Epidural Injections for Spinal Pain

A Systematic Review and Meta-analysis Evaluating the "Control" Injections in Randomized Controlled Trials

Mark C. Bicket, M.D.,* Anita Gupta, D.O.,† Charlie H. Brown IV, M.D.,‡ Steven P. Cohen, M.D.§

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ABSTRACT

Background: Epidural steroid injection is the most frequently performed pain procedure. This study of epidural steroid "control" injections aimed to determine whether epidural nonsteroid injections constitute a treatment or true placebo in comparison with nonepidural injections for back and neck pain treatment.

Methods: This systematic review with direct and indirect meta-analyses used PubMed and EMBASE searches from inception through October 2012 without language restrictions. Study selection included randomized controlled trials with a treatment group receiving epidural injections of corticosteroids or another analgesic and study control groups receiving either an epidural injection devoid of treatment drug or a nonepidural injection. Two reviewers independently extracted data including short-term (up to 12 weeks) pain scores and pain outcomes. All reviewers evaluated studies for eligibility and quality.

Results: A total of 3,641 patients from 43 studies were included in this systematic review and meta-analysis. Indirect comparisons suggested epidural nonsteroid were more likely than nonepidural injections to achieve positive outcomes (risk ratio, 2.17; 95% CI, 1.87–2.53) and provide greater pain score reduction (mean difference, −0.15; 95% CI, −0.55 to 0.25). In the very limited direct comparisons, no significant differences were noted between epidural nonsteroid and nonepidural injections for either outcome (risk ratio [95% CI], 1.05 [0.88–1.25]; mean difference [95% CI], 0.22 [−0.50 to 0.94]).

Conclusion: Epidural nonsteroid injections may provide improved benefit compared with nonepidural injections on some measures, though few, low-quality studies directly compared controlled treatments, and only short-term outcomes (≤12 weeks) were examined.

What We Already Know about This Topic

- Epidural nonsteroid injections (primarily local anesthetics) may provide treatment for neuropathic pain *via* several potential mechanisms

What This Article Tells Us That Is New

- This systematic review of the literature found that the few available trials directly comparing epidural nonsteroid with nonepidural injections showed no benefit
- Indirect comparisons of the techniques from a larger number of trials suggested epidural nonsteroid injections may confer some benefit

SPINAL pain is a leading cause of disability in the industrialized world. The lifetime prevalence for low back pain ranges between 50 and 80%[1]; for neck pain, the estimates are between 50 and 67%.[2,3] Compounding the high disease burden is the absence of any reliably effective treatment.

More than one third of back pain cases can be classified as predominantly "neuropathic."[4] The distinction between nociceptive and neuropathic spinal pain has significant treatment implications in that the latter may be more

* Resident, ‡ Assistant Professor, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland. † Associate Professor and Medical Director, University Pain Institute, Department of Anesthesiology and Perioperative Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania. § Professor, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, and Professor, Walter Reed National Military Medical Center, Bethesda, Maryland.

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Address correspondence to Dr. Cohen: Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, 550 North Broadway, Suite 301, Baltimore, Maryland 21029. scohen40@jhmi.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.com.

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amenable to therapy. A cornerstone of conservative treatment for radiculopathy is epidural steroid injections (ESI), which have been used for more than 50 yr.[5] In the United States, ESI are the most commonly performed intervention for pain.[6]

Despite their frequent use, the question of whether ESI afford long-term benefit is mired in controversy. Recent reviews demonstrate a glaring lack of consensus. Most experts concede that ESI provide at least short-term palliation in well-selected patients, but the results are divided as to whether they confer long-term benefit.[7–26] In one review that evaluated the effect physician specialty has on conclusions regarding efficacy, 15 of 23 systematic or evidence-based review articles concluded that ESI are effective, with those reviews performed by interventionalists being approximately three times more likely to be positive compared with reviews conducted by noninterventionalist physicians.[27]

Challenges in evaluating ESI studies include disparities in selection criteria, injection parameters, and criteria for success. It is generally acknowledged that patients with shorter duration of symptoms, radicular symptomatology, lesser disease burden, and the absence of coexisting psychosocial pathology, fare better with therapeutic interventions.[9,16,28–31] But what is not commonly appreciated is the impact the "control" injection has on outcomes.

Two main types of "control" injections are used in ESI randomized controlled trials (RCTs): epidural saline or local anesthetic [epidural nonsteroid injection (ENSI)]; and intramuscular or ligamentous injections (nonepidural). In evaluating the literature, most experts fail to discern the differences, considering them as "equivalent placebos." However, the potential benefit of corticosteroids for a chronic condition devoid of an inflammatory component is minimal. In addition, recent studies suggest that radiculopathy may also result from chemical irritation of nerve roots due to inflammatory cytokines released from herniated discs.[32,33] Hence, ENSI may provide significant pain relief by several mechanisms: diluting inflammatory cytokines; lysing scar tissue; enhancing blood flow to ischemic nerve roots[34]; suppressing ectopic discharges from injured nerves[35]; and "unwinding" central sensitization. However, few investigators have entertained this possibility.[9,28,31,36,37] If ENSI provide benefit, then the proportion of controlled studies evaluating ESI in which the results are positive should be less when the control group received ENSI than for nonepidural injections, because the former constitutes a comparative-effectiveness study. The purpose of this study is to examine whether epidural injections of noncorticosteroid mixtures constitute a treatment or true placebo in patients with spinal pain. This was done by comparing between-group differences for pain outcomes from RCTs in which the "control" injectate was administered epidurally (ENSI), with those in which it was injected into the soft tissue (nonepidural injection).

Materials and Methods

Data Sources and Searches

This quantitative systematic review and meta-analysis followed recent methodological guidelines.[38,39] A search of PubMed and EMBASE databases using the terms "epidural steroid," "epidural injection," "caudal," "segmental nerve block," "nerve root block," and "transforaminal injection" was performed without publication date or language restriction in April 2009, and repeated in October 2012. Besides online language tools, in-person translation services were provided through the Johns Hopkins Hospital international services translation program. Search limitations included RCTs and adults older than 18 yr of age. Additional studies were identified through hand searches of ESI review reference lists. Figure 1 and table 1 show further details of the search strategy. Among 690 potentially eligible studies, 244 duplicate references were excluded leaving 446 studies for evaluation, with another 356 deemed ineligible after initial abstract screening. This left 90 articles for final review.

Study Selection

All authors performed study selection by consensus. Eligible studies included only RCTs with: (1) patients with back or neck pain with or without radiculopathy; (2) a treatment group receiving epidural injections of corticosteroids or another analgesic; (3) a control group receiving either an epidural injection devoid of treatment drug or a nonepidural injection; and (4) short-term outcome data up to 12 weeks after the initial injection (if the injection scheme was open-ended) or after the final injection in an injection series. On the basis of these criteria, 47 studies were further excluded. The remaining 43 studies comprised the systematic review. For inclusion in the meta-analysis, studies had to present numeric pain data including SD.

