Annals of Internal Medicine | ORIGINAL RESEARCH

Epidural Steroids, Etanercept, or Saline in Subacute Sciatica

A Multicenter, Randomized Trial

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Background: Perineural inhibitors of tumor necrosis factor have recently generated intense interest as an alternative to epidural steroid injections for lumbosacral radiculopathy.

Objective: To evaluate whether epidural steroids, etanercept, or saline better improves pain and function in adults with lumbosacral radiculopathy.

Design: A multicenter, 3-group, randomized, placebo-controlled trial conducted from 2008 to 2011. Randomization was computer-generated and stratified by site. Pharmacists prepared the syringes. Patients, treating physicians, and nurses assessing outcomes were blinded to treatment assignment. (ClinicalTrials.gov registration number: NCT00733096)

Setting: Military and civilian treatment centers.

Patients: 84 adults with lumbosacral radiculopathy of less than 6 months' duration.

Intervention: 2 epidural injections of steroids, etanercept, or saline, mixed with bupivacaine and separated by 2 weeks.

Measurements: The primary outcome measure was leg pain 1 month after the second injection. All patients had 1-month follow-up visits; patients whose condition improved remained blinded for the 6-month study period.

Results: The group that received epidural steroids had greater reductions in the primary outcome measure than those who received saline (mean difference, −1.26 [95% CI, −2.79 to 0.27]; $P = 0.11$) or etanercept (mean difference, −1.01 [CI, −2.60 to 0.58]; $P = 0.21$). For back pain, smaller differences favoring steroids compared with saline (mean difference, −0.52 [CI, −1.85 to 0.81]; $P = 0.44$) and etanercept (mean difference, −0.92 [CI,−2.28 to 0.44]; $P = 0.18$) were observed. The largest differences were noted for functional capacity, in which etanercept fared worse than the other treatments: steroids vs. etanercept (mean difference, −16.16 [CI, −26.05 to −6.27]; $P = 0.002$), steroids vs. saline (mean difference, −5.87 [CI, −15.59 to 3.85]; $P = 0.23$), and etanercept vs. saline (mean difference, 10.29 [CI, 0.55 to 20.04]; $P = 0.04$). More patients treated with epidural steroids (75%) reported 50% or greater leg pain relief and a positive global perceived effect at 1 month than those who received saline (50%) or etanercept (42%) ($P = 0.09$).

Limitation: Short-term follow-up, small sample size, and a possibly subtherapeutic dose of etanercept.

Conclusion: Epidural steroid injections may provide modest short-term pain relief for some adults with lumbosacral radiculopathy, but larger studies with longer follow-up are needed to confirm their benefits.

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Low back pain continues to exert an enormous toll on industrialized societies, despite the inexorable growth of health care expenditures (1, 2). According to some estimates, the total annual economic cost of this epidemic in the United States approaches $100 million (3). Between 37% and 55% of all cases of spinal pain are estimated to be neuropathic in origin (4, 5). This distinction is important, because classification informs treatment. Herniated disc is the most common cause of neuropathic low back pain in persons younger than 50 years (6). Herniated discs may cause radiculopathy by mechanical compression of a nerve root, initiation of an inflammatory state in a compressed nerve leading to ectopic activity, and an increase in proinflammatory mediators produced from changes in the chemical milieu or inflammatory cell migration (7).

A major contributor to the burden of neuropathic back pain is the lack of reliable treatment. Analgesic agents are associated with high rates of adverse effects and small treatment effects (8, 9). Surgery is effective for acute radicular symptoms, but the long-term benefits remain unproven (10, 11). The confluence of these factors has led to a soaring increase in epidural steroid injections (12, 13), but this treatment is mired in controversy.

Although virtually all reviews acknowledge the effectiveness of epidural steroid injections in certain contexts, conclusions about long-term efficacy are mixed (14–19). There is evidence that transforaminal epidural steroid injections are more effective than the conventional interlaminar approach (20–22). However, burgeoning reports of catastrophic consequences related to the particulate nature of depot steroids (that is, spinal cord infarction)—especially with the transforaminal approach—have led to a quest for safer alternatives (23–25).

See also:

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Appendix Table
Conversion of graphics into slides

Context

Steroid injections are commonly used to treat lumbosacral radiculopathy.

