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Randomized Trial

Transforaminal Hypertonic Saline for the Treatment of Lumbar Lateral Canal Stenosis: A Double-Blinded, Randomized, Active-Control Trial

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Background: Degenerative lumbar spinal stenosis is one of the most common causes of chronic lower back pain and radiculopathy. Spinal stenosis is anatomically classified as central and lateral spinal canal stenosis. Many treatment modalities and techniques, including surgery and epidural injection, have been used to manage the pain. However, the effect of hypertonic saline injection via the transforaminal approach has not yet been studied.

Objectives: The aim of this study is to determine the effect of adding hypertonic saline to conventional transforaminal epidural steroid injections (TFEI) to provide pain relief for chronic radiculopathy patients secondary to lateral canal spinal stenosis.

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

Setting: An interventional pain management practice in a hospital, Republic of Korea.

Methods: Two groups: the hypertonic group received hypertonic saline combined with triamcinolone and the control group received normal saline combined with triamcinolone. A total of 68 patients were randomly allocated into either 2 groups by a computer-generated randomization program. Twenty-seven patients in the hypertonic group and 26 patients in the control group were assessed. A total of 53 patients were included in this analysis. Outcome measures were taken at baseline, one, 2, 3, 4, and 6 months post-procedure. The primary outcome measures included the numerical rating scale (NRS) and the proportion of substantial responders. The secondary outcome measures included the Oswestry disability index (ODI), the proportion of substantial and moderate responders, and patient satisfaction.

Results: Transforaminal epidural injection of steroids, with or without the addition of 10% hypertonic saline, was effective and provided significant pain relief with the improvement of functional outcome within 4 months. The addition of hypertonic saline was superior in efficacy compared with conventional TFEI at 3 months follow-up. The differences in the absolute pain scores did not demonstrate statistical significance between the 2 groups. The reduction in pain intensity from the baseline was greater in the hypertonic group and demonstrated higher rates of satisfaction. The use of hypertonic saline also extended the duration of significant pain relief to 6 months compared with baseline.

Limitations: The lack of placebo group and small sample size.

Conclusion: Superior short-term pain relieving efficacy, but limited long-term effects of hypertonic saline, when added to TFEIs.

Key words: Chronic pain, lumbar radiculopathy, lateral canal, spinal stenosis, transforaminal, epidural steroid injections, hypertonic saline, local anesthetic

Clinical trial: KCT0000500

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Degenerative lumbar spinal stenosis is one of the most common causes of chronic lower back pain and radiculopathy in individuals of advanced age (1). It was first described in 1954 by Henk Verbiest as radicular syndrome due to the narrowing of the vertebral canal (2). Over 30% of people ≥ 65 years report the symptoms of lower back pain, and symptomatic spinal stenosis presents in approximately 1.7 – 8.4% of the population (3-5). Symptomatic spinal stenosis is also one of the most common reasons for patient ≥ 65 years to receive back surgery (1,6-9).

Spinal stenosis is anatomically classified as central and lateral spinal canal stenosis (10,11). The lateral spinal canal is subdivided into the lateral recess (or entrance zone), the mid-zone, and the exit zone (12). Lateral spinal canal stenosis is a common cause of chronic lumbar radicular symptoms, with an incidence of 8 – 11% among symptomatic patients (13,14). Conservative management is the initial treatment for chronic lumbar radicular pain, which includes exercises, oral medications, physiotherapy, and epidural injections (15). When conservative treatments fail, decompressive surgery is usually recommended. However, older individuals with various comorbidities are not always surgical candidates due to their limited physical status and controversies regarding efficacy (9,16,17).

Epidural steroid injections (ESI) are used to treat chronic lumbar radiculopathy including spinal stenosis and this practice has improved since the introduction of fluoroscopic guidance (18). Various ESI techniques, including caudal, interlaminar, and transforaminal epidural steroid injections (TFEI), have been studied. However data on the benefits of epidural steroid injections for the treatment of chronic lower back pain and radiculopathy are conflicting, and most studies report short-term benefit, with limited evidence of mid and long-term efficacy (19-26). There is some evidence that TFEIs are superior to interlaminar epidural injections (27,28), and percutaneous adhesiolysis has been shown to be effective for the management of chronic lower back pain and spinal stenosis (29-32).

An experimental animal study and several cadaveric studies have demonstrated that formation of epidural adhesion and fibrosis in the spinal canal is possible without a history of prior surgical interventions (33-35). Adhesiolysis can be used to eliminate adhesion and fibrosis and deliver injected agents to the targeted areas, and hypertonic saline (hyperosmolar sodium chloride) is frequently used as an adjuvant for adhesiolysis, but the effects of administering hypertonic saline remain unclear (29,31,32,36,37). In the present double-blinded, randomized controlled study, we examine the effect of adding hypertonic saline to transforaminal epidural steroid injections for the treatment of symptomatic lateral canal spinal stenosis.

Methods

Participants

This study was conducted at the Pain Clinic of the Asan Medical Center in Seoul, Republic of Korea. Permission to conduct this study was granted by the Institutional Review Board of the Asan Medical Center (AMC IRB), and written informed consent was received from each patient who participated in this study. This study is registered in the Clinical Research Information Service (cris.cdc.go.kr/KCT0000500).

Between January 2011 and January 2012, 259 patients with unilateral radiculopathy were screened for eligibility in this randomized, double-blinded, active-control study. Because our institution is currently the largest hospital in Korea and functions as a third-line referral center, most of the patients were referred from specialists in other medical fields, including orthopedics, neurosurgery, rehabilitation medicine, neurology, and rheumatology.

The inclusion criteria included age ≥ 20 years, chronic lumbosacral radiculopathy secondary to spinal stenosis lasting ≥ 12 weeks, dominant leg pain with less severe back pain, unilateral leg pain with the symptoms restricted to one-level of dermatome, and the previous failure of conservative management including physiotherapy, exercise therapy, analgesic medication and acupuncture. Epidural injections administered earlier than 12 weeks prior to recruitment were permitted because most of the patients visiting our institute had a history of interlaminar or transforaminal injections. Magnetic resonance imaging (MRI) was performed on all participants, and experienced board-certified radiologists unaware of the study at our institute assessed the images and confirmed the cases of lateral canal spinal stenosis, including lateral recess and foraminal spinal stenosis.

The exclusion criteria included unbearable pain > 9 on the numerical rating scale (NRS) (38,39), pain < NRS 4, acute back or leg pain, patients who had developed signs of progressive motor weakness or neurologic deficits, patients with a history of prior spinal surgery, allergies to steroids or contrast dyes, coagulopathy, injection of steroids or hyaluronic acids within the previous

12 weeks, systemic infections, injection site infections, and unstable medical or psychiatric condition. Patients with bilateral radiculopathy, spondylolisthesis, multilevel spinal stenosis, and radiographic confirmation of severe central canal stenosis were also excluded.

Objectives

The aim of this study is to determine the effect of adding hypertonic saline to conventional TFEIs to provide pain relief for chronic radiculopathy patients secondary to lateral canal spinal stenosis.

Randomization and Blinding

Patients were randomly assigned to one of the 2 groups: the hypertonic group (n = 27) and the control group (n = 26). The allocation of patients into either group was performed using a computer-generated randomization program. Each patient's randomization number was concealed throughout the study from both the study patients and the outcome assessor, who was an independent physician from the outpatient pain clinic. The injection procedure and type of drug used for treatment were not disclosed or discussed with the patients until completion of the study.

Intervention

Transforaminal epidural injection procedures were performed at our department under fluoroscopic guidance. A single fluoroscopy C-arm system (OEC 9800, General Electric Healthcare, Little Chalfont, Buckinghamshire, UK) was used and all procedures were performed by a single experienced anesthesiologist with 10-year career in pain medicine.