Data Extraction

Data extraction was performed independently by two authors (Drs. Bicket and Gupta), and included patient characteristics, control and treatment injections, rating scores for pain, pain symptoms, and disability scores. Variables including number and percentage of patients, and mean with SD, were extracted, calculated from primary data, or estimated from figures. When not given, SD was calculated using standard errors (SE) and 95% CI.

Quality and Risk of Bias Assessment

Study risk of bias was assessed using a Cochrane risk of bias tool‖ and secondarily using Jadad[40] methodological quality scale, whereas an ESI technical quality scale evaluated stringency of selection criteria (table 2). The ESI technical

‖ Higgins JPT, Altman DG, Sterne JAC: Assessing risk of bias in included studies, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Edited by Higgins JPT, Green S. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. Accessed June 3, 2013.

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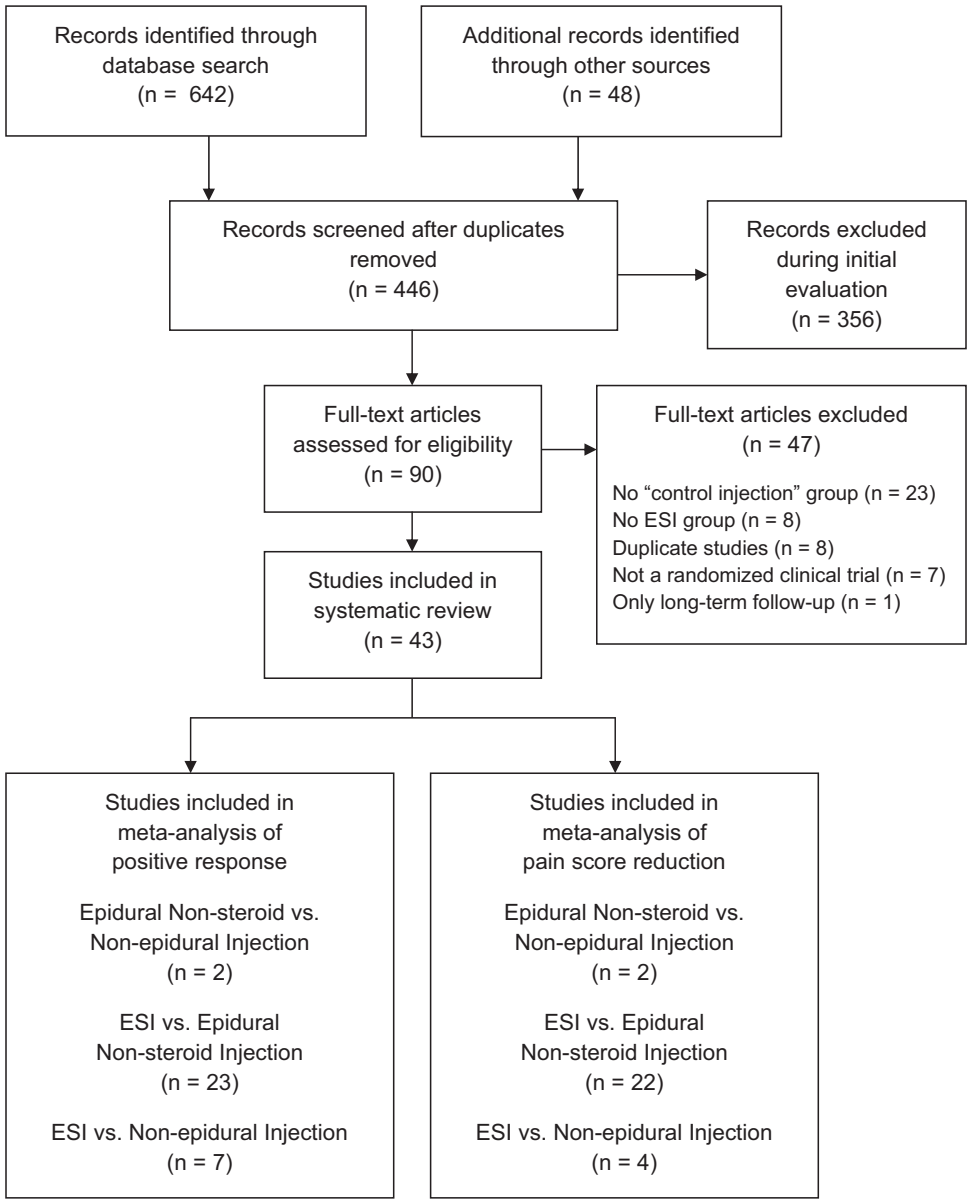

Fig. 1. Flow diagram demonstrating study search results. ESI = epidural steroid injection.

quality scale was developed by the investigators after a review of clinical studies evaluating factors associated with treatment outcomes for ESI and back pain in general.[29,30,41–60] The questions chosen were designed to identify those factors most likely to be associated with treatment response, and to address relevant methodological concerns not reflected in the methodological assessments (*e.g.*, avoidance of cointerventions). This scale was then reviewed with slight modifications by two disinterested Pain Medicine Program Directors at nonstudy institutions, underwent test–retest reliability assessments (>95%) by three study investigators, and is consistent with other rating scales used to evaluate technical quality and clinical relevance for procedural interventions.[61] Although its design suggests possible face, content, and construct validity,[62–64] the scale was not formally validated in a clinical trial. All bias and technical ratings were performed by two of three authors independently (Drs. Brown, Gupta, and Bicket). In the event of disparate ratings, a third author (Dr. Cohen) adjudicated the results. Low methodological quality studies had at least one high likelihood of bias Cochrane risk domain or fulfilled less than three Jadad criteria, whereas low technical quality studies scored less than 4 points on the ESI technical quality scale.