Contribution

This 3-group randomized trial involving 84 adults with lumbosacral radiculopathy of less than 6 months' duration compared 2 epidural injections, separated by 2 weeks, of steroids, etanercept, or saline, mixed with bupivacaine. Leg pain, measured 1 month after the second injection, was reduced more with steroids than with etanercept or saline, although differences were modest and not statistically significant. Differences in back pain and function associated with steroids versus saline also were not statistically significant.

Implication

Larger trials of longer duration are needed to establish the benefits of epidural steroids for lumbosacral radiculopathy.

—The Editors

Cytokine inhibitors have generated intense interest as a possible treatment for radiculopathy. Preclinical and clinical studies, including 1 small controlled study demonstrating favorable results (26), provide a compelling case for tumor necrosis factor (TNF)-α, a prototypical cytokine, in the treatment of radicular pain (27–31). Even more favorable is that biological agents that antagonize TNF can prevent neuropathologic activity that follows dorsal root ganglia–TNF receptor activation, such as edema formation, demyelination, and decreased conduction (30, 32–34).

Because local administration of cytokine antagonists enables higher drug concentrations to be reached at the site of pathology, this method may be more effective and safer than systemic use of these agents (33, 35–37). Previous animal studies established both the safety and efficacy of off-label neuraxial etanercept (26, 38). A major obstacle in evaluating the literature on epidural administration is that no randomized study has compared treatments. To address this gap, we conducted a multicenter, placebo-controlled study comparing epidural steroids, etanercept, and saline for lumbosacral radiculopathy.

METHODS

Design Overview

We performed a randomized, controlled, parallel-group study in which participants were allocated in a 1:1:1 ratio to receive epidural etanercept, epidural steroids, or epidural saline. Patients, treating physicians, and evaluators were blinded to treatment assignments. Permission to conduct this study was granted by the internal review boards of Walter Reed Army Medical Center, Brooke Army Medical Center, Landstuhl Regional Medical Center, Womack Army Hospital at Fort Bragg, Massachusetts General Hospital, and The Johns Hopkins Hospital. All study participants gave written informed consent. No patients were recruited from Massachusetts General Hospital. All procedures and follow-up visits were performed between June 2008 and March 2011.

Settings and Participants

The study sites included 3 large U.S. military medical centers (Womack Army Hospital at Fort Bragg, Brooke Army Medical Center, and 2 separate pain clinics at Walter Reed Army Medical Center) that treat service members, military dependents, and retirees; 1 military hospital in Germany (Landstuhl Regional Medical Center) that treats coalition forces from Operations Iraqi Freedom and Enduring Freedom and Department of Defense beneficiaries throughout Europe and the Middle East; and 2 civilian hospitals. Patients were recruited from the regular pain clinic populations at the respective institutions, as well as primary care settings at affiliated sites (for example, community hospitals at Fort Meade and Fort Belvoir for Walter Reed Army Medical Center). Advertisements provided to specialists and primary care providers and lectures were used to facilitate referrals.

Inclusion criteria were age 18 years or older and age younger than 70 years, lumbosacral radiculopathy more than 4 weeks but 6 months or less in duration, leg pain that is more than or as severe as back pain, failure of conservative therapy, and evidence on magnetic resonance imaging of a pathologic disc condition correlating with symptoms (for example, herniated disc or annular tear). Persons with coagulopathy or systemic infection, an unstable medical or psychiatric condition, previous spinal surgery, previous epidural steroid injection, or an allergy to contrast dye were excluded.

Randomization, Blinding, and Interventions

Eighty-four participants were apportioned equally into 1 of the 3 treatment groups. The main research nurse performed randomization schemes in groups of 6 through computer-generated randomization tables, stratified by study site. An investigator-physician enrolled the participants, and a research assistant divulged treatment allocation. Three syringes were prearranged to enable blinding: contrast dye; 0.5% bupivacaine; and the study drug, which was prepared by the research pharmacist and concealed from the treating physician. In group 1, the study drug was 60 mg of methylprednisolone acetate plus 0.5 mL of saline for a total volume of 2 mL; in group 2, the intervention was Enbrel (Immunex, Seattle, Washington) (4 mg of etanercept reconstituted in 2 mL of sterile water); and in group 3, it was 2 mL of normal saline. Before the allocated treatment, all groups received 0.5 mL of 0.5% bupivacaine.

Each procedure was performed by a board-certified pain medicine physician or at teaching hospitals (for example, Walter Reed Army Medical Center) by either the attending physician or a pain management fellow supervised

by the attending physician. The segmental level at which the patient was injected was chosen on the basis of symptoms and radiologic findings. In patients with single-level pathology, 1 level was targeted. In patients with less discrete symptoms or multilevel pathology, 2 levels were injected by using divided drug doses with the same volume per level (that is, 30 mg of a steroid or 2 mg of etanercept in 2 mL of sterile water at 2 injection sites).