The patient was placed in a prone position with a pillow under the lower abdomen in order to minimize lumbar lordosis and provide an easy approach to the intervertebral foramen. After sterile preparation and draping of the insertion area, the skin was infiltrated with 1% lidocaine and a 25-gauge, 3.5-inch spinal needle was gently advanced under fluoroscopic guidance. The oblique radiographic view was obtained to ensure proper positioning. Anatomic landmarks were identified, and the needle approach technique was used to achieve proper positioning under fluoroscopic guidance with reference to previous descriptions (40,41). The needle was advanced and positioned in the upper quadrant of the target foramen located under the pedicle of the upper vertebral body. Anteroposterior and lateral views were obtained to confirm correct needle positioning, and special care was taken to prevent undesirable injection. After aspiration for blood or cerebrospinal fluid, a real-time fluoroscopically guided injection of 0.5–2.0 mL contrast dye (Omnipaque, Nycomed Imaging AS, Oslo, Norway) was used to confirm adequate flow to the epidural space and prevent further possible intravascular or intrathecal injection.

After confirmation of correct needle positioning and adequate radiographic imaging, 2 mL of 1% lidocaine with 1,500 units of hyaluronidase (Hylase Dessau®, Riemser, Germany) was administered. Five minutes after the administration of local anesthetics and hyaluronidase, the patient was asked about any motor or sensory change in the ipsilateral and contralateral lower extremity. This was checked by the physician, and the patients received the study drug. The study drugs were not administered to any patient presenting severe paresthesia or pain during injection and possible signs of intrathecal or intravascular local anesthetic administration. The hypertonic group received 2 mL of 10% sodium chloride solution mixed with 20 mg triamcinolone acetonide; the control group received 2 mL of 0.9% saline mixed with 20 mg of triamcinolone acetonide. The attending physician and the participating patient were unaware of the concealed study drug throughout the procedure. No sedatives were used and all patients were kept awake and conscious during the procedure. The patients were then sent to the outpatient post-anesthesia care unit for recovery, and additional post-procedure sensory testing and motor function evaluations were performed by a nurse or an anesthesiologist blind to the study group. Patients showing no responses or responses different than the dermatome level of the affected location were recorded, and these patients were removed from additional analyses.

Outcome Measures and Follow-up

All baseline and post-procedure outcome data were obtained by an independent physician in the pain clinic who was blinded to the design of the study and assigned treatment groups. Baseline data were collected for all participants. Categorical data included sex, current analgesic medication, medical history, target level, and location of the foraminal stenosis. Numerical data included age, weight, height, body mass index (BMI), total duration of pain, and number of prior epidural injections. The baseline values of the continuous data included NRS and Oswestry disability index (ODI).

The post-procedure outcome variables consisted of the 11-point NRS (0 = no pain, 10 = unbearable pain) for assessing radicular pain, the Korean version of 10-item self-administered ODI questionnaire (ranging from 0 – 100; 0 = no disability) for functional outcomes (42), responder rates (0 – 100% of patients), and the global perceived effect (GPE) measured using the 7 -point Likert scale for satisfaction (7 = best ever; 6 = much improved; 5 = improved; 4 = not improved but not worse; 3 = worse; 2 = much worse; 1 = worst ever) (43). NRS, ODI, and responder rates were collected at the one-, 2-, 3-, 4-, and 6-month follow-up examinations following injection, and GPE was collected at one, 3, and 6 months after injection. The responder rate was defined in terms of the proportion of patients reporting a substantial response (≥ 50% or ≥ 4-point reduction in the pain score compared with baseline), or moderate response (≥ 30% or ≥ 2-point reduction in the pain score compared with baseline) (43-45).

The primary outcome measures included the mean pain score compared with baseline, reduction in NRS pain score, and the proportion of substantial responders at one, 2, 3, 4, and 6 months. The secondary outcomes included functional changes, as measured by ODI at one, 2, 3, 4, and 6 months, the proportion of moderate and substantial responders at one, 2, 3, 4, and 6 months, patient satisfaction with treatment measured at one, 3, and 6 months, and the incidence of adverse effects. Patients were instructed to report any adverse events to the physician during the procedure and on each follow-up visit. The patients also could call to request further management or advice. The observed adverse events included paresthesia, pain on injection, neuralgia, numbness, and motor weakness.

During follow-up, all patients were advised to continue taking their medications that they had been previously prescribed. Altering their previous medications during the first 3 months was prohibited, and patients were informed of this guideline prior to study participation. After the first 3 months, the patients who had persistent symptoms or pain were allowed to increase their dose of analgesics or receive other interventional treatments: these patients were withdrawn from further data collection.

Statistical Analysis

A 2-arm pilot study that included 10 patients in the hypertonic group and 8 patients in the control group was performed before this study. The sample size was calculated based on the results of the pilot study (not published). According to the pilot study, the minimum detectable difference in the means was approximately 1.6 and the expected standard deviation (SD) of the residuals was 2.0 on NRS scores. Based on the desired power (80%) and the 2-tailed significance level of 5%, 26 patients would be required in each study group, in order to obtain a total sample size of 52 participants. A total of 34 patients in each group was required in order to adjust for the 30% dropout rate.

The continuous variables are presented as the means ± SDs or as the 95% confidence intervals (CI), and the categorical variables are presented in terms of percentages and absolute numbers. The continuous variables were analyzed on an intention to treat basis beyond the first follow-up period. The patients who did not participate in the first follow-up examination (one month) were dropped from the study and their data were excluded. Data on the remaining patients were analyzed according to the allocated group, regardless of further loss on follow-up or withdrawal. Regarding the categorical variables of the remaining patients, the baseline observation carried-forward method was adopted to analyze further dropout data, and the number needed to treat (NNT) was calculated based on the substantial responder analysis.

As data loss due to drop outs were expected, the linear mixed effect model (LMEM) analysis was used to compare changes within and between the groups in terms of the NRS and ODI values at baseline, one-, 2-, 3-, 4-, and 6-month post-procedure. Compared with the analysis of variance, the LMEM is known to be more flexible to accommodate longitudinal data features, and is more efficient with ability to achieve more power in dealing missing data (46-48). Adjustment of the baseline NRS and ODI values were made in order to compare the estimated differences from baseline for each group. Changes from baseline at each time point between the 2 treatment groups were compared using the Mann-Whitney U test. The Mann-Whitney U test or the unpaired t-test was used at one, 3, and 6 months to compare differences on the GPE scale. For the results of responder analysis, the chi-square test was used to compare differences between groups in each observation period. Demographic data within groups was compared using the chi-square test, Fisher exact test, or the unpaired t-test, as appropriate. We analyzed the data using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA) and SigmaPlot version 12.0 (Systat Software Inc, Richmond, CA, USA). A P value < 0.05 was considered statistically significant.

Results

Between January 2011 and January 2012, 259 patients diagnosed with spinal stenosis were assessed for eligibility; 86 patients fulfilling the inclusion criteria with radiographic evidence of lateral canal spinal stenosis were enrolled. Of the 173 excluded patients, 108 did not meet the study inclusion criteria and 65 met the study exclusion criteria. Before randomization of the 86 eligible patients, 12 patients declined to participate in the study, 2 patients were residents abroad, 4 patients did not demonstrate a correlation between the MRI findings and the clinical symptoms of radiculopathy; in total, 68 patients agreed to participate in the study protocol and were randomized for analysis. After randomization, an additional 5 patients were excluded because they did not show any response to the procedure (n = 2), the response did not correlate with the affected dermatome that was checked at the post-anesthesia care unit (PACU; n = 3), and one patient in the hypertonic group experienced a severe burning sensation after injection of the hypertonic saline and declined to further participate in the study. The pain spontaneously relieved within 2 hours of recovery in the PACU, and the patient was discharged without any sequelae. Four patients in the hypertonic group and 5 patients in the control group were lost on follow-up examination before the first visit to the outpatient pain clinic and withdrawn from the data analysis. Thus, a total of 53 patients (27 in the hypertonic group; 26 in the control group) were included in the intention to treat analysis (Fig. 1). All 53 patients received follow-up at one, 2, and 3 months. After the third visit, subsequent withdrawals from further data collection due to increase in opioid analgesics, additional interventions, or loss on follow-up did occur. By the 4-month follow-up examinations, 4 patients (14.8%) in the hypertonic group, and 6 patients (23.1%) in the control group had dropped out. At the last follow-up examination at 6 months, a total of 14 patients in each group had dropped out. At study completion, 13 patients (48.1%) in the hypertonic group and 12 patients (46.2%) in the control group (Fig. 2) were still enrolled.

