The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 3, 2014 VOL. 371 NO. 1

A Randomized Trial of Epidural Glucocorticoid Injections for Spinal Stenosis

Janna L. Friedly, M.D., Bryan A. Comstock, M.S., Judith A. Turner, Ph.D., Patrick J. Heagerty, Ph.D., Richard A. Deyo, M.D., M.P.H., Sean D. Sullivan, Ph.D., Zoya Bauer, M.D., Ph.D., Brian W. Bresnahan, Ph.D., Andrew L. Avins, M.D., M.P.H., Srdjan S. Nedeljkovic, M.D., David R. Nerenz, Ph.D., Christopher Standaert, M.D., Larry Kessler, Ph.D., Venu Akuthota, M.D., Thiru Annaswamy, M.D., Allen Chen, M.D., M.P.H., Felix Diehn, M.D., William Firtch, M.D., Frederic J. Gerges, M.D., Christopher Gilligan, M.D., Harley Goldberg, M.D., David J. Kennedy, M.D., Shlomo Mandel, M.D., Mark Tyburski, M.D., William Sanders, M.D., David Sibell, M.D., Matthew Smuck, M.D., Ajay Wasan, M.D., Lawrence Won, M.D., and Jeffrey G. Jarvik, M.D., M.P.H.

ABSTRACT

BACKGROUND

Epidural glucocorticoid injections are widely used to treat symptoms of lumbar spinal stenosis, a common cause of pain and disability in older adults. However, rigorous data are lacking regarding the effectiveness and safety of these injections.

METHODS

In a double-blind, multisite trial, we randomly assigned 400 patients who had lumbar central spinal stenosis and moderate-to-severe leg pain and disability to receive epidural injections of glucocorticoids plus lidocaine or lidocaine alone. The patients received one or two injections before the primary outcome evaluation, performed 6 weeks after randomization and the first injection. The primary outcomes were the score on the Roland–Morris Disability Questionnaire (RMDQ, in which scores range from 0 to 24, with higher scores indicating greater physical disability) and the rating of the intensity of leg pain (on a scale from 0 to 10, with 0 indicating no pain and 10 indicating "pain as bad as you can imagine").

RESULTS

At 6 weeks, there were no significant between-group differences in the RMDQ score (adjusted difference in the average treatment effect between the glucocorticoid–lidocaine group and the lidocaine-alone group, −1.0 points; 95% confidence interval [CI], −2.1 to 0.1; P=0.07) or the intensity of leg pain (adjusted difference in the average treatment effect, −0.2 points; 95% CI, −0.8 to 0.4; P=0.48). A prespecified secondary subgroup analysis with stratification according to type of injection (interlaminar vs. transforaminal) likewise showed no significant differences at 6 weeks.

CONCLUSIONS

In the treatment of lumbar spinal stenosis, epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone. (Funded by the Agency for Healthcare Research and Quality; ClinicalTrials.gov number, NCT01238536.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Friedly at the Department of Rehabilitation Medicine, University of Washington, 325 Ninth Ave., Seattle, WA 98104, or at friedlyj@uw.edu.

This article was updated on July 3, 2014, at NEJM.org.

N Engl J Med 2014;371:11-21.
DOI: 10.1056/NEJMoa1313265

Lumbar spinal stenosis, a common cause of spine-related disability, is the leading reason for spinal surgery in older adults.[1,2] Degenerative changes resulting in narrowing of the spinal canal and nerve-root compression can cause back and leg pain, lower-extremity paresthesias, and weakness.[3,4] The treatment of symptomatic lumbar stenosis remains controversial.

Symptoms of lumbar stenosis are commonly treated with epidural glucocorticoid injections. These injections typically contain a glucocorticoid and an anesthetic, which are thought to relieve pain by reducing nerve-root inflammation and ischemia.[1] An estimated 25% of all epidural glucocorticoid injections administered in the Medicare population and 74% of those administered in patients at Veterans Affairs medical centers are for spinal stenosis.[5,6] Rates and associated costs of these injections for spinal stenosis increased nearly 300% over the past two decades, and it is estimated that more than 2.2 million lumbar epidural glucocorticoid injections are performed each year in the Medicare population.[5-8] Uncontrolled studies suggest that these injections provide short-term pain relief for at least some patients with spinal stenosis,[9-15] but data are lacking from rigorous randomized, controlled trials evaluating effectiveness and safety.[16] Therefore, we designed the Lumbar Epidural Steroid Injections for Spinal Stenosis (LESS) trial to compare the effectiveness of epidural injections of glucocorticoids plus anesthetic with injections of anesthetic alone in patients with lumbar spinal stenosis.

Methods

Study Design and Oversight

This double-blind, randomized, controlled trial was conducted at 16 sites in the United States. Details of the trial design and methods were published previously.[17] The study was approved by the institutional review board at each site and was overseen by an independent data and safety monitoring board. All patients provided written informed consent. There was no commercial sponsorship. The first and last authors vouch for the accuracy of the data and analyses and adherence to the study protocol (available with the full text of this article at NEJM.org). This report is focused on the patient-reported outcomes at the primary evaluation 6 weeks after randomization.

Enrollment and Randomization

Patients with spinal stenosis who were referred for epidural glucocorticoid injections were invited to participate in this study by the treating physician or research coordinator. To be eligible, participants had to be at least 50 years of age and have evidence of central lumbar spinal stenosis on magnetic resonance imaging or computed tomography. Additional eligibility criteria were an average pain rating of more than 4 (on a scale of 0 to 10, with 0 indicating no pain and 10 indicating "pain as bad as you can imagine") for pain in the lower back, buttock, leg, or a combination of these sites on standing, walking, or spinal extension in the past week; worse pain in the buttock, leg, or both than in the back; and a score of 7 or higher on the Roland–Morris Disability Questionnaire (RMDQ) (with scores ranging from 0 to 24, and higher scores indicating greater disability). Patients who did not have stenosis of the central canal, those with spondylolisthesis requiring surgery, and those who had a history of lumbar surgery or had received epidural glucocorticoid injections within the previous 6 months were excluded. Additional inclusion and exclusion criteria are provided in Table 1 in the Supplementary Appendix, available at NEJM.org.