Statistical Analysis

Categorical pain ratings were transformed into a dichotomous "positive response" variable, with "positive response," "success," "relief of pain," and "50% or more reduction in pain" representing positive responses. Visual and numerical pain ratings were transformed into a continuous 0–10

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Table 1. Details of Search Strategy

Search strategy terms for PubMed and EMBASE databases completed on October 16, 2012.
PubMed search terms were:
(Epidural[All Fields] AND ("steroids"[MeSH Terms] OR "steroids"[All Fields] OR "steroid"[All Fields]))
OR caudal[All Fields]
OR (selective[All Fields] AND nerve[All Fields] AND ("roots"[All Fields] OR "root"[All Fields]) AND block[All Fields])
OR (segmental[All Fields] AND nerve[All Fields] AND ("roots"[All Fields] OR "root"[All Fields]) AND block[All Fields])
OR (transforaminal[All Fields] AND ("pain"[MeSH Terms] OR "pain"[All Fields]))
AND ("humans"[MeSH Terms] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms])
EMBASE search terms were:
#1 "epidural"/exp OR epidural AND ("steroid"/exp OR steroid)
#2 caudal
#3 segmental AND ("nerve"/exp OR nerve) AND root AND block
#4 selective AND ("nerve"/exp OR nerve) AND root AND block
#5 transforaminal AND ("pain"/exp OR pain)
#6 #1 OR #2 OR #3 OR #4 OR #5 AND "randomized controlled trial"/de AND ([adult]/lim OR [aged]/lim)

rating scale and, when presented, analyzed by body site (global, leg, back). When global pain ratings were not available for aggregate analysis, leg pain ratings were used in their place.[37,52,65–69] Baseline and comparison data were the most recent data points available before and after the first injection (or injection series), respectively. All comparison data were observed within 12 weeks of the initial injection (if the injection scheme was open-ended) or after the final injection in the first injection series. Data on intramuscular steroids and intramuscular saline/local anesthetic were combined as a comparison group for nonepidural injections, a decision consistent with RCTs and systematic reviews demonstrating a lack of efficacy of parenteral steroids for sciatica.[70,71]

The principal summary measures were positive response (dichotomous) and pain score reduction on an 11-point rating scale (continuous). Effect size of dichotomous data was calculated as relative risk (RR), which represents the risk of a positive response for pain relief in the ESI treatment group divided by risk of a positive response in the control group. Effect size of continuous data was calculated as mean difference (MD), which represents the difference in pain score reduction between the two groups.

Random effects models were examined. Heterogeneity was measured by I^2 which assessed variability among studies not attributable to chance alone. Significant heterogeneity was present with I^2 values of more than 50%. To assess for small study effects and possible publication bias, a funnel plot was analyzed when more than 10 studies were present. Indirect comparisons of aggregate data were performed by calculating differences in pertinent treatment outcomes using the formulas $\log(RR_{AB}) - \log(RR_{AC}) = \log(RR_{BC})$; $MD_{AB} - MD_{AC} = MD_{BC}$; and $SE_{AB}^2 + SE_{AC}^2 = SE_{BC}^2$.[72] Quality analysis was performed excluding each group of low-quality studies for both methodological and technical scores, and body site analysis was performed by substituting back pain for leg pain data. Calculations were done using Microsoft Excel 2011 (Microsoft Corp., Redmond, WA), RevMan Version 5.1.7. (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark, 2011), and Stata 12 (StataCorp LP, College Station, TX). Statistical significance for all tests was set at a P value of 0.05 or less.

Table 2. ESI Technical Quality Rating Scale

1. Excluded patients with previous surgery: 1 point[41,42]
2. Excluded patients with poorly controlled coexisting psychiatric diagnosis: 1 point[28,43,44]
3. Excluded patients with ongoing litigation, secondary gain (*e.g.*, Workers' compensation) or signs of nonorganic pathology (*i.e.*, Waddell signs): 1 point[45,46]
4. Included only patients with pain <6 months (2 points) or 1 yr (1 point): up to 2 points[28,47]
5. Radiographic guidance used (1 point) and contrast injected (1 point); injection under direct visualization acceptable substitute; up to 2 points[48–50]
6. Included only patients with leg/arm pain > back/neck pain (1 point); presence of signs or symptoms of nerve root tension (*e.g.*, positive straight leg raising test, EMG/NCS evidence of radiculopathy, or sensory or motor changes) (1 point); up to 2 points[16,28–30,51]
7. Included only patients with herniated disc (2 points), or herniated disc, foraminal narrowing, osteophyte formation, and spinal stenosis (1 point); up to 2 points[13,16,24,52]
8. Study appropriately powered or >50 patients enrolled[53,54]: 1 point
9. Cointerventions avoided or controlled[12,16,38]: 1 point

EMG = electromyography; ESI = epidural steroid injection; NCS = nerve conduction study.

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Study	Systematic Review				Meta-analysis: Positive Response			Meta-analysis: Pain Score Reduction		
	All	ENSI vs NEI	ESI vs ENSI	ESI vs NEI	ENSI vs NEI	ESI vs ENSI	ESI vs NEI	ENSI vs NEI	ESI vs ENSI	ESI vs NEI
Anderberg 2007[52]	✔		-	-		✔				
Arden 2005[73]	✔			-						✔
Becker 2007[74]	✔		-						✔	
Beliveau 1971[75]	✔		-			✔				
Breivik 1976[76]	✔		+			✔				
Bush 1991[77]	✔		+			✔			✔	
Carette 1997[65]	✔		-						✔	
Cohen 2009[78]	✔		+			✔			✔	
Cohen 2012[37]	✔		-			✔			✔	
Cuckler 1985[79]	✔		-			✔				
Dilke 1973[80]	✔			+			✔			
Ghahreman 2010[81]	✔	-	+	+	✔	✔	✔	✔	✔	✔
Hesla 1979[66]	✔			+			✔			
Iversen 2011[67]	✔	-	-	-				✔	✔	✔
Karppinen 2001[62]	✔		-						✔	
Klenerman 1984[83]	✔	-	-		✔	✔				
Kraemer 1997[84]	✔		+	+		✔	✔			
Manchikanti 2008[85]	✔		-			✔			✔	
Manchikanti 2008[86]	✔		-			✔			✔	
Manchikanti 2011[87]	✔		-						✔	
Manchikanti 2012[88]	✔		-			✔			✔	
Manchikanti 2012[89]	✔		-			✔			✔	
Manchikanti 2012[90]	✔		-			✔			✔	
Manchikanti 2012[91]	✔		-			✔			✔	
Manchikanti 2012[92]	✔		-			✔			✔	
Manchikanti 2012[93]	✔		-			✔			✔	
Manchikanti 2012[94]	✔		-			✔			✔	
Manchikanti 2012[95]	✔		-			✔			✔	
Mathews 1987[96]	✔			-			✔			
Meadeb 2001[97]	✔		-						✔	
Nam & Park 2011[68]	✔		+			✔				
Ng 2005[69]	✔		-						✔	
Price 2005[98]	✔			-			✔			✔
Ridley 1988[99]	✔			+						
Rocco 1989[100]	✔		-			✔				
Rogers 1992[101]	✔		-							
Sayegh 2009[102]	✔		+							
Snoek 1977[103]	✔		-			✔				
Stav 1993[104]	✔			+			✔			
Tafazal 2009[105]	✔		-							
Vad 2002[106]	✔			+						
Valat 2003[107]	✔		-						✔	
Wilson-MacDonald 2005[108]	✔		+							
Total	**43**	**3**	**35**	**12**	**2**	**23**	**7**	**2**	**22**	**4**

Fig. 2. Study inclusion by comparison group. "✔" = studies included in analysis; "+" = studies showing benefit; "–" = studies not showing benefit; ENSI = epidural nonsteroid injection; ESI = epidural steroid injection; NEI = nonepidural injection.