There were no statistically significant differences in the baseline characteristics of the 2 treatment groups. Although difference between the baseline NRS and ODI scores was not statistically significant, the hypertonic group demonstrated higher baseline NRS (7.26 vs. 6.60) and ODI values (42.6 vs. 37.5) compared with the control group (Table 1).

Primary Outcomes

In the hypertonic group, there was a statistically significant improvement in the mean pain score compared with the baseline pain score throughout the whole study period ($P < 0.001$, $P = 0.004$ at 6 months); in the control group, statistical significance was observed at one ($P < 0.001$), 2 ($P < 0.001$), 3 ($P < 0.001$), and 4 months ($P < 0.001$; Table 2). When the NRS pain score was compared between the 2 groups using the LMEM, using time as the random effect and the group as the fixed effect, no significant interactions were observed that affected the mean changes in the NRS scores between the hypertonic group and control group over the course of the study (omnibus $P = 0.111$; Fig. 3). The estimated decrease in the NRS pain score was greater in the hypertonic group compared with the control group throughout the whole study period, demonstrating a statistically significant difference between the 2 group at the 2- ($P = 0.024$) and 3-month ($P = 0.012$) follow-up examinations (Table 3).

According to the results of the responder analysis, the proportion of substantial responders was higher in the hypertonic group compared with the control group throughout the total observation period (Fig. 4). There was a statistically significant difference between the 2 groups at 3 months. Sixteen patients (59.3%) in the hypertonic group demonstrated ≥ 50% or ≥ 4-point reduction in the NRS pain score, whereas only 5 patients (19.2%) in the control group did ($P = 0.007$). The NNT for the hypertonic group relative to the control group ranged between 3 and 8 treatments at different time points. The NNT tended to decrease gradually from one to 3 months, and then increased gradually from 3 to 6 months. The 95% CI extended from a negative number, except at 3 months (CI: 1.6 – 6.2). We expressed the negative numbers of the CIs as previously recommended by Altman (49). Because the control group in this study was an active comparator group (38), we did not interpret the negative numbers as the number needed to harm (NNH), but as NNTH (hypertonic) and NNTC (control; Table 4).

Secondary Outcomes

The ODI decreased significantly compared with baseline until 4 months after the procedure in both groups ($P < 0.001$; $P = 0.006$ at 4 months in the control group). However, neither group demonstrated significant functional improvement at 6 months (hypertonic: $P = 0.135$; control: $P = 0.455$; Table 5). When differences

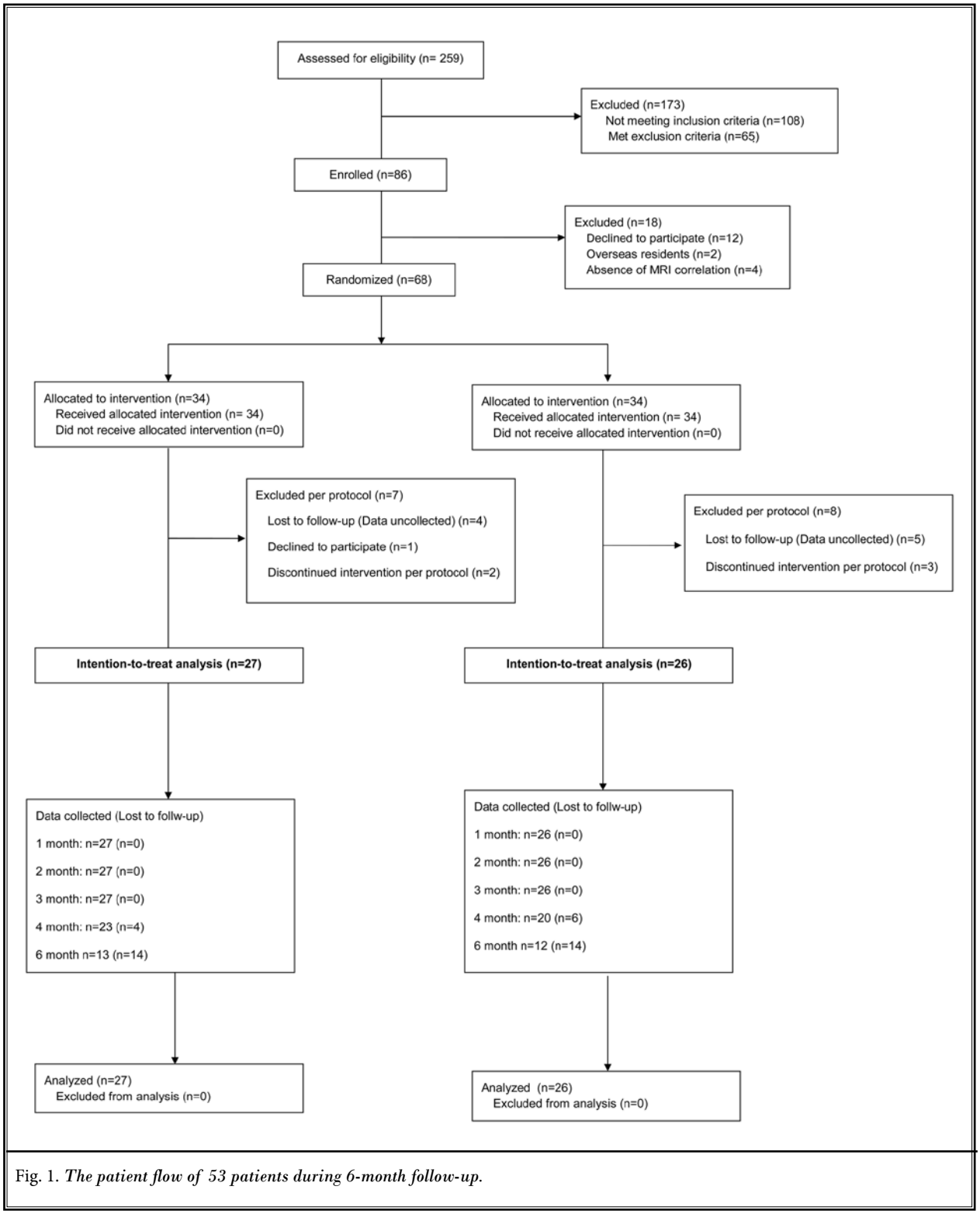

Fig. 1. *The patient flow of 53 patients during 6-month follow-up.*

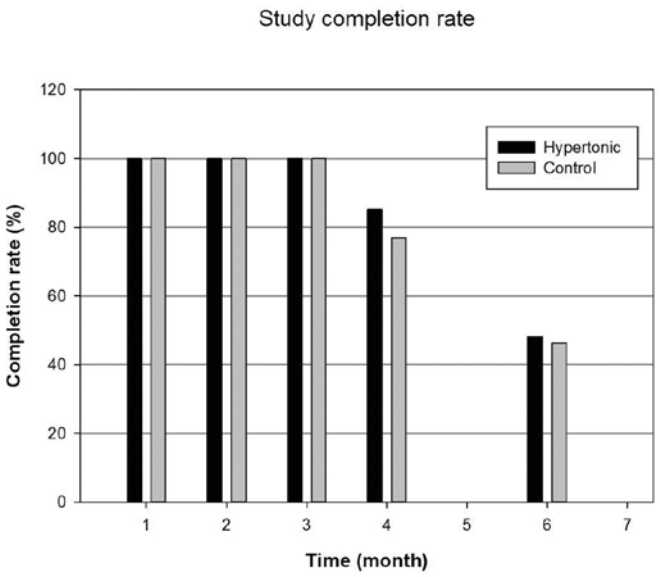

Fig. 2. *The rate of enrolled patients throughout 6-month follow-up in the 2 groups. The data are presented as percentage (%).*