A study physician reviewed each potential participant's imaging studies to confirm the presence of stenosis in the central spinal canal and rated it as mild, moderate, or severe. Patients were informed that they would be randomly assigned to receive a standard epidural injection of either glucocorticoids plus lidocaine or lidocaine alone, that they could receive a repeat injection at 3 weeks if they wished (at the discretion of the treating physician), and that they could cross over to the other treatment after the 6-week assessment.

The data coordinating center generated electronically concealed, permuted-block randomized assignments for each recruitment site. Two opaque syringes — one with glucocorticoids plus lidocaine and the other with lidocaine alone — were prefilled for each procedure. At the time of the procedure, the randomization assignment was obtained through a password-protected study website by a clinical assistant who was not involved with subsequent data collection. The assignment indicated which syringe should be labeled "inject" and which should be labeled "discard." The assistant confirmed the physician's use of the syringe marked "inject." In this blinded trial, the treating physicians, patients, and re-

search staff who conducted follow-up were unaware of the treatment received.

INTERVENTIONS

Twenty-six board-certified anesthesiologists, physiatrists, and radiologists with expertise in administering epidural glucocorticoid injections performed the procedures. Study physicians were trained by the study investigators to administer the injections in a standardized manner with the use of fluoroscopic guidance.[17] Physicians were instructed to choose the injection level (e.g., L5–S1) one spinal level below the maximal canal stenosis for interlaminar injections and at the root level where symptoms were most pronounced for transforaminal injections, although bilateral and multilevel transforaminal injections were allowed. The physician chose the approach (transforaminal or interlaminar), which remained consistent with subsequent injections for each patient. The glucocorticoid injectable solution consisted of 1 to 3 ml of 0.25% to 1% lidocaine followed by 1 to 3 ml of triamcinolone (60 to 120 mg), betamethasone (6 to 12 mg), dexamethasone (8 to 10 mg), or methylprednisolone (60 to 120 mg). The physician selected the glucocorticoid according to his or her usual practice. The procedure for the lidocaine injection was identical to that for the glucocorticoid–lidocaine injection except that the injectable solution was an equivalent volume of 0.25% to 1% lidocaine alone.

OUTCOMES

Two primary outcomes were measured at 6 weeks: the RMDQ score[18] and the patient's rating of average buttock, hip, or leg pain in the previous week. The RMDQ wording was modified slightly to specify problems due to back pain or leg pain (sciatica) rather than solely back pain.

Secondary outcomes included the proportion of patients with at least minimal clinically meaningful improvement (≥30%) and the proportion with substantial clinically meaningful improvement (≥50%)[19-21] from baseline to 6 weeks on each measure. Other secondary outcomes were ratings of average back pain in the previous week (on a scale of 0 to 10, with higher scores indicating a higher intensity of back pain); scores on the Brief Pain Inventory (BPI) interference scale (from 0 to 10, with higher scores indicating more pain-related interference with activity)[22]; scores on the eight-question version of the Patient Health Questionnaire (PHQ-8; on a scale from 0 to 24, with higher scores indicating more depressive symptoms)[23]; scores on the Generalized Anxiety Disorder 7 scale (GAD-7; on a scale from 0 to 21, with higher scores indicating more severe anxiety)[24]; scores on the EQ-5D (formerly called the European Quality of Life–5 Dimensions) questionnaire (with scores ranging from 0 to 1 and lower scores indicating worse quality of life)[25]; and scores on the Swiss Spinal Stenosis Questionnaire (SSSQ),[26] which was composed of subscales for symptoms (scores of 1 to 5, with higher scores indicating worse symptoms), physical function (scores of 1 to 4, with higher scores indicating worse function), and satisfaction with treatment (scores of 1 to 4, with higher scores indicating less satisfaction).

ASSESSMENTS

At baseline, patients provided demographic, clinical, and disease-history information and rated their expectations of pain relief after receiving an injection. All outcomes were assessed at baseline and at 3 and 6 weeks after randomization. Research staff who were unaware of the patients' treatment assignments conducted all assessments by telephone, in-person interview, or mailed questionnaires. Five weeks after randomization, the patients and providers were asked to guess which treatment the patient had received. Morning serum cortisol levels (before 9 a.m.) were also obtained at baseline, 3 weeks, and 6 weeks as a measure of the degree of systemic glucocorticoid absorption.

ADVERSE-EVENT REPORTING

Participants were asked at each follow-up about unexpected medical events, including hospitalizations and emergency department visits, since the last contact. Treating physicians documented adverse events during or immediately after the procedure.

STATISTICAL ANALYSIS

For the primary analyses, we used an intention-to-treat strategy. The differences in treatment effects and 95% confidence intervals were calculated with the use of analysis of covariance (ANCOVA) with adjustment for the baseline value of the outcome measure. Adjustment was also made for the recruitment site. An indicator of treatment group was coded such that negative values of the treatment effect indicated greater improvement in the glucocorticoid–lidocaine group. We conducted parallel analyses of RMDQ