Results

Systematic Review

In the systematic review, 43 studies provided data for ESI treatment and control groups representing 3,641 patients[37,52,65–69,73–108] (fig. 2). Table 3 summarizes study design, patient population, injection groups, outcome measures, and results. Sample sizes ranged from 22 to 228 patients. Injections varied by location, route, frequency, volume, and steroid and local anesthetic content. The number of injections was one in 9 studies, two in 5 studies, three in 4 studies, and a variable number in the remaining 25 studies. Five studies reported on cervical injections, 25 studies on lumbar injections, and 13 on caudal injections. Twenty-eight studies were of both high methodological and technical quality (fig. 3 and table 4).

Three studies directly compared epidural nonsteroid with nonepidural injections.[67,81,83] Both injections were examined in one study of high methodological and technical quality with 130 patients using four "control" groups. In this study[81] the proportion of patients with 50% or more pain relief was not significantly different among all comparison groups: 7% for transforaminal local anesthetic, 19% for transforaminal saline, 21% for intramuscular steroids, and 13% for intramuscular saline. No difference in pain score reduction was

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Table 3. Characteristics of Included Studies

Author	Study Design	Patient Population	Treatment Group
Anderberg[52]	RCT P	40 patients with cervical radiculopathy diagnosed by MRI and selective nerve root blocks.	One TF cervical epidural injection with 0.5 ml mepivicaine 1% and 40 mg methylprednisolone at 1 or 2 levels.
Arden[73]	RCT P DB	228 patients with a clinical diagnosis of unilateral lumbar radiculopathy. Acute symptoms in one third of patients.	Up to three IL ESI every 3 wk containing 80 mg triamcinolone and 10 ml bupivacaine 0.25%.
Becker[74]	RCT P DB	32 patients with unilateral lumbar radiculopathy.	Group A: three oblique lumbar IL epidural injections with 10 mg triamcinolone and 1 ml LA at weekly intervals Group B: three oblique lumbar IL epidural injections with 5 mg triamcinolone and 1 ml LA.
Béliveau[75]	RCT	48 patients with unilateral lumbosacral radiculopathy.	One or more epidural injections of 80 mg depomethylprednisolone and 40 ml procaine 0.5% in saline.
Breivik[76]	RCT P DB	35 patients with chronic lumbar radiculopathy.	Up to three caudal injections of 20 cc bupivacaine 0.25% with 80 mg methylprednisolone at 1-wk intervals.
Bush[77]	RCT P DB	23 patients with lumbosacral radiculopathy.	Two caudal injections at a 2-wk interval of 80 mg triamcinolone and 25 ml procaine 0.5% in saline.
Carette[65]	RCT P DB	158 patients with lumbosacral radiculopathy <12 mo in duration due to herniated nucleus propulsus.	Up to three epidural injection with 80 mg methylprednisolone in 8 ml saline at 3-wk intervals.

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Control Group	Outcome Measures	Results	Comments
One TF cervical epidural injection with 0.5 ml mepivacaine 1% and 1 ml saline at 1 or 2 levels.	VAS, unvalidated questionnaire developed by authors. Follow-up at 3 wk.	Both groups experienced modest improvement at 3 wk, but no differences between groups.	Same technique used for diagnostic blocks and therapeutic TF injections. Study not blinded or adequately powered.
Up to three interspinous ligament injections with 2 ml of saline.	VAS, ODI, missed work, analgesic usage, and surgery. Followed up to 1 yr.	Within-group VAS, ODI improvement in treatment group noted at 3 wk and throughout study. No within-group differences for control at 3 wk but some afterward. Between-group differences in VAS, ODI only at 3 wk. No differences in other outcomes.	Fluoroscopy not used. MRI not used to confirm pathology.
Oblique lumbar IL injection with interleukin-1 receptor antagonist enriched autologous conditioned serum.	VAS, ODI. Followed up to 22 wk.	Within-group VAS, ODI improvements in all groups. Trend toward superiority with interleukin-1 antagonist at all time points. Between-group difference in VAS only at 22 wk with autologous serum group >5 mg triamcinolone. No between-group differences in ODI.	Fluoroscopy not used. Oblique IL approach poorly described. Study not adequately powered. No mention of volume injected in "serum" group.
One or more epidural injection with 40 ml procaine 0.5% in saline.	Pain scale and physical exam. Followed up to 3 mo.	Within-group differences throughout 3 mo in both groups. No between-group differences.	Fluoroscopy not used. Study not blinded. Authors felt steroids superior in patients with long duration of severe pain.
Up to three caudal injections of 20 cc bupivacaine 0.25% followed by 100 ml saline at 1-wk intervals.	Pain, work status, and physical exam. Followed up to 3–20 mo.	Within groups, both improved from baseline at follow-up. Treatment group > control group.	No fluoroscopy used. Significant heterogeneity between groups. Unclear when outcomes assessed. Some radiculographies were normal.
Two caudal injections at a 2-wk interval of 25 ml of saline.	VAS, QOL, and physical exam. Followed up to 1 yr.	Within groups at 4 wks, there was no improvement in the control group but improvement in the treatment group. At 1 yr, there was significant within-group improvement in both groups, with minimal differences between groups.	Fluoroscopy not used. Of five patient dropouts due to worsening symptoms, four were in placebo group.
Up to three epidural injections of 1 ml saline.	VAS, ODI, functional capacity, perceived improvement, physical exam, sickness profile, analgesic consumption. Followed up to 12 wks.	Both groups improved from baseline between 3 and 12 wk. No significant differences between groups except treatment patients had greater finger-to-floor movement and less sensory deficits at different time points.	Fluoroscopy not used. Mean number of injections was similar in each group.