Under sterile conditions, the image intensifier was adjusted to confer an oblique view and the treating physician inserted a 22-gauge spinal needle into the upper quadrant of the targeted foramen under fluoroscopic guidance. Correct position was confirmed in anteroposterior, oblique, and lateral views, with the injection of 1 mL of contrast dye revealing a neurogram and epidural uptake.

Once the needle was properly located, the treating physician who performed the procedure left the room and a disinterested physician administered the 0.5 mL of 0.5% bupivacaine, followed by the concealed study drug. Neither the treating physician nor the patient was aware of the contents of the preprepared syringe. The same procedure was repeated 2 weeks after the initial injection by either the same or a different physician, unless clinical circumstances dictated otherwise (that is, the patient declined a second injection because of lack of improvement in symptoms [$n = 5$] or satisfaction with pain relief [$n = 5$]). Between the first injection and first follow-up visit, no patient had any additional therapeutic interventions.

Participants received written instructions from the treating physician about how to increase or decrease analgesic medications based on their response to therapy. For patients with debilitating pain who required interval rescue analgesics, breakthrough opioids (if previously prescribed) could be temporarily increased, or a nonsteroidal anti-inflammatory drug or tramadol was prescribed.

Outcome Measures and Follow-up

Outcome data were obtained by a physician or research nurse blinded to treatment group. The first follow-up visit occurred 1 month after the second injection or 1 month after the first injection in the 10 persons who received only 1 injection. The primary outcome measure was a numeric rating scale score of 0 to 10 for leg pain at 1 month, reflecting the average pain experienced by the patient for 1 week before follow-up. Secondary outcome measures included the Oswestry Disability Index (ODI), version 2.0 (MODEMS, Des Plaine, Illinois), score (39), a numeric rating scale score of 0 to 10 for back pain during the preceding week; reduction in analgesic medications (≥20% reduction in opioid use or cessation of nonopioid analgesics) (26); and global perceived effect (GPE).

The ODI is a 10-question survey commonly used to assess function in people with low back pain that has been validated in multiple languages. Scores of 0% to 20% signify minimal disability, 21% to 40% signify moderate disability, 41% to 60% signify severe disability, and greater than 60% indicate a patient who is crippled or bedbound. Global perceived effect was previously defined as a positive response to the questions, "My pain has improved/worsened/stayed the same since my last visit" and "I am satisfied/not satisfied with the treatment I received and would recommend it to others" (26).

In addition to these discrete variables, a positive categorical outcome measure was predefined as a reduction of 50% or more in leg pain with a positive GPE, obviating the need for further interventions. Complications were assessed via both fixed (for example, headache) and open-ended questions immediately after the procedure, 1 day after the injection, and at 1-month follow-up visits by clinic nurses and physicians. Causality was determined on a case-by-case basis through discussion among investigators and treating physicians.

Subsequent follow-up visits took place 3 and 6 months after the final injection in patients who received a positive categorical outcome at the preceding visit. For participants who remained in the study, no concomitant therapy or injection was permitted. Allowing patients who received no benefit from treatment to exit the study to pursue other treatments was done for ethical reasons and is consistent with other controlled trials evaluating epidural and other injections (26, 40–42). In all persons, unblinding was accomplished after termination of study participation (**Figure**). For participants with a positive outcome who remained in the study, only descriptive statistics are presented for subsequent follow-up visits.