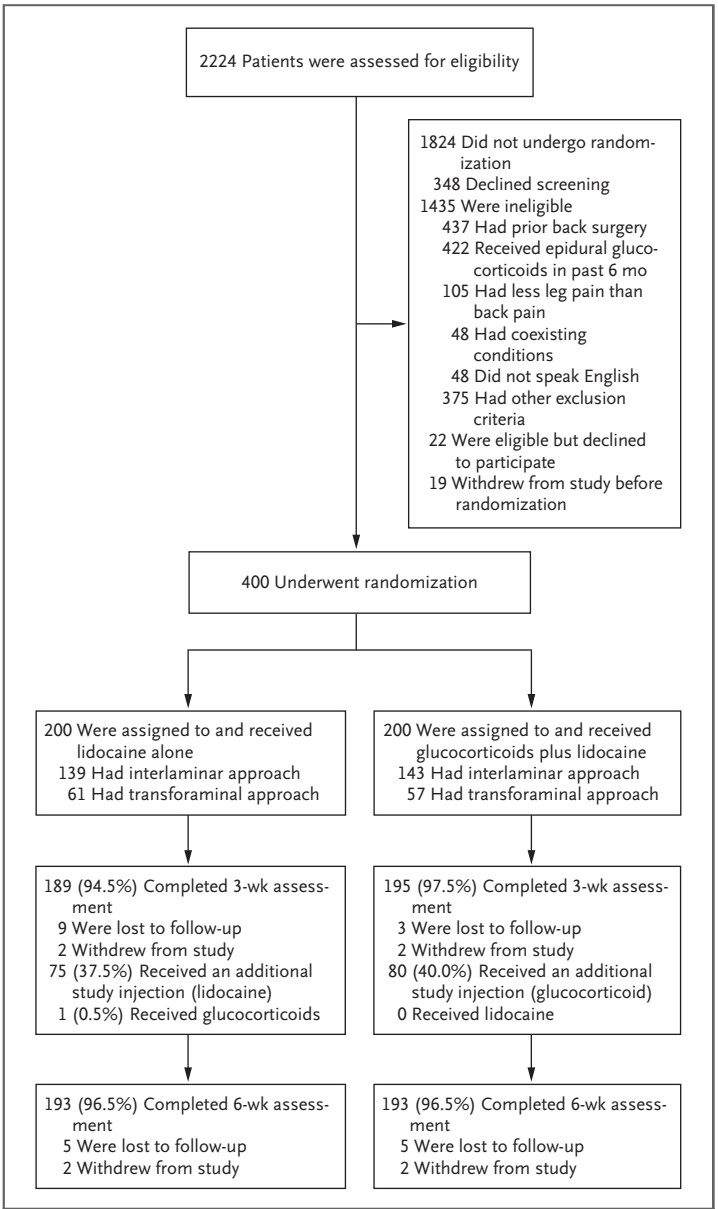

Figure 1. Enrollment, Randomization, and Follow-up.

scores and leg pain and did not prespecify a correction for multiple comparisons. Separate ANCOVA models were used to estimate the differences within subgroups defined according to race (white or nonwhite) and injection approach (interlaminar or transforaminal). Because there was an imbalance between groups at baseline with respect to the duration of pain, we conducted a post hoc analysis of the primary outcomes at 6 weeks, adjusting for baseline duration of pain.

In separate analyses, we used logistic-regression models to compare the proportions of patients in each group who had 30% or more improvement and 50% or more improvement in RMDQ scores and ratings of the intensity of leg pain, had scores on the SSSQ satisfaction scale indicating satisfaction with treatment, had one or more adverse events in the first 6 weeks, and had morning cortisol levels that were consistent with suppression of the hypothalamic–pituitary axis (Table 3 in the Supplementary Appendix). We used Poisson regression models with robust standard errors to compare the 6-week rates of adverse events per person. The blinding index described by Bang et al.,[27] which ranges from –1 to 1, with –1 indicating that all patients guessed the incorrect treatment, 0 indicating that all patients randomly guessed their study-group assignments, and 1 indicating that all patients correctly guessed their study-group assignments, was used to evaluate the effectiveness of blinding within each treatment group.

We used a Bonferroni-corrected significance threshold of 0.05 divided by 2 (or 0.025) in analyses within subgroups for race and injection approach. All other reported P values are based on two-sided tests, with a P value of less than 0.05 considered to indicate statistical significance.

We powered the study to evaluate the overall effectiveness of glucocorticoids plus lidocaine versus lidocaine alone, as well as the effectiveness within subgroups based on race (white or nonwhite) and injection approach (interlaminar or transforaminal). The study was powered for the outcome of the RMDQ score at 6 weeks, conservatively assuming a standard deviation of 7.5 in each group, a correlation between baseline and 6-week scores of 0.30, a retention rate of 85%, and a two-sided alpha level of 0.05. Assuming a common treatment effect among the subgroups in an ANCOVA model, with 400 randomly assigned participants, the overall comparison in an assessment of glucocorticoids plus lidocaine versus lidocaine alone would have 83% power to detect a difference of 2.25 points or more in the RMDQ score (a conservative estimate of the minimal clinically important difference for the RMDQ score[28]) and a difference of 3.25 points or more for prespecified subgroups. With the use of the observed study data in a post hoc power analysis, the study design had 80% power to detect differences between the groups of 1.6 points in the RMDQ score and 0.8 points in the rating of leg pain.

RESULTS

PATIENTS

Between April 2011 and June 2013, a total of 2224 patients were screened, of whom 441 were eligible and 400 were randomly assigned to receive an epidural injection of glucocorticoids plus lidocaine (200 patients) or lidocaine alone (200 patients). A total of 282 patients received interlaminar injections and 118 received transforaminal injections (Fig. 1). The two groups were similar with respect to baseline characteristics, except that the duration of pain was shorter in the lidocaine-alone group (Table 1, and Table 2 in the Supplementary Appendix).

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Lidocaine (N=200)	Glucocorticoid–Lidocaine (N=200)
Age — yr	68.1±10.2	68.0±9.8
Female sex — no. (%)	104 (52.0)	117 (58.5)
Race or ethnic group — no. (%)†		
White	139 (69.5)	137 (68.5)
Black	52 (26.0)	53 (26.5)
Other	9 (4.5)	10 (5.0)
Hispanic	6 (3.0)	11 (5.5)
Educational level — no. (%)		
High school, GED diploma, or less	67 (33.5)	60 (30.0)
Some college, vocational, or technical education	56 (28.0)	72 (36.0)
Undergraduate degree	32 (16.0)	33 (16.5)
Professional or graduate degree	45 (22.5)	35 (17.5)
Married or living with partner — no. (%)	111 (55.5)	126 (63.0)
Employment status — no. (%)		
Employed full-time or part-time	71 (35.5)	57 (28.5)
Retired, not disabled	88 (44.0)	93 (46.5)
Retired, disabled	23 (11.5)	31 (15.5)
Other	18 (9.0)	19 (9.5)
Current smoker — no. (%)‡	32 (16.1)	25 (12.5)
Diabetes, receiving insulin — no. (%)	15 (7.5)	16 (8.0)
Body-mass index§	29.7±6.0	31.1±6.5
Duration of pain — no. (%)‡¶		
<3 mo	40 (20.1)	24 (12.0)
3 to <12 mo	62 (31.2)	59 (29.5)
1 to 5 yr	42 (21.1)	67 (33.5)
>5 yr	55 (27.6)	50 (25.0)
Rating for expectation of pain relief‖	7.8±1.9	7.7±1.8
RMDQ score**	15.7±4.3	16.1±4.5
Score on numerical rating scale for intensity of leg pain††	7.2±1.8	7.2±1.9