Table 1. *Baseline characteristics of patients.*

	Hypertonic group (n = 27)	Control group (n = 26)	*P*-values
Age, y. [mean (SD)]	66.0 (10.0)	63.7 (10.0)	0.406
Gender			1.000
Male	8	7	
Female	19	19	
Weight, kg [mean (SD)]	61.8 (8.5)	61.9 (9.7)	0.973
Height, cm [mean (SD)]	157.7 (6.0)	155.5 (7.5)	0.336
Body mass index [mean (SD)]	24.7 (3.4)	25.5 (3.2)	0.474
Total duration of pain, mo. [mean (SD)]	18.3 (18.6)	22.3 (18.1)	0.431
Concurrent medical history			0.334
Diabetes mellitus	5	3	
Hypertension	8	13	
Others	0	1	
Opioid use			
None	20	20	1.000
Strong opioid	5	3	0.704
Weak opioid	2	3	0.669
Non-opioid analgesics	18	22	0.202
Prior ESI number [mean (SD)]	2.41 (1.47)	2.35 (1.60)	0.887
Target level of spinal stenosis			0.588
L3–4	1	0	
L4–5	10	11	
L5–S1	16	15	
Treatment location (left/right)	10/17	13/13	0.412
Numerical rating scale [mean (SD)]	7.26 (1.20)	6.60 (1.36)	0.065
Oswestry disability index [mean (SD)]	42.6 (14.1)	37.5 (15.1)	0.210

ESI: epidural steroid injection; SD: standard deviation

Table 2. *Mean pain scores and estimated differences from baseline for each study groups*

Time	Least square means (95% CI)*		Estimated difference from baseline (SE)		P-value compared with baseline	
	Hypertonic (n = 27)	Control (n = 26)	Hypertonic (n = 27)	Control (n = 26)	Hypertonic (n = 27)	Control (n = 26)
Baseline	7.26 (6.55 – 7.97)	6.60 (5.96 – 7.24)	0	0		
one month	4.13 (3.42 – 4.84)	4.04 (3.40 – 4.68)	-3.13 (0.42)	-2.56 (0.35)	< 0.001	< 0.001
2 months	4.04 (3.32 – 4.75)	4.65 (4.01 – 5.30)	-3.22 (0.42)	-1.94 (0.35)	< 0.001	< 0.001
3 months	4.33 (3.62 – 5.05)	5.08 (4.44 – 5.72)	-2.93 (0.42)	-1.52 (0.35)	< 0.001	< 0.001
4 months	4.80 (4.04 – 5.56)	5.18 (4.47 – 5.88)	-2.46 (0.45)	-1.42 (0.38)	< 0.001	< 0.001
6 months	5.68 (4.71 – 6.65)	6.29 (5.43 – 7.14)	-1.58 (0.54)	-0.31 (0.45)	0.004	0.492

NRS: numerical rating scale; CI: confidence intervals; SE: standard error
*Omnibus $P = 0.111$ comparing the hypertonic and control groups.

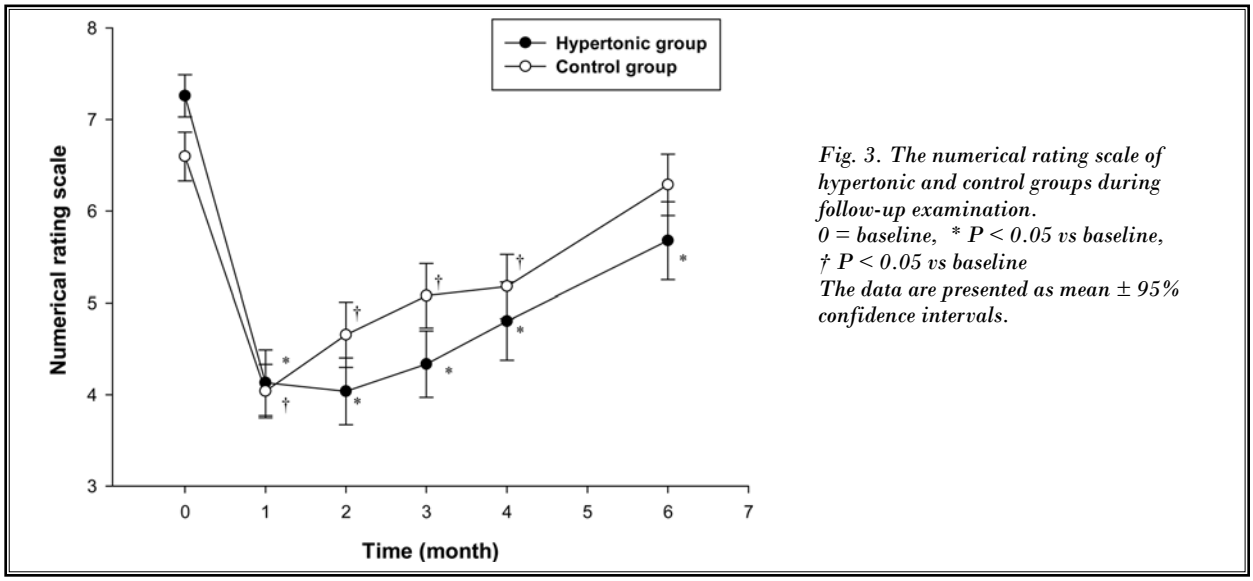

Fig. 3. The numerical rating scale of hypertonic and control groups during follow-up examination.
*0 = baseline, * $P < 0.05$ vs baseline,*
† $P < 0.05$ vs baseline
The data are presented as mean ± 95% confidence intervals.

Table 3. *Estimated reduction in the NRS and ODI scores of the hypertonic group compared with the control group.*

	Groups		*P*-value
Variable	Hypertonic (n = 27)	Control (n = 26)	
NRS (0 – 10)			
one month	3.13 (2.11)	2.56 (2.14)	0.247
2 months	3.22 (2.42)	1.94 (2.04)	0.024
3 months	2.93 (2.54)	1.52 (1.83)	0.011
4 months	2.78 (2.35)	1.50 (1.70)	0.054
6 months	2.15 (2.70)	0.58 (1.73)	0.168
ODI (0 - 100)			
one month	13.22 (14.25)	10.08 (12.05)	0.556
2 months	13.81 (19.08)	10.31 (11.88)	0.449
3 months	12.70 (18.21)	8.08 (11.39)	0.345
4 months	12.22 (15.64)	6.90 (8.60)	0.414
6 months	6.85 (8.72)	3.83 (9.44)	0.339

All data are presented as the mean (SD). The Mann-Whitney U test was used to compare differences between the groups at each time point following normality testing using the Shapiro-Wilk test. NRS: numerical rating scale; ODI: Oswestry disability index