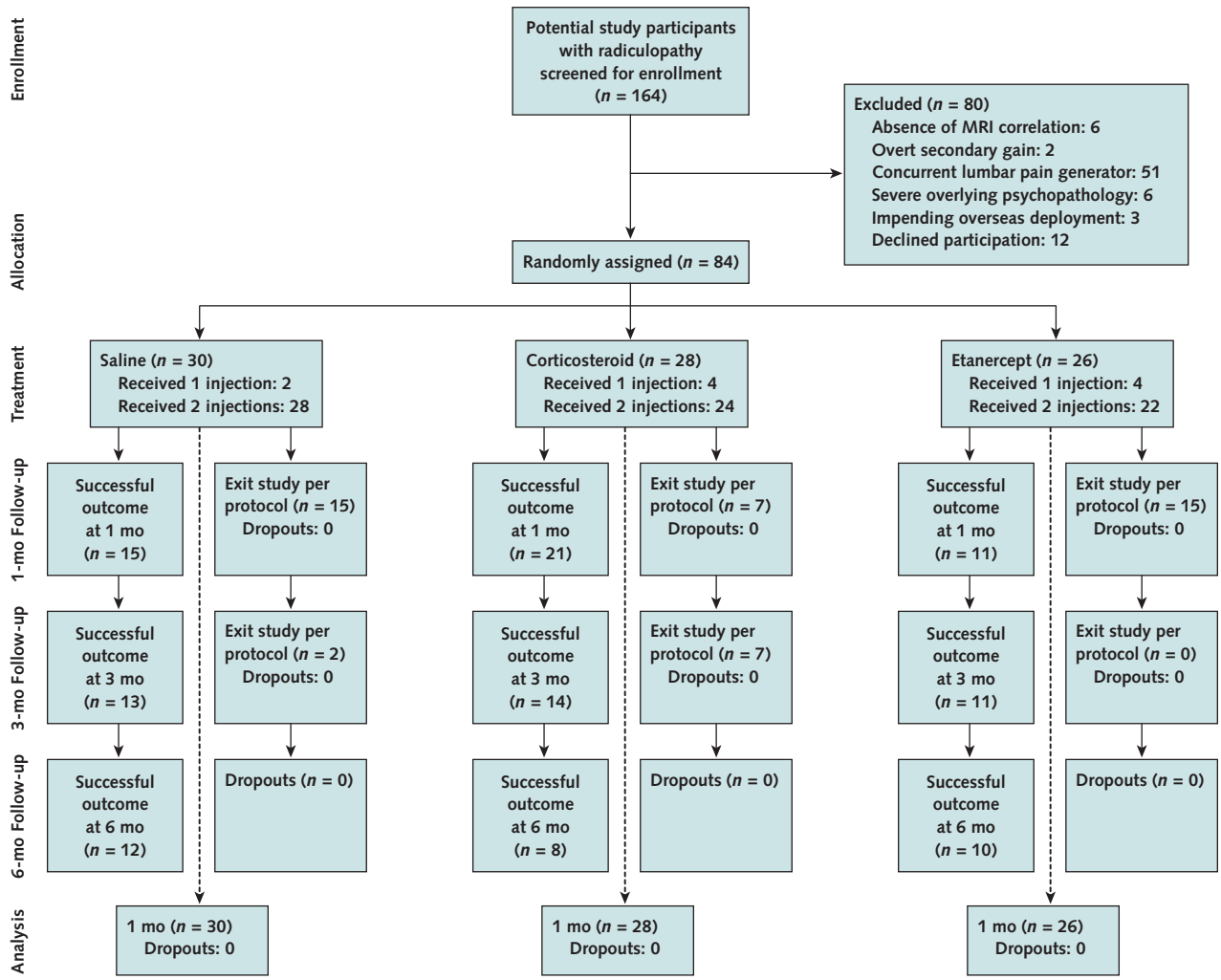
Statistical Analysis

Before the study began, a power analysis conducted on the basis of the following assumptions determined that 26 patients in each group had an 80% probability of detecting a 2-point difference between the control group and 1 or both of the treatment groups: adjusted α of 0.0167 to account for 3 pairwise comparisons, a mean baseline numeric rating scale score for leg pain of 6.5 and an SD of 2, and a 10% dropout rate. An interim analysis was performed after 45 patients were enrolled to determine whether there were any large effect sizes or safety concerns and to determine the efficacy of blinding, which was shown to be valid by using crosstabulations.

Continuous variables are presented by using means and SDs or 95% CIs, and categorical variables are presented by using frequencies and percentages. Analysis of covariance models were used to assess group differences for continuous outcome variables, and logistic regression models were used to analyze secondary binary outcomes. Covariates in the analysis of covariance models included study site, sex, duration of pain, opioid use, and baseline outcome scores.

The logistic regression models included the same covariates, except that baseline leg pain score was used instead of baseline outcome. Pairwise comparisons were done without regard for omnibus P values. P values of 0.05 or

Figure. **Study flow diagram.**



Data from all study participants were analyzed for intention to treat. Data available from those who remained in the study were used only for subsequent descriptive analyses (e.g., $n = 30$ at 1 mo, $n = 15$ at 3 mo, and $n = 13$ at 6 mo for the saline group). Ten patients received only 1 injection, 5 because of satisfactory pain relief (etanercept = 1, steroids = 3, and saline = 1) and 5 because of no pain relief (steroids = 1) or worsening pain (etanercept = 3, saline = 1). MRI = magnetic resonance imaging.

less were considered statistically significant. Data were analyzed by using SPSS for Windows, version 18 (IBM SPSS, Chicago, Illinois).