* Plus–minus values are means ±SD. GED denotes General Educational Development.
† Race or ethnic group was self-reported. The categories of race and ethnic group are not mutually exclusive.
‡ Data were missing for one patient in the lidocaine group.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The difference between the groups was significant (P=0.02 by the chi-square test).
‖ Patients rated their expectation of pain relief from the epidural injection on a scale from 0 to 10, with 0 indicating "not at all helpful" and 10 indicating "extremely helpful."
** The composite score on the Roland–Morris Disability Questionnaire (RMDQ) is the numerical sum of 24 yes-or-no items. Total scores range from 0 to 24, with 0 indicating no physical limitations and 24 indicating extreme physical limitations from back pain, leg pain, or both.
†† Scores on the numerical rating scale for the intensity of buttock, hip, and leg pain range from 0 to 10, with 0 indicating no pain and 10 indicating "pain as bad as you can imagine."

OUTCOMES

At 6 weeks, both the glucocorticoid–lidocaine group and the lidocaine-alone group had improvement in the RMDQ score as compared with the baseline score (–4.2 points and –3.1 points, respectively), but there was no significant between-group difference in the RMDQ score (adjusted difference in the average treatment effect between the glucocorticoid–lidocaine group and the lidocaine-alone group, –1.0 points; 95% confidence interval [CI], –2.1 to 0.1; P=0.07) or the intensity of leg pain (adjusted difference in the av-

Table 2. Primary Outcomes According to Treatment Group and Injection Approach.*

Variable	Lidocaine			Glucocorticoid–Lidocaine			Treatment Comparison	
	No. of Patients	Overall Mean	Mean Change from Baseline	No. of Patients	Overall Mean	Mean Change from Baseline	Adjusted Difference (95% CI)†	P Value
Overall								
RMDQ score								
Baseline	200	15.7±4.3	—	200	16.1±4.5	—	—	—
3 wk	189	13.1±5.7	–2.6±4.4	195	11.7±6.1	–4.4±5.7	–1.8 (–2.8 to –0.9)	<0.001
6 wk‡	193	12.5±6.4	–3.1±5.3	193	11.8±6.3	–4.2±5.8	–1.0 (–2.1 to 0.1)	0.07
Score on numerical rating scale for leg pain								
Baseline	200	7.2±1.8	—	200	7.2±1.9	—	—	—
3 wk	188	5.0±2.8	–2.2±2.9	195	4.4±2.7	–2.9±2.8	–0.6 (–1.2 to –0.1)	0.02
6 wk	193	4.6±2.9	–2.6±3.0	193	4.4±2.9	–2.8±3.1	–0.2 (–0.8 to 0.4)	0.48
Interlaminar approach								
RMDQ score								
Baseline	139	16.0±4.1	—	143	16.7±4.3	—	—	
3 wk	135	13.2±5.6	–2.9±4.6	139	11.3±6.3	–5.4±5.8	–2.5 (–3.7 to –1.3)	<0.001
6 wk§	136	12.6±6.3	–3.3±5.3	136	11.8±6.5	–4.8±6.0	–1.4 (–2.8 to –0.1)	0.04
Score on numerical rating scale for leg pain								
Baseline	139	7.4±1.8	—	143	7.3±1.9	—	—	—
3 wk	134	5.0±2.7	–2.4±3.0	139	4.1±2.7	–3.2±2.9	–0.9 (–1.5 to –0.3)	0.005
6 wk	136	4.5±2.9	–2.8±3.1	136	4.2±3.0	–3.1±3.3	–0.3 (–1.0 to 0.4)	0.37
Transforaminal approach								
RMDQ score								
Baseline	61	14.8±4.5	—	57	14.4±4.4	—	—	—
3 wk	54	13.0±6.1	–1.8±3.9	56	12.6±5.4	–1.8±4.7	–0.1 (–1.7 to 1.6)	0.94
6 wk§	57	12.1±6.6	–2.6±5.3	57	12.0±5.6	–2.4±4.7	0.3 (–1.9 to 1.8)	0.95
Score on numerical rating scale for leg pain								
Baseline	61	7.0±1.8	—	57	7.0±2.0	—	—	—
3 wk	54	5.1±2.7	–2.0±2.6	56	5.0±2.5	–1.9±2.1	–0.0 (–0.9 to 0.9)	0.99
6 wk	57	4.9±2.7	–2.0±2.8	57	4.9±2.6	–2.0±2.6	0.1 (–0.9 to 1.0)	0.89

* Plus–minus values are means ±SD. CI denotes confidence interval.
† Differences were adjusted for baseline outcome values as well as recruitment site. Negative analysis-of-covariance coefficients favor the glucocorticoid–lidocaine group; positive coefficients favor the lidocaine-only group.
‡ In the primary outcome assessment, P<0.05 was considered to indicate statistical significance.
§ In the prespecified subgroup analysis, P<0.025 was considered to indicate statistical significance.