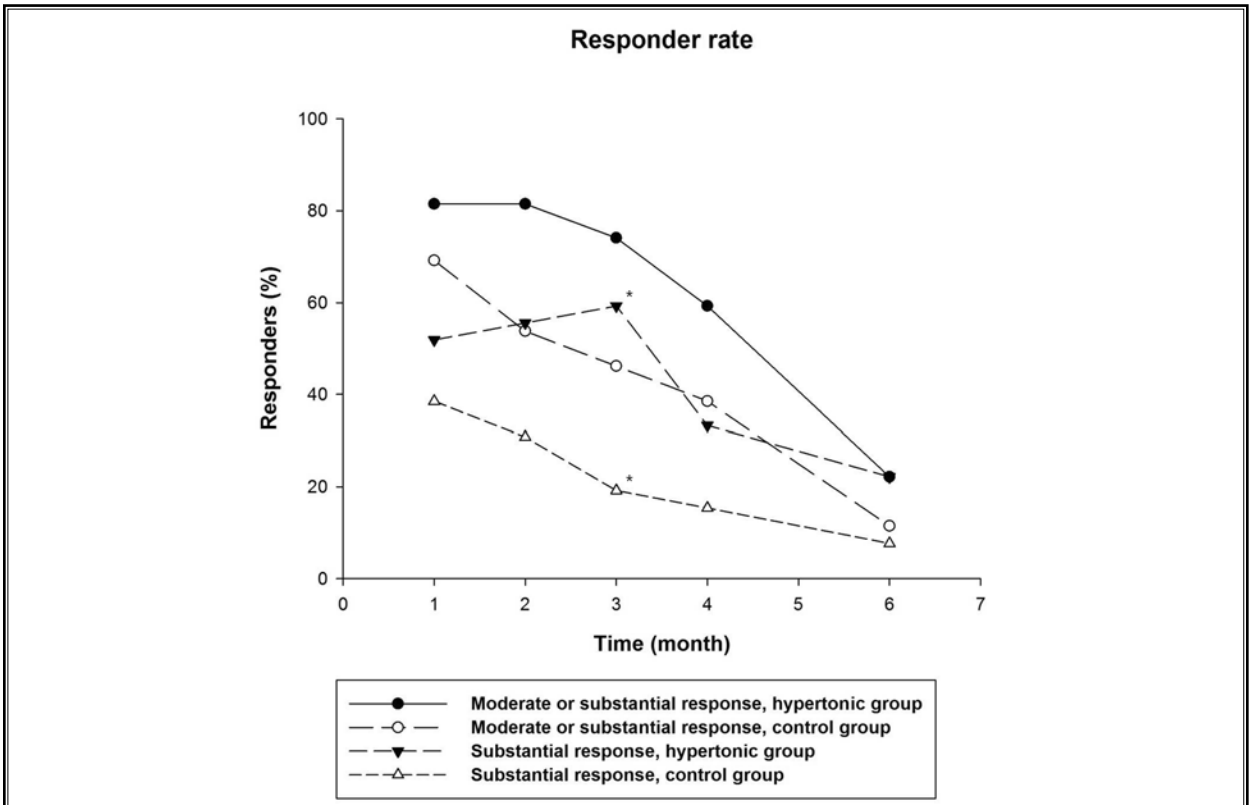

Fig. 4. *The responder rate of the 2 groups during follow-up examination. * P = 0.007, hypertonic vs control The data are presented as percentage (%).*

Table 4. *Number needed to treat substantial responders exceeding the minimum efficacy criteria of 50% or 4 points improvement in NRS at each time point.*

Time	NNT	95% CI
one month	8	NNTC 7.6 to NNTH 2.5
2 months	5	NNTC 97.9 to NNTH 2
3 months	3	1.6 to 6.2
4 months	6	NNTC 21.7 to NNTH 2.5
6 months	7	NNTC 23.8 to NNTH 3

NNT: number needed to treat; CI: confidence interval; NNTC: number needed to treat (control); NNTH: number needed to treat (hypertonic)

were compared between the 2 groups using the linear mixed model, no significant differences were detected from baseline through 6 months (omnibus $P = 0.764$; Fig. 5). The proportion of substantial or moderate responders (≥ 30% or ≥ 2-point reduction in NRS score) was higher in the hypertonic group, but we did not observe any significant differences between the 2 groups (Fig. 4). The patient satisfaction score (GPE) was higher in the hypertonic group, demonstrating statistical significance at 3 months ($P = 0.02$; Table 6). Patient satisfaction gradually decreased in both groups.

There were no reports of serious complications during injection, except one patient in the hypertonic group experienced burning pain during injection and declined to participate further in the study. Other complications were minor, mostly temporary pain during needle approach and injection, which were tolerable and required no additional care. There were no cases

Table 5. *Mean ODI and estimated differences from baseline*

Time	Least square means (95% CI)*		Estimated difference from baseline (SE)		P-value compared with baseline	
	Hypertonic (n = 27)	Control (n = 26)	Hypertonic (n = 27)	Control (n = 26)	Hypertonic (n = 27)	Control (n = 26)
Baseline	42.63 (37.15 – 48.12)	37.54 (32.64 – 42.44)	0	0		
one month	29.41 (23.93 – 34.88)	27.46 (22.57 – 32.36)	-13.22 (2.57)	-10.08 (1.89)	< 0.001	< 0.001
2 months	28.82 (23.34 – 34.29)	27.23 (22.34 – 32.13)	-13.82 (2.57)	-10.31 (1.89)	< 0.001	< 0.001
3 months	29.93 (24.45 – 35.40)	29.46 (24.57 – 34.36)	-12.70 (2.57)	-8.08 (1.35)	< 0.001	< 0.001
4 months	32.49 (26.78 – 38.20)	31.81 (26.67 – 36.95)	-10.14 (2.71)	-5.73 (2.06)	< 0.001	0.006
6 months	37.67 (30.88 – 44.46)	35.69 (29.92 – 41.46)	-4.96 (3.29)	-1.85 (2.46)	0.135	0.455

ODI: Oswestry disability index; CI: confidence intervals; SE: standard error
*Omnibus P = 0.764 comparing the hypertonic and the control groups.

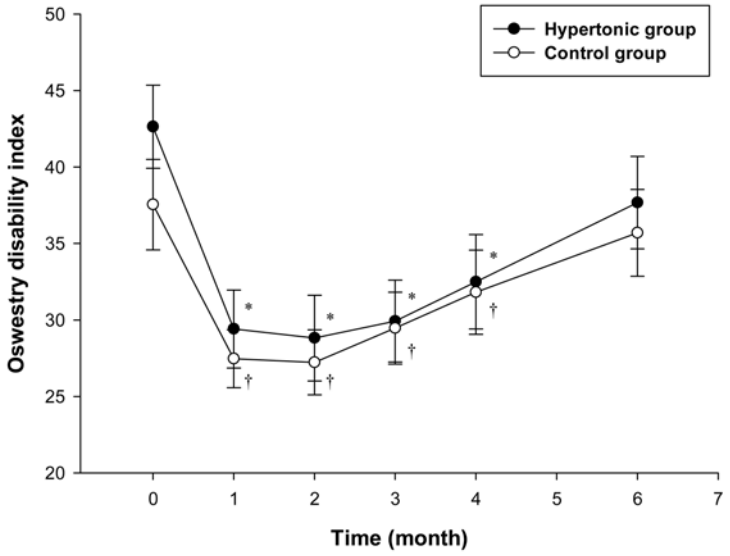

Fig. 5. *The Oswestry disability index of hypertonic and cotrol groups during follow-up examination.*
*0 = baseline * P < 0.05 vs basline, † P < 0.05 vs baseline*
The data are presented as mean ± 95% confidence intervals.