Role of the Funding Source

The John P. Murtha Neuroscience and Pain Institute, the International Spinal Intervention Society, and the Center for Rehabilitation Sciences Research provided funding for the study. The role of the funding sources included provisions to treat patients, research personnel, and medication costs. No funding source participated in the study design, data analysis, or drafting of this article.

RESULTS

Table 1 shows baseline demographic and clinical data. The mean age of the patients was 42.29 years (SD, 10.80), with an average pain duration of 2.70 months (SD, 1.73). Participants recruited from the Walter Reed Healthcare System were more likely to be male (78% vs. 57%; $P = 0.05$) than were those from other sites. When broken down by military status, service members were younger (mean age, 37.4 vs. 48.8 years; $P < 0.001$) and more likely to be male (90% vs. 44%; $P < 0.001$) than their civilian counterparts. One-month positive categorical outcomes were identical (56%) in military and nonmilitary personnel, with no significant differences among study sites. In the overall cohort, leg pain was in the high to moderate range (mean numeric rating scale score, 6.21 [SD, 1.90]) and was accompanied by significant levels of disability.

There were no statistically significant baseline differences among treatment groups. The results of the interim

analysis revealed no significant differences in leg pain scores at 1 month (mean for etanercept, 2.39 [SD, 3.1]; mean for steroids, 2.0 [SD, 1.9]; and mean for saline, 3.59 [SD, 3.1] [$P = 0.26$]), or 1-month positive categorical outcomes (etanercept, 50%; steroid, 80%; and saline, 50% [$P = 0.47$]) among treatment groups.

Within-Group Changes at 1 Month

Leg and back pain improved in all groups; the largest decrease in leg pain occurred in the steroid group: mean change for steroids, −3.57 (95% CI, −4.43 to −2.71); for etanercept, −2.98 (CI, −4.41 to −1.55); and for saline, −2.48 (CI, −3.59 to −1.37). The reductions in scores for back pain were less profound than were those for leg pain (mean difference for steroids, −2.14 (CI, −3.23 to −1.06); for etanercept, −1.56 (CI, −2.83 to −0.28); and for saline, −1.07 (CI, −1.96 to −0.17).

For functional capacity, both the steroid (mean change, −20.50 [CI, −27.70 to −13.30]) and saline (mean change, −12.07 [CI, −18.11 to −6.01]) groups experienced sizeable improvements, whereas the etanercept group reported little interval change (mean change, −2.85 [CI, −11.78 to 6.09]). The lack of improvement in the etanercept group was largely attributed to worsening in the sections for sleep and sex life.

Differences Between Groups

One-Month Follow-up

For the primary outcome measure, the unadjusted pain scores in the steroid group decreased to 2.14 (SD, 1.99), compared with 3.63 (SD, 3.10) in the etanercept group and 3.83 (SD, 3.57) in the saline group. When covariates were controlled for by using analysis of covariance models, the mean adjusted leg pain score was 2.54 (CI, 1.36 to 3.69) in the steroid group, 3.56 (CI, 2.35 to 4.72) in the etanercept group, and 3.78 (CI, 2.72 to 4.85) in the saline control group ($P = 0.24$).

Unadjusted back pain scores were 3.16 (SD, 2.51) in the steroid group, 4.52 (SD, 2.65) in the etanercept group, and 3.68 (SD, 3.06) in the saline group. Adjusted back pain scores did not differ among groups ($P = 0.40$). The most prominent differences between groups were noted for the ODI, with unadjusted scores averaging 22.43 (SD, 16.72) in the steroid group, 38.27 (SD, 24.69) in the etanercept group, and 28.80 (SD, 21.22) in the saline group. The ODI scores at 1 month differed by group; improvements were noted in the steroid and saline groups but not in the etanercept group ($P = 0.006$) (**Table 2**). When adjusted means were compared, statistically significant differences were noted between steroids and etanercept ($P = 0.002$) and between saline and etanercept ($P = 0.04$), but not between steroids and saline ($P = 0.23$).