erage treatment effect, −0.2 points; 95% CI, −0.8 to 0.4; P=0.48) (Table 2). At 3 weeks, there were small between-group differences in the RMDQ score (average treatment effect, −1.8 points; 95% CI, −2.8 to −0.9; P<0.001) and the intensity of leg pain (average treatment effect, −0.6 points; 95% CI, −1.2 to −0.1; P=0.02). There were no significant differences in the proportions of patients in the glucocorticoid–lidocaine group and the lidocaine-alone group who had 30% improvement in the RMDQ score (37.3% and 31.6%, respectively; P=0.24), 50% improvement in the RMDQ score (23.8% and 20.2%, P=0.39), 30% improvement in the rating of leg pain at 6 weeks (49.2% and 49.7%, P=0.88), and 50% improvement in the rating of leg pain at 6 weeks (38.3% and 38.3%, P=0.97). Post hoc adjustment for the baseline duration of pain resulted in a statistically significant but small between-group difference in the RMDQ score (average treatment effect, −1.2 points; 95% CI, −2.3 to −0.1; P=0.03) at 6 weeks, but with no significant between-group difference in the intensity of leg pain (average treatment effect, −0.3 points; 95% CI, −0.9 to 0.3; P=0.32).

Secondary Outcomes

At 6 weeks, there were no significant differences between the treatment groups with respect to the BPI, SSSQ symptoms and physical function, EQ-5D, or GAD-7 scales (Fig. 2). On the PHQ-8 scale, the glucocorticoid–lidocaine group had more improvement with respect to symptoms of depression (P=0.007). On the SSSQ satisfaction scale, 67% of patients who received glucocorticoids plus lidocaine reported being very or somewhat satisfied with their treatment, as compared with 54% of those who received lidocaine alone (P=0.01).

Subgroup Analyses

Among patients who received interlaminar injections, those assigned to glucocorticoids plus lidocaine, as compared with those assigned to lidocaine alone, reported better physical function on the RMDQ (average treatment effect, −2.5 points; 95% CI, −3.7 to −1.3; P<0.001) and less leg pain (average treatment effect, −0.9 points; 95% CI, −1.5 to −0.3; P=0.005) at 3 weeks. However, there were no significant differences between the two treatment groups in any outcome at 6 weeks. Among patients who received transforaminal injections, there were no significant differences between the groups in any outcome at 3 or 6 weeks (Table 2). There were no significant interactions between race and treatment in analyses of RMDQ scores (P=0.73 for interaction) or leg pain (P=0.99 for interaction) at 6 weeks.

ADVERSE EVENTS

The proportion of patients reporting one or more adverse events was 21.5% in the glucocorticoid–lidocaine group and 15.5% in the lidocaine-alone group (P=0.08). There were more adverse events on average per person in the glucocorticoid–lidocaine group than in the lidocaine-alone group (P=0.02) (Table 3). Among the patients who received glucocorticoids plus lidocaine, the rate of adverse events was higher among patients who received transforaminal injections (0.46) than among patients who received interlaminar injections (0.22) (Table 3, and Table 3 in the Supplementary Appendix).

CORTISOL SUPPRESSION

At both 3 and 6 weeks, a significantly higher proportion of patients in the glucocorticoid–lidocaine group than in the lidocaine-alone group had morning serum cortisol levels of less than 3 μg per deciliter (<80 nmol per liter) or less than 10 μg per deciliter (300 nmol per liter) (Table 3).

BLINDING

The physicians, patients, and outcome assessors were unaware of the assigned treatment (blinding index in the glucocorticoid–lidocaine group, 0.04; 95% CI, −0.02 to 0.09; blinding index in the lidocaine-alone group, 0.04; 95% CI, −0.02 to 0.10).

DISCUSSION

In a multicenter, double-blind trial of fluoroscopically guided epidural injections for lumbar spinal stenosis, we observed no significant differences at 6 weeks between patients assigned to glucocorticoids plus lidocaine and those assigned to lidocaine alone with respect to pain-related functional disability (as measured by the RMDQ) or pain intensity. At 3 weeks, the glucocorticoid–lidocaine group had greater improvement than the lidocaine-alone group, but the differences were clinically insignificant.

Despite a rapid increase in the use of epidural glucocorticoid injections for lumbar spinal