(*Continued*)

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Table 3. (*Continued*)

Author	Study Design	Patient Population	Treatment Group
Cohen[78]	RCT P DB	24 patients with lumbosacral radiculopathy <9 mo duration.	Two TF epidural injections at 2-wk intervals of etanercept 2, 4, or 6 mg diluted in 2 ml.
Cohen[37]	RCT P DB	84 patients with lumbosacral radiculopathy <6 mo in duration secondary to disc pathology.	Two TF injections of 0.5 ml bupivacaine 0.5% + 60 mg depomethylprednisolone 60 mg at 2-wk intervals. Two TF injections of 0.5 ml bupivacaine 0.5% + 4 mg etanercept at 2-wk intervals.
Cuckler[79]	RCT P DB	73 patients with acute lumbar herniated disc or spinal stenosis.	Epidural injection at L3-4 with 5 ml 1% procaine 1%, 80 mg methylprednisolone, and 2 ml water.
Dilke[80]	RCT P DB	100 patients with unilateral lumbosacral radiculopathy.	Epidural injection of 80 mg methylprednisolone in 10 ml saline. Repeat injection at 1 wk if required.
Ghahreman[81]	RCT P DB	130 patients with lumbosacral radiculopathy secondary to herniated disc.	Single TF injection of 70 mg triamcinolone + 0.75 ml bupivacaine 0.5%. Repeat injection at 1 wk if required.
Hesla[66]	RCT P DB crossover	26 patients with chronic lumbosacral radiculopathy.	Three caudal injections of 20 ml bupivacaine 0.25% + 80 mg methylprednisolone.
Iversen[67]	RCT P DB	116 patients with lumbar radiculopathy >12 wk.	Two caudal injection of 1 ml triamcinolone 40 mg + 29 ml saline at 2-wk intervals.
Karppinen[82]	RCT P DB	160 patients with unilateral lumbosacral radiculopathy <6 mo in duration.	Single lumbar TF ESI of 40 mg methylprednisolone in 2 ml bupivacaine 0.5%. S1 TF ESI of 40 mg methylprednisolone in 3 ml bupivacaine 0.75%.
Klenerman[83]	RCT P	63 patients with unilateral sciatica <6-mo duration.	Single lumbar IL ESI of 80 mg methylprednisolone in 20 ml saline.

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Control Group	Outcome Measures	Results	Comments
Two TF epidural injections at 2 wk-intervals of 2 ml saline.	VAS of leg and back pain, functional capacity, analgesic usage, satisfaction. Followed up to 6 mo.	Within-group improvement at baseline throughout study. Etanercept > control.	Small pilot study. Patients unblinded at 3 mo. No dose–response.
Two TF injections of 0.5 ml bupivacaine 0.5% + 1.5 ml saline at 2-wk intervals.	VAS, functional capacity, medication usage, satisfaction, and surgery rate. Followed up to 6 mo.	Within-group differences throughout 6 mo. In all groups. Nonstatistically significant differences favoring steroids at 1 mo but not 3 or 6 mo.	Treatment failures unblinded at 1 mo.
Epidural injection at L3-4 with 5 ml procaine 1% + 2 ml saline. If <50% improvement within 24 h then treatment injection given.	>75% pain relief. Followed up to 24 h and 13–30 mo postinjection.	After 24 h, significant improvement in both groups. No difference between groups. At mean 21-mo follow-up, 24% of treatment group improved *vs.* 15% of control group (*P* value not significant).	Fluoroscopy not used. 36 patients (18 in each group) with <50% improvement at 24 h had a nonblinded steroid + LA injection. Steroids take >24 h to exert full effect.
1 ml saline injected into ligament. Repeat injection at 1 wk if required.	Pain relief, physical exam, analgesic consumption, and work status. Followed up to 3 mo.	Within-group difference only in treatment group. Treatment > control group throughout study.	Fluoroscopy not used. All patients received rehabilitation.
Single TF injection of 2 ml bupivacaine 0.5%. Single TF injection of 2 ml saline. Intramuscular triamcinolone 70 mg (1.75 ml). Intramuscular 2 ml saline. Repeat injection at 1 wk if required.	Proportion of patients with ≥50% pain relief lasting ≥1 mo, functional and psychological improvement, use of rescue medications and other treatment, and surgery rate, followed up to 1 mo. Responders followed up to 1 yr.	Within-group differences at 1 mo for TF steroids, TF saline, and intramuscular steroids. Between groups: TF steroids > TF saline = intramuscular steroids ≥ intramuscular saline and TF local anesthetic.	Most patients followed up for only 1 mo. No difference in rates of surgery between groups. Minimal differences between groups in duration of relief. Nonsignificant lower percentage of treatment group had chronic pain.
Caudal 20 ml bupivacaine + 80 mg methylprednisolone intramuscular.	Return to work. Followed up to 1 yr.	Within-group improvement in both groups. Treatment > control.	Fluoroscopy not used.
Two subcutaneous injections of 2 ml saline at 2-wk intervals. Two caudal injections of 30 ml saline at 2-wk intervals.	ODI, VAS of leg/back, and QOL. Followed up to 1 yr.	Within-group differences for all groups. No significant differences between treatment and control groups.	Sham group had greater baseline disease burden. MRI findings not an inclusion criterion. 1 ml steroid diluted in 30 ml is extremely small dose for caudal injection.
Same TF injection scheme and volume of saline	VAS of leg/back, ODI, QOL, physical exam, and economic assessment. Followed up to 1 yr.	Within groups, both groups improved for leg and back pain at all time points. At 2 wk, treatment > control group for leg pain. No difference at 1 yr, although at 6 mo, the control group > treatment group.	
Single lumbar IL injection of 20 ml bupivacaine 0.25%. Single lumbar IL injection of 20 ml saline. Dry needling into the interspinous ligament.	VAS, physical exam, clinician-judged patient response. Followed up to 10 wk.	Within groups, improvement in all groups. Between groups, no difference at 10 wk.	Fluoroscopy not used.

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Table 3. (*Continued*)

Author	Study Design	Patient Population	Treatment Group
Kraemer[84] (1)	RCT P	133 patients with unilateral lumbosacral radiculopathy secondary to single nerve root compression.	Three TF epidural injections of 10 mg triamcinolone + 1 ml LA in 1 wk. Three IL epidural injections of same injectate.
Kraemer[84] (2)	RCT P DB	49 patients with unilateral lumbosacral radiculopathy secondary to single nerve root compression.	Three TF epidural injections of 10 mg triamcinolone + 1 ml LA in 1 wk.
Manchikanti[85]	RCT P DB	84 patients with lumbar disc herniation or radiculitis of at least 6 mo duration.	Caudal ESI with betamethasone 6 mg or 40 mg of methylprednisolone + 9 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.
Manchikanti[86]	RCT P DB	40 patients with failed back surgery syndrome of at least 6-mo duration. All subjects had leg pain.	Caudal ESI with betamethasone 6 mg + 9 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.
Manchikanti[87]	RCT P DB	120 patients with lumbar discogenic pain without herniation or radiculitis of at least 6-mo duration.	Caudal ESI with betamethasone 6 mg or methylprednisolone 40 mg + 9 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.
Manchikanti[88]	RCT P DB	56 patients with cervical postsurgery syndrome of at least 6-mo duration.	Cervical IL ESI with betamethasone 6 mg + 4 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.
Manchikanti[89]	RCT P DB	120 patients with lumbar disc herniation or radiculitis of at least 6-mo duration.	Caudal ESI with betamethasone 6 mg or methylprednisolone 40 mg + 9 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.
Manchikanti[90]	RCT P DB	100 patients with lumbar spinal stenosis with radiculopathy of at least 6-mo duration.	Caudal ESI with betamethasone 6 mg + 9 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.
Manchikanti[91]	RCT P DB	60 patients with lumbar spinal stenosis of at least 6-mo duration.	Lumbar IL ESI with betamethasone 6 mg + 6 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.
Manchikanti[92]	RCT P DB	60 patients with cervical spinal stenosis of at least 6-mo duration.	Cervical IL ESI with betamethasone 6 mg + 4 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.