Table 6. *Patient satisfaction at one, 3, 6 months according to GPE.*

Time	Least square means (95% CI)*		*P*-value†
	Hypertonic	Control	
one month	5.82 (5.40 – 6.23)	5.65 (5.26 – 6.05)	0.245
3 month	5.41 (5.00 – 5.12)	4.73 (4.33 – 5.13)	0.02
6 month	4.59 (4.02 – 5.16)	4.22 (3.65 – 4.80)	0.397

*Mean values were calculated using the linear mixed model.
† The Mann-Whitney U test and unpaired t-test were used to determine the GPE differences between groups. Normality was tested using the Shapiro-Wilk test.

of dural puncture during the procedure, and no cases of inappropriate drug delivery. Post-procedure complications were not reported on follow-up, and other complications such as infection, sensory deficits, and deterioration of motor function were not registered throughout the study period. No withdraws from the study due to adverse effects were noted.

Discussion

Transforaminal epidural injection of steroids, with or without the addition of 10% hypertonic sodium chloride, is effective and provides significant pain relief with the improvement of functional outcome within 4 months. The present study provides further information that the addition of hypertonic saline is superior in efficacy compared with conventional TFEI at 3 months, although the differences in the absolute pain scores did not demonstrate statistical significance. The reduction in pain intensity from the baseline was greater in the hypertonic group over the short-term and demonstrated higher rates of satisfaction in comparison with the control. The use of hypertonic saline also extended the duration of significant pain relief to 6 months compared with baseline. However, as a consequence of the high drop-out rates, the long-term results of hypertonic saline at 6 months were underpowered, demonstrating only a limited long-term effect, and the use of hypertonic saline did not provide any additional benefits in terms of the improvement in functional outcomes.

The transforaminal approach for administering epidural injections provides target-specific advantages for delivering local anesthetics and steroids to the desired site of pathology in comparison with interlaminar or caudal epidural injections for the management of lumbar radiculitis and disc herniation (27,50). This technique has also been used to manage patients with spinal stenosis, demonstrating positive results, including short-term pain relief and functional improvement, that have been reported in a number of randomized and nonrandomized studies (26,51-55). The short-term findings of our research are consistent with previous studies that included both experimental and control groups. However, the long-term effects of TFEI for the treatment of spinal stenosis are conflicting, with only one randomized control study reporting positive results beyond 6 months of follow-up examination (26). Two other retrospective studies reported that 19% to 37% of patients demonstrated long-term improvements, including ≥ 50% reduction in pain scores (54,55). Our results also failed to describe meaningful long-term effects in either pain reduction or functional improvements, although the use of 10% hypertonic saline demonstrated some degree of advantage over conventional TFEI.

In our study, the addition of 10% hypertonic saline seemed to be an effective treatment modality, because it improved the short-term efficacy of TFEIs and provided a greater amount of pain reduction compared with controls. This can be explained by 1) the adhesiolysis of the potential adhesions and fibrous tissues in the epidural and perineural space, and 2) the possible neuromodulatory effects of the high concentration sodium chloride solution. The effect of percutaneous adhesiolysis have been described and reported by numerous studies, and favorable short- and long-term results have been reported (31,32,36,56,57). A preliminary study comparing caudal epidural adhesiolysis with caudal epidural injections for the management of chronic lower back pain secondary to spinal stenosis reported that adhesiolysis demonstrates a significant advantage over only caudal epidural injection for providing long-term pain relief (29). However, no mechanical adhesiolysis was performed in this study, and previous studies demonstrated considerable evidence that the critical factor in adhesiolysis is the mechanical factor rather than chemical, and the effect of hypertonic saline in adhesiolysis is still controversial (31,36). The neuromodulation effects of chloride solutions and the effect of hyperosmolar solutions on nerve conduction have been studied previously in experimental animal studies (58,59). Localized alteration of the intracellular chloride ion level is also associated with changes in pain pathway (60), making it possible to assume that the effects of the localized administration of high concentration sodium chloride may have contributed to changes in pain conductivity.

There are several limitations to the present study that should be discussed. First, the control group of this study was an active comparator; thus, this study lacks a placebo group. The placebo effect is important in clinical pain research: it is powerful and may last for prolonged periods (61,62). However, the placebo effect is very complex and it is difficult to apply a sham-placebo group for ethical reasons, as this study involved invasive procedures. The second limitation is whether the control group can be strictly considered as an active comparator. According to the chronic pain research guidelines, an active comparator is defined as a treatment with a well-established efficacy (39). Transforaminal epidural steroid injection is a well-established treatment for treating lower back pain and radiculopathy secondary

to spinal stenosis (50), but in the present study we administered an additional 0.9% sodium chloride solution in the control group in order to blind the operator to the study. The effects of normal saline on pain reduction and its effects on altering neurostimulation have been previously described by many comparative studies (19,63-66), so there is a concern that the normal saline group could be considered the placebo group (67). The use of normal saline in the control group can be criticized, because it may have had positive effects in terms of pain reduction.

The baseline NRS scores of the study groups, although not statistically different, did show some degree of difference. As a result, although the reduction in the NRS scores was significantly greater in the experimental group after 2 – 3 months, group differences in terms of the NRS scores were not significant; the small sample size also contributed to this finding. Fourth, the severity of lateral spinal stenosis was not considered. Although MRI was performed on all patients who participated in this study, and a formal interpretation was performed by radiologist, we did not further classify the patients according to severity of the stenosis. The correlation between the radiographic severity of spinal stenosis and clinical symptoms, along with treatment effectiveness were found to be insignificant in previous studies (68-71). Thus, further evaluations of the severity of stenosis and treatment effects were not considered in this study. Fifth, the effect of emotional function was not evaluated in this study. Many patients suffering from chronic pain are in depressed and the assessment of emotional functioning is an important core outcome in chronic pain research (72). This is due to the reluctance of Korean patients to face psychiatric consultation, along with the lack of appropriate isolated counseling offices in our outpatient clinic at the time our research was carried out. Furthermore, the high rates of withdrawal between the fourth and sixth months underpowered this study, making the long-term results less reliable.

The adverse effects and complications reported during this study were relatively infrequent, and the reported events were all minor and did not influence the results of this study. Generally known complications of hypertonic saline administration include severe pain during injection, paresthesia, and chemical arachnoiditis (73,74). Special care was taken in the current study to avoid possible complications as previously described, but further safety guidelines are essential for general application of the transforaminal hypertonic saline injection. First, we recommend the use of hypertonic saline in patients presenting unsatisfactory responses to conservative managements. Second, patients who demonstrate limited response to conventional TFEI, or those who are responsive, but when the response is short-lived, can be candidates for the use of hypertonic saline. During clinical practice, adequate contrast spread should be confirmed by real-time fluoroscopy, and the use of blunt needles can be helpful to prevent intra-arterial and intrathecal injections. Catheter utilized techniques and the Kambin triangle approach can also ensure safety compared with our single needle technique (75,76), and larger volumes of local anesthetic test-dose with longer waiting time can further increase the margin of safety. However, to obtain safety profiles and more valid information regarding possible complications, further studies with larger cohorts are needed.

Conclusion

The results of this study suggests that the TFEI is a useful modality in treating pain secondary to lateral canal spinal stenosis, and the short-term functional outcomes were also improved significantly, but the TFEI showed limited long-term effects in treating patients with spinal stenosis. The addition of hypertonic saline demonstrated superior short-term pain relieving efficacy compared with conventional lumbar TFEI, but the overall mid- and long-term results showed no advantage. To confirm the long-term efficacy and ensure safety in general practice, larger scale studies with longer follow-up periods and accurate guidelines for the use of hypertonic saline are needed.

References

1. Kim HJ, Lee HM, Kim HS, Moon ES, Park JO, Lee KJ, Moon SH. Life expectancy after lumbar spine surgery: One- to eleven-year follow-up of 1015 patients. *Spine (Phila Pa 1976)* 2008; 33:2116-2121; discussion 2122-2113.
2. Verbiest H. A radicular syndrome from developmental narrowing of the lumbar vertebral canal. *J Bone Joint Surg Br* 1954; 36-B:230-237.
3. Kalichman L, Cole R, Kim DH, Li L, Suri P, Guermazi A, Hunter DJ. Spinal stenosis prevalence and association with symptoms: The Framingham Study. *Spine J* 2009; 9:545-550.
4. Deyo RA, Weinstein JN. Low back pain.