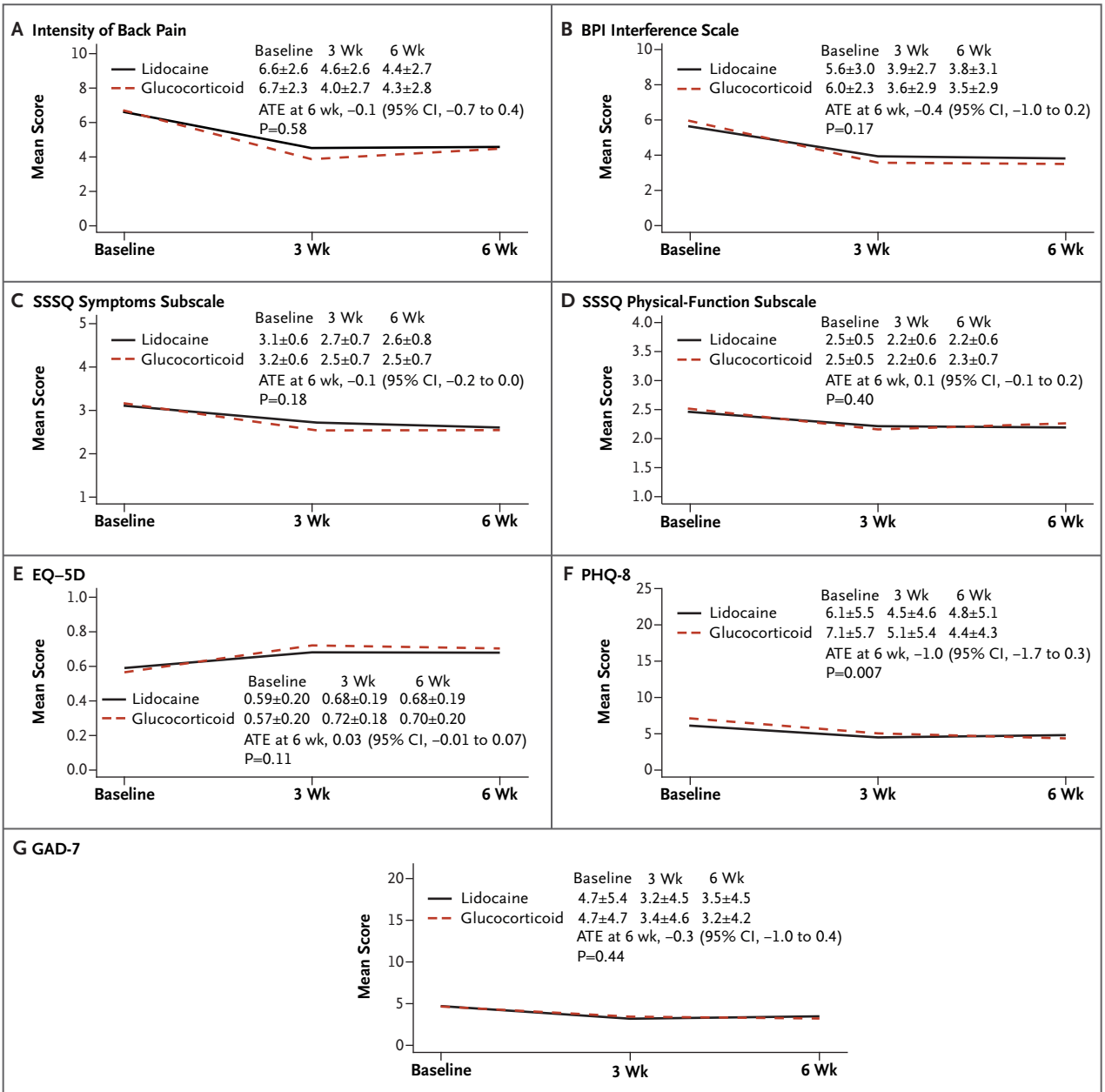

Figure 2. Secondary Outcomes.

Secondary outcomes were the mean (±SD) scores on the numerical rating scale for the intensity of back pain (Panel A), the Brief Pain Inventory (BPI) interference scale (Panel B), the Swiss Spinal Stenosis Questionnaire (SSSQ) subscales for symptoms (Panel C) and physical function (Panel D), the EQ-5D (formerly called the European Quality of Life–5 Dimensions) questionnaire (Panel E), the eight-question version of the Patient Health Questionnaire (PHQ-8) (Panel F), and the Generalized Anxiety Disorder 7 (GAD-7) scale (Panel G). The numerical rating scale for the intensity of back pain indicates ratings of average back pain in the past week (on a scale of 0 to 10, with higher scores indicating a higher intensity of back pain). Scores on the BPI interference scale range from 0 to 10, with higher scores indicating greater pain-related interference with activity. Scores on the SSSQ subscale for symptoms range from 1 to 5, with higher scores indicating worse symptoms, and scores on the SSSQ subscale for physical function range from 1 to 4, with higher scores indicating worse function. Scores on the EQ-5D scale range from 0 to 1, with lower scores indicating worse quality of life. Scores on the PHQ-8 range from 0 to 24, with higher scores indicating more depressive symptoms. Scores on the GAD-7 scale range from 0 to 21, with higher scores indicating more severe anxiety. The average treatment effect (ATE) — the between-group difference in the outcomes at 6 weeks — is shown for each outcome.

stenosis, there is little evidence of effectiveness from clinical trials. Limited conclusions can be drawn from the few previous trials of epidural glucocorticoid injections for spinal stenosis, because they were small, uncontrolled, or conducted without the use of fluoroscopy.[29] Our large, controlled trial, in which both patients and clinicians were unaware of the treatment assignments, provides no evidence of a treatment effect at 6 weeks with fluoroscopically guided epidural injections of glucocorticoids plus lidocaine as compared with lidocaine alone.

In analyses adjusted for the duration of pain (which was longer in the glucocorticoid group), the glucocorticoid–lidocaine group had significantly greater improvement in the RMDQ score at 6 weeks, but the difference was small. Patients who received glucocorticoids plus lidocaine also reported greater treatment satisfaction and greater reductions in depressive symptoms. At 3 weeks, patients in the glucocorticoid–lidocaine group had slightly more improvement in pain and function outcomes than did patients who received lidocaine alone. This small treatment benefit observed at 3 weeks or other unmeasured glucocorticoid effects (e.g.,

Table 3. Adverse Events and Cortisol Suppression at 6 Weeks.

Adverse Event	Lidocaine (N=200)	Glucocorticoid–Lidocaine (N=200)	P Value
≥1 event — no. of patients (%)	31 (15.5)	43 (21.5)	0.08
Total adverse events — no. of events (event rate)	34 (0.17)	58 (0.29)	0.02
Adverse events according to approach — no. of events/total no. of patients (event rate)			
Interlaminar approach	14/139 (0.10)	32/143 (0.22)	0.02
Transforaminal approach	20/61 (0.33)	26/57 (0.46)	0.27
Reported symptoms or events — no.			
Excessive pain	7	5	
Headache	3	8	
Fever, infection, or both	2	10	
Dizziness, light-headedness, or both	4	4	
Numbness, tingling, or both	4	5	
Cardiovascular problems, lung problems, or both	2	6	
Falls	2	4	
Facial flushing	0	3	
Skin irritation	4	2	
Leg swelling	1	2	
Dural puncture	1	1	
Other	4	11	
Serious adverse events: hospitalization, surgery, or both — no.	4	5	
Morning cortisol level — no. of patients/total no. (%)*			
3 wk			
<3 μg/dl	1/151 (0.7)	16/163 (9.8)	<0.001
<10 μg/dl	64/151 (42.4)	98/163 (60.1)	0.001
6 wk			
<3 μg/dl	0/148 (0)	5/152 (3.3)	0.06
<10 μg/dl	56/148 (37.8)	81/152 (53.3)	0.01

* Because of the small number of patients, 3-week and 6-week cortisol levels below 3 μg per deciliter were compared with the use of Fisher's exact test. To convert the values for cortisol to nanomoles per liter, multiply by 27.59.

reduced fatigue) may have decreased symptoms of depression and increased patient satisfaction with glucocorticoids.