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Control Group	Outcome Measures	Results	Comments
Three paravertebral LA injections in 1 wk.	Leg/back pain ratings, work status, ability to do sports, physical exam. Followed up to 3 mo.	Within-group differences in all groups. TF epidural steroid > IL epidural steroid > control group.	CT guidance used for some injections.
Intramuscular triamcinolone 10 mg + 1 ml TF epidural saline.	Leg/back pain ratings, work status, ability to do sports, physical exam. Followed up to 3 mo.	For within-group analysis, >75% of patients in both groups had fair or good results Treatment group > control group.	CT guidance used for some injections. All injections by same doctor.
Caudal epidural injection with 10 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.	NRS, ODI, employment, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups. Preliminary results for a 120-patient study.
Caudal epidural injection with 10 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.	NRS, ODI, employment, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups. Preliminary results for a 120-patient study. Beneficial effect may have been partly due to lysis of adhesions.
Caudal ESI with 10 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.	NRS, ODI, employment status, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups.
Cervical IL epidural injection with 4 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.	NRS, NDI, employment status, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups. Preliminary results for a 120-patient study.
Caudal epidural injection with 10 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.	NRS, ODI, employment status, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups.
Caudal ESI with 10 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.	NRS, ODI, employment status, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups.
Lumbar IL epidural injection with 5 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.	NRS, ODI, employment status, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups. Preliminary results for a 120-patient study.
Cervical IL epidural injection with 4 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.	NRS, NDI, employment status, opioid intake. Followed up to 1 yr	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups. Preliminary results for a 120-patient study.

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Table 3. (*Continued*)

Author	Study Design	Patient Population	Treatment Group
Manchikanti[93]	RCT P DB	120 patients with chronic lumbar axial or discogenic pain of at least 6-mo duration.	Lumbar IL ESI with betamethasone 6 mg + 5 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.
Manchikanti[94]	RCT P DB	120 patients with cervical disk herniation or radiculitis of at least 6-mo duration.	Cervical IL ESI with betamethasone 6 mg + 4 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline
Manchikanti[95]	RCT P DB	140 patients with post lumbar surgery syndrome of at least 6-mo duration.	Caudal ESI with betamethasone 6 mg + 9 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.
Mathews[96]	RCT P DB	57 patients with uniradicular lumbar pain with neurological deficit.	Up to three caudal ESI with 2 ml methylprednisolone 80 mg + 20 ml bupivacaine 0.125% at 2 wk intervals as needed.
Meadeb[97]	RCT P DB	47 patients with postsurgical lumbosacral radiculopathy not caused by nerve compression.	Three caudal epidural injections with 125 mg prednisolone + 20 ml saline at 1-mo intervals. Three caudal epidural injections with 125 mg prednisolone only at 1-mo intervals.
Nam and Park[68]	RCT P	36 patients with lumbar scoliosis and stenosis.	Up to two TF ESIs of 20 mg triamcinolone + 1.5 ml lidocaine 0.5% at 3-wk intervals if only partial benefit.
Ng[69]	RCT P DB	86 patients with unilateral lumbosacral radiculopathy.	Single TF ESI with 1 ml methylprednisolone + 1 ml bupivacaine 0.25%.
Price[98]	RCT P DB	228 patients with unilateral lumbosacral radiculopathy <18 mo in duration.	Up to three epidural injections of triamcinolone 80 mg + 10 ml bupivacaine 0.125% at 3-wk intervals if persistent disability.
Ridley[99]	RCT P DB crossover	39 patients with symptoms of sciatic nerve compression.	Up to two ESIs with methylprednisolone 80 mg in 12 ml saline at 1-wk interval if no improvement.

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Control Group	Outcome Measures	Results	Comments
Lumbar IL epidural injection with 6 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.	NRS, ODI, employment status, opioid intake. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups.
Cervical IL epidural injection with 4 ml lidocaine 0.5%. Procedures repeated as required when pain returned to 50% of baseline.	NRS, ODI, employment status, opioid intake, employment status, weight. Followed up to 1 yr.	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups
Caudal epidural injection with 9 ml lidocaine 0.5%. Procedures repeated as needed when pain returned to 50% of baseline.	NRS, ODI, employment status, opioid intake, employment status. Followed up to 1 yr	Within-group pain improvement in both groups. No differences in any outcome measure for between-group differences.	Repeat injections limited differences between groups.
2 ml lidocaine injected over sacral hiatus or most tender spot.	Pain scores, treatment usage. Followed up to 1 yr.	Within-group improvement in both groups at 1 mo. At 3 mo but not 1 mo, treatment group > control group.	No fluoroscopy used. Raw pain score data not presented. One of four separate trials presented.
Three caudal epidural injections of 2 ml saline at 1-mo intervals.	VAS, physical exam, functional and psychological improvement. Followed up to 4 mo.	Within groups, nonsignificant trend of improvement in steroid + saline and saline only groups, but not steroid only group. Nonsignificant trend of steroid only group > steroid + saline, saline only groups up to 30 d. After 30 d, strong trend toward superiority of saline only *vs.* other two groups.	Steroid only group considered control as volume not sufficient to reach pathology. Patients excluded due to failure to respond to initial injection. Greater disease burden in saline group.
Up to two TF epidural injections of 2 ml lidocaine 0.5% at 3-wk intervals if only partial benefit.	VAS, ODI, and clinical and radiological measures (*e.g.*, Cobb and lordosis angles). Followed up to 12 wk.	Within-group differences for both groups to 12 wk. Steroid > control for function and pain scores.	No blinding of patients, researchers. Patients excluded due to failure to respond to initial injection. No difference in clinical or radiological measures.
Single TF epidural injection with 2 ml bupivacaine 0.25%.	VAS of leg/back, ODI, satisfaction. Followed up to 12 wk.	Within-group differences from baseline throughout trial period in both groups. No between-group differences.	Longer duration of symptoms associated with worse outcome. Treatment group had longer symptom duration.
Up to three injections of 2 ml saline into interspinous ligament at 3-wk intervals if persistent disability.	VAS leg/back, ODI, physical exam, QOL, psychological status, analgesic consumption, and work status. Followed up to 1 yr.	Within-group improvements across all time points for both groups. Between groups, treatment group > control group for pain and function better at 3 wk but not after.	Fluoroscopy not used. MRI findings not an inclusion criterion. Randomization stratified by duration.
Up to two interspinous ligament injections of 2 ml saline at 1-wk interval if no improvement. Crossover to treatment if placebo injections failed.	VAS rest/walking, physical exam. Followed up to 6 mo.	Within-group improvement only in the treatment group. Treatment > control group.	Fluoroscopy not used. Of control group, 14 of 16 (87%) crossed over to treatment arm at 2 wk. Only median VAS data presented