N Engl J Med 2001; 344:363-370.

5. Hart LG, Deyo RA, Cherkin DC. Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns from a U.S. national survey. *Spine (Phila Pa 1976)* 1995; 20:11-19.
6. Deyo RA, Ciol MA, Cherkin DC, Loeser JD, Bigos SJ. Lumbar spinal fusion. A cohort study of complications, reoperations, and resource use in the Medicare population. *Spine (Phila Pa 1976)* 1993; 18:1463-1470.
7. Waldron J, Warde P, Irish J, Pintilie M, Sellmann S, Bayley A, Cummings B, Kim J, Liu FF, Payne D, Ringash J, Brown D, Freeman J, Gilbert R, Gullane P, Witterick I, O'Sullivan B. A dose escalation study of hyperfractionated accelerated radiation delivered with integrated neck surgery (HARDWINS) for the management of advanced head and neck cancer. *Radiother Oncol* 2008; 87:173-180.
8. Deyo RA, Gray DT, Kreuter W, Mirza S, Martin BI. United States trends in lumbar fusion surgery for degenerative conditions. *Spine (Phila Pa 1976)* 2005; 30:1441-1445; discussion 1446-1447.
9. Kovacs FM, Urrutia G, Alarcon JD. Surgery versus conservative treatment for symptomatic lumbar spinal stenosis: A systematic review of randomized controlled trials. *Spine (Phila Pa 1976)* 2011; 36:E1335-1351.
10. Spivak JM. Degenerative lumbar spinal stenosis. *J Bone Joint Surg Am* 1998; 80:1053-1066.
11. Storm PB, Chou D, Tamargo RJ. Lumbar spinal stenosis, cauda equina syndrome, and multiple lumbosacral radiculopathies. *Phys Med Rehabil Clin N Am* 2002; 13:713-733, ix.
12. Lee CK, Rauschning W, Glenn W. Lateral lumbar spinal canal stenosis: Classification, pathologic anatomy and surgical decompression. *Spine (Phila Pa 1976)* 1988; 13:313-320.
13. Park HJ, Kim SS, Lee SY, Park NH, Rho MH, Hong HP, Kwag HJ, Kook SH, Choi SH. Clinical correlation of a new MR imaging method for assessing lumbar foraminal stenosis. *AJNR Am J Neuroradiol* 2012; 33:818-822.
14. Jenis LG, An HS. Spine update. Lumbar foraminal stenosis. *Spine (Phila Pa 1976)* 2000; 25:389-394.
15. Kim SH, Koh WU, Park SJ, Choi WJ, Suh JH, Leem JG, Park PH, Shin JW. Clinical experiences of transforaminal balloon decompression for patients with spinal stenosis. *Korean J Pain* 2012; 25:55-59.
16. Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis: Updated Cochrane Review. *Spine (Phila Pa 1976)* 2005; 30:2312-2320.
17. Tosteson AN, Tosteson TD, Lurie JD, Abdu W, Herkowitz H, Andersson G, Albert T, Bridwell K, Zhao W, Grove MR, Weinstein MC, Weinstein JN. Comparative effectiveness evidence from the spine patient outcomes research trial: Surgical versus nonoperative care for spinal stenosis, degenerative spondylolisthesis, and intervertebral disc herniation. *Spine (Phila Pa 1976)* 2011; 36:2061-2068.
18. Botwin KP, Gruber RD, Bouchlas CG, Torres-Ramos FM, Sanelli JT, Freeman ED, Slaten WK, Rao S. Fluoroscopically guided lumbar transformational epidural steroid injections in degenerative lumbar stenosis: an outcome study. *Am J Phys Med Rehabil* 2002; 81:898-905.
19. 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.
20. Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. *Spine (Phila Pa 1976)* 2009; 34:1078-1093.
21. Chou R, Loeser JD, Owens DK, Rosenquist RW, Atlas SJ, Baisden J, Carragee EJ, Grabois M, Murphy DR, Resnick DK, Stanos SP, Shaffer WO, Wall EM. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: An evidence-based clinical practice guideline from the American Pain Society. *Spine (Phila Pa 1976)* 2009; 34:1066-1077.
22. Parr AT, Manchikanti L, Hameed H, Conn A, Manchikanti KN, Benyamin RM, Diwan S, Singh V, Abdi S. Caudal epidural injections in the management of chronic low back pain: A systematic appraisal of the literature. *Pain Physician* 2012;15;E159-E198.
23. Ammendolia C, Stuber K, de Bruin LK, Furlan AD, Kennedy CA, Rampersaud YR, Steenstra IA, Pennick V. Nonoperative treatment of lumbar spinal stenosis with neurogenic claudication: A systematic review. *Spine (Phila Pa 1976)* 2012; 37:E609-616.
24. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJ. Lumbar interlaminar epidural injections in central spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:51-63.
25. Manchikanti L, Cash KA, 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.
26. Jeong HS, Lee JW, Kim SH, Myung JS, Kim JH, Kang HS. Effectiveness of transforaminal epidural steroid injection by using a preganglionic approach: A prospective randomized controlled study. *Radiology* 2007; 245:584-590.
27. Kraemer J, Ludwig J, Bickert U, Owczarek V, Traupe M. Lumbar epidural perineural injection: A new technique. *Eur Spine J* 1997; 6:357-361.
28. Ackerman WE, 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007; 104:1217-1222.
29. Manchikanti L, Cash KA, McManus CD, Pampati V, Singh V, Benyamin R. 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:E341-354.
30. Manchikanti L, Pampati V, Fellows B, Rivera JJ, Damron KS, Beyer C, Cash KA. Effectiveness of percutaneous adhesiolysis with hypertonic saline neurolysis in refractory spinal stenosis. *Pain Physician* 2001; 4:366-373.
31. Manchikanti L, Rivera JJ, Pampati V, Damron KS, McManus CD, Brandon DE, Wilson SR. One day lumbar epidural adhesiolysis and hypertonic saline neurolysis in treatment of chronic low back pain: A randomized, double-blind trial. *Pain Physician* 2004; 7:177-186.
32. Manchikanti L, Pampati V, Fellows B, Rivera J, Beyer CD, Damron KS. Role of one day epidural adhesiolysis in management of chronic low back pain: A randomized clinical trial. *Pain Physician* 2001; 4:153-166.
33. Harrington JF, Messier AA, Hoffman L, Yu E, Dykhuizen M, Barker K. Physiological and behavioral evidence for focal nociception induced by epidural glutamate infusion in rats. *Spine (Phila Pa 1976)* 2005; 30:606-612.
34. Cooper RG, Freemont AJ, Hoyland JA, Jenkins JP, West CG, Illingworth KJ, Jay-

son MI. Herniated intervertebral disc-associated periradicular fibrosis and vascular abnormalities occur without inflammatory cell infiltration. *Spine (Phila Pa 1976)* 1995; 20:591-598.