In analyses stratified according to injection approach, transforaminal injections of glucocorticoids plus lidocaine showed no significant benefit over transforaminal injections of lidocaine alone at 3 or 6 weeks. Interlaminar injections of glucocorticoids plus lidocaine were associated with significant advantages over interlaminar injections of lidocaine alone with respect to function and pain at 3 weeks, but the observed between-group differences were of minimal clinical significance and were not apparent at 6 weeks. Previous studies have suggested greater efficacy of transforaminal glucocorticoid injections than of interlaminar injections.[30-32] Our study was not designed to directly compare the effectiveness of transforaminal versus interlaminar injections. Because we did not randomly assign patients according to injection approach, we cannot rule out the possibility that other factors associated with the injection approach contribute to or account for the difference.

Serious adverse events were rare in our study. However, there were more reported adverse events in the glucocorticoid–lidocaine group than in the lidocaine-alone group and in the transforaminal subgroup than in the interlaminar subgroup. Exogenously administered glucocorticoids have systemic effects that can include suppression of the hypothalamic–pituitary axis[33,34] and reduced bone mineral density, with an increased risk of fracture.[35,36] We observed higher rates of cortisol suppression at 3 and 6 weeks among patients who received injections that included glucocorticoids; these findings are consistent with systemic absorption of glucocorticoids.

Patients in both treatment groups had decreased pain and improved function. Potential explanations for the similar improvements in the two groups include placebo effects, regression to the mean, the natural history of spinal stenosis, and other factors present in both study groups, including contact with study personnel and receipt of lidocaine. We did not include a sham injection group and thus cannot assess whether lidocaine alone conferred a benefit. Although it has been proposed that epidural lidocaine alone may have longer-term therapeutic effects,[37-39] a sustained benefit from lidocaine injection alone has not been rigorously demonstrated.

In conclusion, in the treatment of symptoms of lumbar spinal stenosis, epidural injections of glucocorticoids plus lidocaine offered minimal or no benefit over epidural injections of lidocaine alone at 6 weeks.

Supported by a grant (1R01HS019222-01) from the Agency for Healthcare Research and Quality.

Dr. Bresnahan reports holding stock in and being a former employee of Johnson & Johnson. Dr. Smuck reports receiving consulting fees from ArthroCare and grant support through his institution from Cytonics and Seikagaku. Dr. Jarvik reports receiving fees for serving on an advisory board for General Electric and consulting fees from HealthHelp and holding patents (issued to PhysioSonics) regarding acoustic palpation with the use of noninvasive ultrasonographic techniques for identification of target sites and assessment of chronic pain disorders. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the LESS scientific advisory board and Pradeep Suri, M.D., for his contributions in the review of adverse events.

APPENDIX

The authors' affiliations are as follows: Comparative Effectiveness, Cost and Outcomes Research Center (J.L.F., B.A.C., J.A.T., P.J.H., S.D.S., Z.B., B.W.B., L.K., J.G.J.), and the Departments of Rehabilitation Medicine (J.L.F., J.A.T., C.S.), Biostatistics (B.A.C., P.J.H.), Psychiatry and Behavioral Sciences (J.A.T.), Radiology (Z.B., B.W.B., J.G.J.), and Health Services (B.W.B., L.K.), University of Washington, Seattle; the Departments of Family Medicine and Internal Medicine (R.A.D.), Public Health and Preventive Medicine (R.A.D.), and Anesthesiology and Perioperative Medicine (D.S.), and the Oregon Institute of Occupational Health Sciences (R.A.D.), Oregon Health and Science University, and Kaiser Permanente Center for Health Research (R.A.D.) — all in Portland; the Division of Research, Kaiser Permanente Northern California, Oakland (A.L.A.), Department of Physical Medicine and Rehabilitation, Kaiser Permanente Martinez Medical Center, Martinez (A.C.), the Department of Physical Medicine and Rehabilitation, Kaiser Permanente Redwood City Medical Center (W.F.), and the Department of Physical Medicine and Rehabilitation, Stanford University Medical Center (D.J.K., M.S.) — both in Redwood City, Spine Care Services, and Complementary and Alternative Medicine (H.G.), and the Department of Physical Medicine and Rehabilitation (L.W.), Kaiser Permanente San Jose Medical Center, San Jose, and the Department of Physical Medicine and Rehabilitation, Kaiser Permanente Roseville Medical Center, Roseville (M.T.) — all in California; the Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Spine Unit, Harvard Vanguard Medical Associates (S.S.N.), Department of Anesthesiology and Pain Medicine, St. Elizabeth's Medical Center (F.J.G.), and Center for Pain Medicine, Massachusetts General Hospital (C.G.) — all in Boston; the Neuroscience Institute, Henry Ford Hospital (D.R.N.), and the Departments of Orthopedic Surgery (S.M.) and Radiology (W.S.), Henry Ford Health System — both in Detroit; the Department of Physical Medicine and Rehabilitation, University of Colorado, Aurora (V.A.); the Department of Physical Medicine and Rehabilitation, Dallas Veterans Affairs Medical Center, Dallas (T.A.); the Department of Radiology, Mayo Clinic, Rochester, MN (F.D.); and the Departments of Anesthesiology and Psychiatry, University of Pittsburgh, Pittsburgh (A.W.).