Overall, 50% of the patients were able to reduce their analgesic consumption at 1 month. The proportion in each group who were able to decrease medication intake ranged from 63% in the steroid group to 36% in the etanercept group, although this difference did not reach statistical significance (adjusted odds ratio, 2.99; $P = 0.09$). As for GPE, 82% of the steroid group were satisfied with their results at 1 month compared with 58% of the etanercept group and 57% of the saline group; these differences also did not meet statistical significance ($P = 0.14$). The proportion of participants with a positive categorical outcome

Table 1. **Baseline Demographic and Clinical Characteristics of Study Participants**

Characteristic	Study Group		
	Epidural Saline (*n* = 30)	Epidural Steroids (*n* = 28)	Epidural Etanercept (*n* = 26)
Mean age (SD), *y*	42.27 (10.73)	41.46 (12.65)	43.19 (8.91)
Women, *n (%)*	11 (37)	6 (21)	8 (31)
Mean duration of pain (SD), *mo*	2.82 (1.70)	2.61 (1.82)	2.67 (1.74)
Spinal levels, *n*			
L3–4	0	3	2
L4–5	8	8	9
L5–S1	14	12	13
S1–2	1	0	0
2 levels	7	5	2
Opioid therapy, *n (%)*	14 (47)	11 (39)	10 (39)
Active duty military, *n (%)*	19 (63)	15 (54)	14 (54)
Recruited at Walter Reed, *n (%)**	17 (57)	20 (71)	17 (65)
Concomitant stenosis, *n (%)*†	9 (30)	6 (21)	6 (23)
Disability, worker's compensation, or medical board‡	3 (10)	1 (4)	3 (12)
Mean baseline NRS score for leg pain (SD)	6.31 (2.02)	5.71 (1.93)	6.62 (1.66)
Mean baseline NRS score for back pain (SD)	4.75 (2.49)	5.30 (2.50)	6.08 (2.51)
Mean baseline ODI score (SD)	40.87 (17.50)	42.93 (15.57)	41.12 (18.29)

L = lumbar; NRS = numeric rating scale; ODI = Oswestry Disability Index; S = sacral.
* The Walter Reed Healthcare System/National Capital Consortium includes the National Naval Medical Center, Joint Base Andrews, Fort Belvoir Community Hospital, Kimbrough Army Hospital, and other military health care facilities in the mid-Atlantic region.
† Defined as moderate central canal stenosis or severe foraminal stenosis not caused solely by a single herniated disc.
‡ The military equivalent of civilian disability.

Table 2. **Outcome Variables Stratified by Treatment Group 1 Month After the Second Injection**

Variable	Adjusted Mean (95% CI)*			
	Saline (n = 30)	Steroids (n = 28)	Etanercept (n = 26)	Omnibus P Value
NRS score for leg pain	3.78 (2.72 to 4.85)	2.54 (1.36 to 3.69)	3.56 (2.35 to 4.72)	0.24
NRS score for back pain	4.01 (3.08 to 4.93)	3.49 (2.48 to 4.50)	4.41 (3.37 to 5.44)	0.40
ODI score	30.00 (23.2 to 36.69)	24.10 (16.64 to 31.55)	40.26 (32.91 to 47.61)	0.006
	Patients, n (%)			
Secondary binary variable				
Medication reduction‡	14 (50)	17 (63)	9 (36)	0.24
Positive GPE	17 (57)	23 (82)	15 (58)	0.14
Positive categorical outcome§	15 (50)	21 (75)	11 (42)	0.09
Proceeded to surgery‖	5 (17)	6 (21)	6 (23)	NA
Remained on active duty‖	17 (90)	15 (100)	13 (93)	NA

GPE = global perceived effect; NA = not applicable (no ORs were computed); NRS = numeric rating scale; ODI = Oswestry Disability Index; OR = odds ratio.
* Adjusted means and between-group differences for continuous variables were adjusted for study site, sex, duration of pain, opioid use, and baseline outcome score by using analysis of covariance models.
† OR for categorical variables between groups were adjusted for study site, sex, duration of pain, opioid use, and baseline leg pain.
‡ Defined as cessation of nonopioid analgesic or ≥20% decrease in opioid use.
§ Defined as ≥50% decrease in leg pain at 1 mo plus a positive GPE obviating the need for further interventions.
‖ Proceeded to surgery and remained on active duty analyzed through 1 y after injection.

was higher in the steroid group (75%) than in the etanercept (42%) or saline (50%) groups (P = 0.09).