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Table 3. (*Continued*)

Author	Study Design	Patient Population	Treatment Group
Rocco[100]	RCT P DB	22 patients with postlaminectomy pain.	Up to three ESI with triamcinolone 75 mg + lidocaine 50 mg in 10 ml at 1-mo intervals. Up to three ESI with triamcinolone 75 mg + lidocaine 50 mg in 10 ml morphine 8 mg in 8 ml at 1 mo intervals
Rogers[101]	RCT P DB	30 patients with sciatica and limited straight leg raise.	One IL ESI with methylprednisolone 80 mg + lidocaine 280 mg in 20 ml.
Sayegh[102]	RCT P DB	183 patients with low back pain with or without radiculopathy >1 mo in duration.	Up to two caudal ESI with 1 ml betamethasone + 12 ml lidocaine 2% at 1 mo intervals if poor results.
Snoek[103]	RCT P DB	51 patients with unilateral lumbosacral radiculopathy.	Single ESI of 80 mg depomethylprednisolone in 2 ml saline.
Stav[104]	RCT P	42 patients with chronic cervicobrachialgia with or without radiculopathy >6 mo.	Up to three cervical ESI with 80 mg methylprednisolone 80 mg + 5 ml lidocaine 1% at 2-wk intervals.
Tafazal[105]	RCT P DB	50 patients with unilateral lumbosacral radiculopathy.	Single TF ESI with 40 mg methylprednisolone + 2 ml bupivacaine 0.25%.
Vad[106]	RCT P	50 patients with lumbosacral radiculopathy due to HNP	Up to three TF ESI with 9 mg betamethasone + lidocaine 30 mg in 3 ml at three levels at random intervals
Valat[107]	RCT P DB	85 patients with lumbosacral radiculopathy secondary to HNP.	Three ESI with 50 mg prednisolone acetate in 2 ml at 2-d intervals.
Wilson-MacDonald[108]	RCT P DB	93 patients with lumbosacral radiculopathy >6 wk in duration.	Up to two IL ESIs with 80 mg methylprednisolone + 8 ml bupivacaine 0.5% at random intervals.

CT = computed tomography; DB = double blinding; ESI = epidural steroid injection; HNP = herniated nucleus pulposus; IL = interlaminar; LA = local anesthetic; MRI = magnetic resonance imaging; NDI = Neck Disability Index; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; P = prospective; QOL = quality of life; RCT = randomized controlled trial; ROM = range of motion; TF = transforaminal; VAS = Visual Analog Scale.

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Control Group	Outcome Measures	Results	Comments
Up to three epidural injections with lidocaine 50 mg + morphine 8 mg in 10 ml at 1 mo intervals.	VAS, vital signs, complications. Followed up to 6 yr	Within-group difference in VAS for 1–3 d in all groups. Between groups no significant differences in short- or long-term pain relief. Trend to improved long-term pain relief in triamcinolone-only group.	Fluoroscopy not used. All patients failed surgery. Study terminated prematurely due to complications in triamcinolone + morphine group.
One IL ESI with lidocaine 280 mg in 20 ml.	Pain rating, work status, analgesic consumption, and physical exam. Followed up to 1 mo.	Within-group differences in both groups in all outcomes except analgesic consumption. Treatment group > control group.	Fluoroscopy not used.
Up to two caudal epidural injections with 12 ml lidocaine 2% + 8 ml sterile water at 1 mo intervals if poor results.	ODI, physical exam. Followed up to 1 yr.	Within-group differences for both groups. Treatment group > control group.	Fluoroscopy not used. Pain not an outcome measure. Function improved more than straight leg raising test.
Single epidural injection of 2 ml saline.	Leg/back pain, physiotherapist assessment, physical exam and analgesic consumption. Followed up to 8–20 mo.	Within-group differences for both groups. No between-group differences.	Fluoroscopy not used. No difference between groups for surgical rate.
Posterior neck muscle injections of same solution at same intervals	VAS, ROM, work status, medication consumption, physical exam. Followed up to 1 yr	Within-groups differences for both groups. Treatment group > control group. Small percentage improving in control group (11%)	Fluoroscopy not used. Patients with chronic refractory disease
Single TF epidural injection of 2 ml bupivacaine 0.25%.	VAS leg/back, ODI, psychological scales, and subjective improvement. Followed up to 1 yr.	Within-group differences in both groups. No between-group differences.	Trend for treatment group to have better relief of leg pain only at 6 wk. Used only one injection. Greater improvement in patients with herniated disc than stenosis at 3 mo.
Up to two trigger point injections with 3 ml saline once at random intervals	Pain scale, physical exam, low back pain questionnaire. Followed up to 16 mo	Within-groups differences for both groups. Treatment group > control group.	Randomization by patient choice. No baseline patient characteristics presented.
Three epidural injections with 2 ml saline.	Categorical improvement at day 20, VAS, physical exam, and functional capacity. Followed up to 35 d.	Within-group improvements in both groups. Nonsignificant trend to larger improvement in treatment group compared with control group at 20 but not 35 d	Fluoroscopy not used. No lumbar exercises allowed.
Single intramuscular injection with 8 ml methylprednisolone + 8 ml bupivacaine 0.5%.	Pain scores, ODI, percentage needing surgery. Followed up to 2 yr.	Improvement in pain within treatment group and between treatment and control group up to 35 d. Within-group differences not noted for control group. No long-term differences between groups, or decrease in rate of operation.	Fluoroscopy not used. Included patients with spinal stenosis. 15% dropout rate. Raw data not presented.