35. Parke WW, Watanabe R. Adhesions of the ventral lumbar dura. An adjunct source of discogenic pain? *Spine (Phila Pa 1976)* 1990; 15:300-303.
36. Heavner JE, Racz GB, Raj P. Percutaneous epidural neuroplasty: Prospective evaluation of 0.9% NaCl versus 10% NaCl with or without hyaluronidase. *Reg Anesth Pain Med* 1999; 24:202-207.
37. Helm Ii S, Benyamin RM, Chopra P, Deer TR, Justiz R. Percutaneous adhesiolysis in the management of chronic low back pain in post lumbar surgery syndrome and spinal stenosis: A systematic review. *Pain Physician* 2012; 15:E435-E462.
38. Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, Jensen MP, Katz NP, Raja SN, Rappaport BA, Rowbotham MC, Backonja MM, Baron R, Bellamy N, Bhagwagar Z, Costello A, Cowan P, Fang WC, Hertz S, Jay GW, Junor R, Kerns RD, Kerwin R, Kopecky EA, Lissin D, Malamut R, Markman JD, McDermott MP, Munera C, Porter L, Rauschkolb C, Rice AS, Sampaio C, Skljarevski V, Sommerville K, Stacey BR, Steigerwald I, Tobias J, Trentacosti AM, Wasan AD, Wells GA, Williams J, Witter J, Ziegler D. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2012; 153:1148-1158.
39. Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, Chappell A, Chartier K, Cleeland CS, Costello A, Cowan P, Dimitrova R, Ellenberg S, Farrar JT, French JA, Gilron I, Hertz S, Jadad AR, Jay GW, Kalliomaki J, Katz NP, Kerns RD, Manning DC, McDermott MP, McGrath PJ, Narayana A, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Reeve BB, Rhodes T, Sampaio C, Simpson DM, Stauffer JW, Stucki G, Tobias J, White RE, Witter J. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain* 2010; 149:177-193.
40. Manchikanti L. Transforaminal lumbar epidural steroid injections. *Pain Physician* 2000; 3:374-398.
41. Lew HL, Coelho P, Chou LH. Preganglionic approach to transforaminal epidural steroid injections. *Am J Phys Med Rehabil* 2004; 83:378.
42. Kim DY, Lee SH, Lee HY, Lee HJ, Chang SB, Chung SK, Kim HJ. Validation of the Korean version of the oswestry disability index. *Spine (Phila Pa 1976)* 2005; 30:E123-127.
43. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94:149-158.
44. Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, Farrar JT, Hertz S, Raja SN, Rappaport BA, Rauschkolb C, Sampaio C. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2009; 146:238-244.
45. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008; 9:105-121.
46. Ma Y, Mazumdar M, Memtsoudis SG. Beyond repeated-measures analysis of variance: Advanced statistical methods for the analysis of longitudinal data in anesthesia research. *Reg Anesth Pain Med* 2012; 37:99-105.
47. Fielding S, Fayers P, Ramsay CR. Analysing randomised controlled trials with missing data: Choice of approach affects conclusions. *Contemp Clin Trials* 2012; 33:461-469.
48. Baron G, Ravaud P, Samson A, Giraudeau B. Missing data in randomized controlled trials of rheumatoid arthritis with radiographic outcomes: a simulation study. *Arthritis Rheum* 2008; 59:25-31.
49. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998; 317:1309-1312.
50. Manchikanti L, Buenaventura RM, Manchikanti KN, Ruan X, Gupta S, Smith HS, Christo PJ, Ward SP. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. *Pain Physician* 2012; 15:E199-245.
51. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain: a randomized, double-blind, controlled trial. *Spine (Phila Pa 1976)* 2005:30:857-862.
52. Yoon SY, Roh DH, Kwon YB, Kim HW, Seo HS, Han HJ, Lee HJ, Beitz AJ, Lee JH. Acupoint stimulation with diluted bee venom (apipuncture) potentiates the analgesic effect of intrathecal clonidine in the rodent formalin test and in a neuropathic pain model. *J Pain* 2009; 10:253-263.
53. Lee JH, Moon J, Lee SH. Comparison of effectiveness according to different approaches of epidural steroid injection in lumbosacral herniated disk and spinal stenosis. *J Back Musculoskelet Rehabil* 2009; 22:83-89.
54. Cooper G, Lutz GE, Boachie-Adjei O, Lin J. Effectiveness of transforaminal epidural steroid injections in patients with degenerative lumbar scoliotic stenosis and radiculopathy. *Pain Physician* 2004; 7:311-317.
55. Rosenberg SK, Grabinsky A, Kooser C, Boswell MV. Effectiveness of transforaminal epidural steroid injections in low back pain: A one year experience. *Pain Physician* 2002; 5:266-270.
56. Veihelmann A, Devens C, Trouillier H, Birkenmaier C, Gerdesmeyer L, Refior HJ. Epidural neuroplasty versus physiotherapy to relieve pain in patients with sciatica: A prospective randomized blinded clinical trial. *J Orthop Sci* 2006; 11:365-369.
57. Gerdesmeyer L, Lampe R, Veihelmann A, Burgkart R, Gobel M, Gollwitzer H, Wagner K. Chronic radiculopathy. Use of minimally invasive percutaneous epidural neurolysis according to Racz. *Schmerz* 2005; 19:285-295.
58. King JS, Jewett DL, Sundberg HR. Differential blockade of cat dorsal root C fibers by various chloride solutions. *J Neurosurg* 1972; 36:569-583.
59. Matsuka Y, Spigelman I. Hyperosmolar solutions selectively block action potentials in rat myelinated sensory fibers: Implications for diabetic neuropathy. *J Neurophysiol* 2004; 91:48-56.
60. Price TJ, Cervero F, Gold MS, Hammond DL, Prescott SA. Chloride regulation in the pain pathway. *Brain Res Rev* 2009; 60:149-170.
61. Koshi EB, Short CA. Placebo theory and its implications for research and clinical practice: A review of the recent literature. *Pain Pract* 2007; 7:4-20.
62. Manchikanti L, Giordano J, Fellows B,

Hirsch JA. Placebo and nocebo in interventional pain management: A friend or a foe--or simply foes? *Pain Physician* 2011; 14:E157-175.

63. 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.
64. 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.
65. Cohen SP, White RL, Kurihara C, Larkin TM, Chang A, Griffith SR, Gilligan C, Larkin R, Morlando B, Pasquina PF, Yaksh TL, Nguyen C. Epidural steroids, etanercept, or saline in subacute sciatica: A multicenter, randomized trial. *Ann Intern Med* 2012; 156:551-559.
66. 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.
67. Manchikanti L, Singh V, Falco FJ, 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.
68. Sirvanci M, Bhatia M, Ganiyusufoglu KA, Duran C, Tezer M, Ozturk C, Aydogan M, Hamzaoglu A. Degenerative lumbar spinal stenosis: Correlation with Oswestry Disability Index and MR imaging. *Eur Spine J* 2008; 17:679-685.
69. Athiviraham A, Yen D, Scott C, Soboleski D. Clinical correlation of radiological spinal stenosis after standardization for vertebral body size. *Clin Radiol* 2007; 62:776-780.
70. Campbell MJ, Carreon LY, Glassman SD, McGinnis MD, Elmlinger BS. Correlation of spinal canal dimensions to efficacy of epidural steroid injection in spinal stenosis. *J Spinal Disord Tech* 2007; 20:168-171.
71. Park CH, Lee SH, Jung JY. Dural sac cross-sectional area does not correlate with efficacy of percutaneous adhesiolysis in single level lumbar spinal stenosis. *Pain Physician* 2011; 14:377-382.
72. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; 113:9-19.
73. Erdine S, Talu GK. Precautions during epidural neuroplasty. *Pain Pract* 2002; 2:308-314.
74. Manchikanti L, Bakhit CE. Percutaneous lysis of epidural adhesions. *Pain Physician* 2000; 3:46-64.
75. Kloth DS, Calodney AK, Derby R, Lagattuta FP, O'Neill C, Yurth E, Miller LE, Block JE. Improving the safety of transforaminal epidural steroid injections in the treatment of cervical radiculopathy. *Pain Physician* 2011; 14:285-293.
76. Glaser SE, Shah RV. Root cause analysis of paraplegia following transforaminal epidural steroid injections: The "unsafe" triangle. *Pain Physician* 2010; 13:237-244.