Three- and 6-Month Outcomes

Patients who had a positive categorical outcome remained blinded and were followed at 3 and 6 months. In the steroid group, 14 (50%) participants had a positive categorical outcome at 3 months, but this number decreased to 8 (29%) by 6 months. In the etanercept group, the number of successful outcomes was 11 (42%) at 3 months and 10 (38%) at 6 months. In the saline group, 13 of the 15 patients with a positive 1-month outcome also had a positive outcome at 3 months (43%). By 6 months, only 1 of these patients experienced a recurrence (success rate, 40%).

Among the patients who remained in the study, 75% (9 out of 12) of the saline group, 92% (11 out of 12) of the steroid group, and 65% (7 out of 11) of the etanercept group continued to require less analgesic medication at 6 months. Three and 6-month GPE percentages were calculated by carrying over negative values and omitting positive GPEs from analysis in patients who discontinued the study because of a negative categorical outcome. The proportion of satisfied patients at 3 months was 48% in the saline group, 65% in the steroid group, and 50% in the etanercept group. These proportions remained stable at 6 months at 48% in the saline group but decreased slightly to 63% in the steroid group and 45% in the etanercept group.

Complications

The **Appendix Table** (available at www.annals.org) shows complications by study group. All noted complications were minor, with the 2 most common complications being worsening pain (n = 7) and infection within 1 month of the second injection (n = 4). One patient in the etanercept group experienced a clinically significant deterioration in function, manifested by a 30-point increase in the ODI score. Aside from temporary worsening of pain, no complication could be causally attributed to treatment.

DISCUSSION

The principal finding of this study is that steroids resulted in a larger reduction in leg pain than etanercept and saline for the primary outcome variable at 1 month, but these differences did not reach statistical significance. The ODI scores at 1 month differed statistically by group, with improvements noted in the saline and steroid groups but not in the etanercept group. On the basis of the CIs for pairwise differences, these results can neither exclude nor prove a modest benefit for steroids.

These findings are consistent with numerous previous studies evaluating epidural steroid injections. In a recent MEDLINE review through September 2011, a literature search of randomized, controlled studies found varying results. Whereas some studies found only short-term relief with this therapy (43–46), others reported persistent benefit (47–50) and several reported no benefit compared with control treatment (51–54).

There are several plausible explanations for our findings. We believe that the most probable explanation is that the analgesic effects of steroids are short-lived and that spontaneous improvement resulted in sustained beneficial effects in all treatment groups. This is the conceptual appeal of epidural steroids and TNF inhibitors (that is, to alleviate pain until the body heals itself), because the natural course of a herniated disc is resorption and symptom

Table 2—Continued

Between-Group Difference (95% CI)*		
Steroids vs. Saline	**Etanercept vs. Saline**	**Steroids vs. Etanercept**
−1.26 (−2.79 to 0.27); $P = 0.11$	−0.25 (−1.80 to 1.30); $P = 0.75$	−1.01 (−2.60 to 0.58); $P = 0.21$
−0.52 (−1.85 to 0.81); $P = 0.44$	0.40 (−0.97 to 1.77); $P = 0.56$	−0.92 (−2.28 to 0.44); $P = 0.18$
−5.87 (−15.59 to 3.85); $P = 0.23$	10.29 (0.55 to 20.04); $P = 0.04$	−16.16 (−26.05 to −6.27); $P = 0.002$
Adjusted OR (95% CI)†		
1.67 (0.48 to 5.77); $P = 0.43$	0.56 (0.16 to 1.89); $P = 0.35$	2.99 (0.83 to 10.75); $P = 0.09$
3.12 (0.91 to 10.75); $P = 0.07$	0.99 (0.33 to 2.94); $P = 0.98$	3.16 (0.88 to 11.29); $P = 0.08$
2.62 (0.82 to 8.37); $P = 0.11$	0.72 (0.24 to 2.16); $P = 0.56$	3.63 (1.10 to 12.03); $P = 0.04$
NA	NA	NA
NA	NA	NA

resolution (55). Randomized, controlled studies evaluating the ability of TNF inhibitors and epidural steroid injections to reduce the rate of surgery have found both treatments to be effective (49, 56).

A second explanation is that all treatments are equally efficacious (or nonefficacious) in the long term, but the steroid effect is realized earlier. This explanation is ostensibly supported by a series of controlled studies demonstrating statistically significant benefit in most patients, regardless of whether they received epidural steroids in addition to local anesthetic or only local anesthetic (53, 54). Possible mechanisms for a therapeutic effect from the epidural injection of nonsteroid solutions include the washout of inflammatory cytokines and other pain mediators, lysis of inflammatory-mediated adhesions, and enhanced blood flow to ischemic nerve roots (57). These nonsteroidal analgesic effects may be 1 reason that higher injectate volumes can afford increased benefit (57).