REFERENCES

1. Harrast MA. Epidural steroid injections for lumbar spinal stenosis. Curr Rev Musculoskel Med 2008;1:32-8.
2. Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. JAMA 2010;303:1259-65.
3. Daffner SD, Wang JC. The pathophysiology and nonsurgical treatment of lumbar spinal stenosis. Instr Course Lect 2009;58:657-68.
4. Englund J. Lumbar spinal stenosis. Curr Sports Med Rep 2007;6:50-5.
5. Friedly J, Chan L, Deyo R. Increases in lumbosacral injections in the Medicare population: 1994 to 2001. Spine (Phila Pa 1976) 2007;32:1754-60.
6. Friedly J, Nishio I, Bishop MJ, Maynard C. The relationship between repeated epidural steroid injections and subsequent opioid use and lumbar surgery. Arch Phys Med Rehabil 2008;89:1011-5.
7. Manchikanti L, Pampati V, Boswell MV, Smith HS, Hirsch JA. Analysis of the growth of epidural injections and costs in the Medicare population: a comparative evaluation of 1997, 2002, and 2006 data. Pain Physician 2010;13:199-212.
8. Manchikanti L, Pampati V, Falco FJ, Hirsch JA. Assessment of the growth of epidural injections in the Medicare population from 2000 to 2011. Pain Physician 2013;16(4):E349-E364.
9. Barre L, Lutz GE, Southern D, Cooper G. Fluoroscopically guided caudal epidural steroid injections for lumbar spinal stenosis: a retrospective evaluation of long term efficacy. Pain Physician 2004;7:187-93.
10. Botwin K, Brown LA, Fishman M, Rao S. Fluoroscopically guided caudal epidural steroid injections in degenerative lumbar spine stenosis. Pain Physician 2007;10: 547-58.
11. Botwin KP, Gruber RD, Bouchlas CG, et al. Fluoroscopically guided lumbar transformational epidural steroid injections in degenerative lumbar stenosis: an outcome study. Am J Phys Med Rehabil 2002;81:898-905.
12. Briggs VG, Li W, Kaplan MS, Eskander MS, Franklin PD. Injection treatment and back pain associated with degenerative lumbar spinal stenosis in older adults. Pain Physician 2010;13(6):E347-E355. [Erratum, Pain Physician 2011;14:217.]
13. 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; 7:311-7.
14. Cosgrove JL, Bertolet M, Chase SL, Cosgrove GK. Epidural steroid injections in the treatment of lumbar spinal stenosis efficacy and predictability of successful response. Am J Phys Med Rehabil 2011; 90:1050-5.
15. Manchikanti L, Cash KA, McManus CD, Pampati V, Abdi S. Preliminary results of a randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 4 — spinal stenosis. Pain Physician 2008;11:833-48.
16. Ammendolia C, Stuber K, de Bruin LK, et al. Nonoperative treatment of lumbar spinal stenosis with neurogenic claudication: a systematic review. Spine (Phila Pa 1976) 2012;37(10):E609-E616.
17. Friedly JL, Bresnahan BW, Comstock B, et al. Study protocol — Lumbar Epidural steroid injections for Spinal Stenosis (LESS): a double-blind randomized controlled trial of epidural steroid injections for lumbar spinal stenosis among older adults. BMC Musculoskelet Disord 2012;13:48.
18. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976) 1983;8:141-4.
19. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-21.
20. Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine (Phila Pa 1976) 2008;33:90-4.
21. Jordan K, Dunn KM, Lewis M, Croft P. A minimal clinically important difference was derived for the Roland-Morris Disability Questionnaire for low back pain. J Clin Epidemiol 2006;59:45-52.
22. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5:133-7.
23. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009;114:163-73.
24. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-7.
25. Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. Qual Life Res 1993;2:169-80.
26. Stucki G, Daltroy L, Liang MH, Lipson SJ, Fossel AH, Katz JN. Measurement properties of a self-administered outcome measure in lumbar spinal stenosis. Spine (Phila Pa 1976) 1996;21:796-803.
27. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials 2004;25:143-56.
28. Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine (Phila Pa 1976) 2000;25:3115-24. [Erratum, Spine 2001;26:847.]
29. Bresnahan BW, Rundell SD, Dagadakis MC, et al. A systematic review to assess comparative effectiveness studies in epidural steroid injections for lumbar spinal stenosis and to estimate reimbursement amounts. PM R 2013;5:705-14.
30. Schaufele MK, Hatch L, Jones W. Interlaminar versus transforaminal epidural injections for the treatment of symptomatic lumbar intervertebral disc herniations. Pain Physician 2006;9:361-6.
31. Lee JH, An JH, Lee SH. Comparison of the effectiveness of interlaminar and bilateral transforaminal epidural steroid injections in treatment of patients with lumbosacral disc herniation and spinal stenosis. Clin J Pain 2009;25:206-10.
32. Thomas E, Cyteval C, Abiad L, Picot MC, Taourel P, Blotman F. Efficacy of transforaminal versus interspinous corticosteroid injection in discal radiculalgia — a prospective, randomised, double-blind study. Clin Rheumatol 2003;22: 299-304.
33. Lansang MC, Farmer T, Kennedy L. Diagnosing the unrecognized systemic absorption of intra-articular and epidural steroid injections. Endocr Pract 2009;15: 225-8.
34. Kay J, Findling JW, Raff H. Epidural triamcinolone suppresses the pituitary-adrenal axis in human subjects. Anesth Analg 1994;79:501-5.
35. Al-Shoha A, Rao DS, Schilling J, Peterson E, Mandel S. Effect of epidural steroid injection on bone mineral density and markers of bone turnover in postmenopausal women. Spine (Phila Pa 1976) 2012;37(25):E1567-E1571.
36. Mandel S, Schilling J, Peterson E, Rao DS, Sanders W. A retrospective analysis of vertebral body fractures following epidural steroid injections. J Bone Joint Surg Am 2013;95:961-4.
37. Bicket MC, Gupta A, Brown CH IV, Cohen SP. Epidural injections for spinal pain: a systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. Anesthesiology 2013;119:907-31.
38. van Eijs F, Geurts J, van Kleef M, et al. Predictors of pain relieving response to sympathetic blockade in complex regional pain syndrome type 1. Anesthesiology 2012;116:113-21.
39. Cohen SP, Kapoor SG, Rathmell JP. Intravenous infusion tests have limited utility for selecting long-term drug therapy in patients with chronic pain: a systematic review. Anesthesiology 2009;111: 416-31.