, randomised controlled trial. *BMJ* 2011; 343:d5278.
87. 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.
88. 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.
89. 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.
90. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010; 11:1149-1168.
91. Gerdesmeyer L, Wagenpfeil S, Birkenmaier C, Veihelmann A, Hauschild M, Wagner K, Al Muderis M, Gollwitzer H, Diehl P, Toepfer A. Percutaneous epidural lysis of adhesions in chronic lumbar radicular pain: A randomized double-blind placebo controlled trial. *Pain Physician* 2013; 16:185-196.
92. Manchikanti L, Falco FJE, Pampati V, Cash KA, Benyamin RM, Hirsch JA. Cost utility analysis of caudal epidural injections in the treatment of lumbar disc herniation, central spinal stenosis, post lumbar surgery syndrome, and axial or discogenic low back pain. *Pain Physician* 2013; 16:E129-E143.