Of interest, slightly more patients in the saline (40%) and etanercept (38%) groups had a positive outcome at 6 months than did those in the steroid group (29%), which resulted from a greater recurrence rate in the steroid group. The most probable explanation for this finding is that a higher proportion of successful outcomes in patients who did not receive steroids was due to a placebo effect, which is very powerful for pain-alleviating procedures and can persist for months or even years (that is, longer than the effects of epidural injections) (58).

Closer examination of the etanercept group, whose results were no better than those of the saline group, may provide additional insight. The dosing regimen used in this study was based on a small pilot study (26) in which the dose of etanercept injected, which was much lower than systemic doses, was calculated on the basis of formulas used for the neuraxial administration of baclofen and opioids. Although animal studies found that much lower doses of intrathecal etanercept have similar efficacy to systemic doses (38), the low dose that we used may have been subtherapeutic, because the doses of other analgesic medications (for example, steroids and clonidine) injected neuraxially are not reduced compared with systemic administration (59, 60). Whether higher epidural doses, which have been used successfully in other settings (31, 61), or a longer-acting TNF inhibitor would provide additional benefit is uncertain.

Several factors may limit the generalizability of our study. Because we sought to establish efficacy and relative effectiveness, we used intermediate selection criteria in a patient population largely composed of persons in excellent physical condition with relatively little secondary gain (that is, military personnel). Selecting inclusion and exclusion criteria is challenging in pain studies, because investigators must weigh the high probability of improvement in patients with a short duration of symptoms and no overlying psychosocial issues—which is likely to lead to higher response rates for control participants—against the refractoriness to treatment among those with a longer duration of symptoms and significant coexisting psychopathology—which is likely to result in lower response rates for treatment participants (62, 63). Therefore, we might expect to observe lower response rates in clinical practice, where epidural steroid injections tend to be done more liberally.

As for the etanercept group, we cannot conclude from this study whether a higher dose would or would not provide more benefit. Another consideration that could enhance outcomes would be to allow for more injections on an as-needed basis, as is frequently done in clinical practice and controlled studies (47, 49, 51, 53, 54, 64).

Additional limitations include the lack of a nonepidural control group, small group sample sizes, the relatively low dose of etanercept, relying on patient recall to record pain scores at follow-up visits, performing injections on a set rather than an as-needed basis, and the decision to allow participants with unsuccessful outcomes to discontinue the study per protocol to pursue alternative treatments. This decision was made because of ethical concerns but limits what can be concluded about long-term outcomes and cost-effectiveness.

In conclusion, the results of our study suggest short-term superiority but limited long-term benefit for epidural steroids compared with epidural saline. At the low doses administered in this study, epidural etanercept seemed to provide no advantages over epidural saline. Whether the long-term improvement noted across all treatment groups was due to a treatment effect from the epidural injection itself or from spontaneous improvement remains uncertain.

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Appendix Table. **Adverse Events, by Study Group**

Adverse Event	Study Group		
	Epidural Saline (n = 30)	Epidural Steroids (n = 28)	Epidural Etanercept (n = 26)
Serious adverse events*	0	0	0
Minor adverse events†	6	1	5
Worsening pain	3	0	4
New neurologic symptoms	1‡	0	1§
No new neurologic symptoms	2‖	0	3¶
Nonlocal infection	3**	0	1††
Nonlocal rash	0	1‡	0

* Including but not limited to death.
† No duplicate events occurred in any patient (i.e., 1 event per patient).
‡ Event occurred within 1 wk of injection series and was possibly related to injection.
§ Event occurred within 1 mo of injection series and was accompanied by worsening disc pathology on magnetic resonance imaging and was deemed unrelated to procedure.
‖ Two events occurred within 1 wk of injection series; 1 event was causally attributed to injection itself and 1 event was possibly related to medications or injection.
¶ Three events occurred within 1 wk of injection series; 2 events were causally attributed to injection itself and 1 event was deemed unrelated to procedure.
** Two events occurred within 2 wk of injection series and 1 event occurred within 1 mo of injection series; all 3 events were sinusitis and were deemed unrelated to procedure.
†† Event was 1 vaginal yeast infection; this event occurred within 1 mo of injection series and was possibly related to medications or injection.