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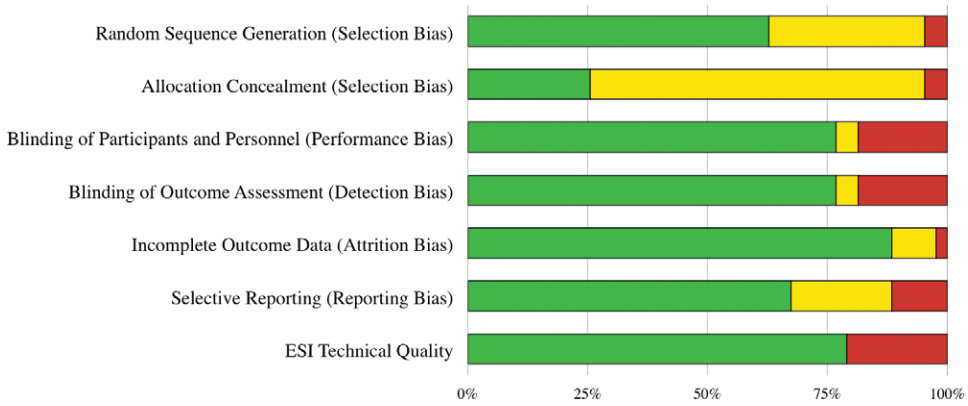

Fig. 3. Risk of bias and technical quality assessment graph. Review authors' judgments regarding each risk of bias category and technical quality ratings presented as percentages across all included studies. *Green* = low risk of bias/high quality; *yellow* = unclear risk of bias; *red* = high risk of bias/low quality. ESI = epidural steroid injection.

found among the four groups. Two other studies were of high technical quality and low methodological quality. In a study by Iversen *et al.*[67] evaluating 116 patients using two "control" groups, there was no significant difference in pain score reduction between epidural and intramuscular saline. In an earlier study by Klenerman *et al.*[83] using three "control" groups in 63 patients, neither reduction in pain scores nor positive response as judged by a physician (sham nonepidural dry needling 83%, epidural local anesthetic 69%, and epidural saline 69%) significantly differed among treatments. Of note, none of these three studies were designed to detect a difference between two "control" groups, and the latter two studies[67,83] used excessively high injectate volumes (≥20 ml) that diluted the steroid dose, resulting in no differences being observed between the steroid and any control group.

Among studies included in the systematic review, 22.9% (8 of 35) of studies comparing ESI with ENSIs demonstrated benefit for the treatment, which was less than the 58.3% (7 of 12) reporting a positive effect when nonepidural injections were used as the control. When low-quality studies were excluded, these numbers changed only slightly, to 27.3% (6 of 22) and 50.0% (2 of 4), respectively.

Meta-analysis

Positive Response. For the positive response outcome, 166 patients from two studies provided data for the direct meta-analysis of ENSIs and nonepidural injections (fig. 4). For the indirect meta-analysis, 1,512 patients from 23 studies provided data comparing ESI *versus* ENSIs and 663 patients from seven studies provided data comparing ESI *versus* nonepidural injections. The indirect meta-analysis revealed a greater than two-fold increased likelihood for a positive response to ENSI, compared with nonepidural injection (RR [95% CI], 2.17 [1.87–2.53]). Differences between epidural nonsteroid and nonepidural injections for the direct meta-analysis were not significant (RR [95% CI], 0.90 [0.60–1.33]). Table 5 presents other effect estimates for positive response. The absolute benefit favoring epidural nonsteroid over nonepidural injections is actually greater (risk difference [95% CI], 0.27 [0.15–0.39]) than the difference between ESI and epidural nonsteroid (0.04 [–0.01 to 0.10]). Heterogeneity was 0% for the direct comparison and 31–33% for the two groups used in indirect comparisons. When studies of low methodological or technical quality were excluded, no significant changes in outcomes or heterogeneity were noted for any comparisons involving a positive response, which is consistent with previous reviews.[54]

Pain Score Reduction

For the pain score reduction outcome, 201 patients from two studies provided data for the direct meta-analysis (fig. 5). For the indirect meta-analysis, 1,936 patients from 22 studies provided data comparing ESI *versus* ENSIs and 619 patients in four studies provided data comparing ESI *versus* nonepidural injections. Differences between epidural nonsteroid and nonepidural injections were nonsignificant in the direct meta-analysis (MD [95% CI], 0.22 [–0.50 to 0.94]). For the indirect meta-analysis, a small, nonsignificant difference favoring ENSIs over nonepidural injections was noted (MD [95% CI], –0.15 [–0.55 to 0.25]). Heterogeneity was 0% for the direct comparison and 60–72% for the two groups used in indirect comparisons. When studies of low methodological or technical quality were excluded, no significant changes in outcome or heterogeneity were noted for all comparisons involving pain score reduction.

Additional Analyses

Estimates of both positive response and pain score reduction did not change significantly with either exclusion of low technical and methodological studies or substitution of back pain scores for leg pain scores for the seven studies stratifying pain by body site. The only comparison group with 10 or more studies was the ESI *versus* epidural nonsteroid

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Table 4. Risk of Bias and Technical Quality Assessment of Included Studies

	Qualitative Bias Assessment							
Study Name	Random Sequence Generation	Allocation Concealment	Blinding of Partici-pants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Jadad Score	ESI Technical Quality Score
Anderberg[52]	?	?	–	–	+	–	3	4
Arden[73]	+	+	+	+	+	+	4	7
Becker[74]	+	+	+	+	+	+	4	4
Béliveau[75]	–	–	–	–	+	?	2	1
Breivik[76]	?	?	+	+	+	?	3	1
Bush[77]	?	?	+	+	+	+	4	4
Carette[65]	+	+	+	+	+	+	5	8
Cohen[78]	?	?	+	+	+	+	4	8
Cohen[37]	+	+	+	+	+	+	5	11
Cuckler[79]	?	?	?	?	+	?	4	5
Dilke[80]	+	?	?	?	+	+	4	5
Ghahreman[81]	?	?	+	+	+	+	4	8
Hesla[66]	+	+	+	+	+	+	5	0
Iversen[67]	?	+	–	–	+	+	3	6
Karppinen[82]	+	+	+	+	+	+	5	9
Klenerman[83]	+	?	–	–	+	?	3	4
Kraemer[84] (1)	?	?	–	–	+	?	2	5
Kraemer[84] (2)	?	?	+	+	+	?	4	4
Manchikanti[85]	+	?	+	+	+	+	5	9
Manchikanti[86]	+	?	+	+	+	+	5	5
Manchikanti[87]	+	?	+	+	+	+	5	5
Manchikanti[88]	+	?	+	+	+	+	5	8
Manchikanti[89]	+	?	+	+	+	+	5	5
Manchikanti[90]	+	?	+	+	+	+	5	7
Manchikanti[91]	+	?	+	+	+	+	5	7
Manchikanti[92]	+	?	+	+	+	+	5	7
Manchikanti[93]	+	?	+	+	+	+	5	6
Manchikanti[94]	+	?	+	+	+	+	5	8
Manchikanti[95]	+	?	+	+	+	+	5	4
Mathews[96]	+	?	+	+	?	+	5	4
Meadeb[97]	?	?	+	+	+	+	4	2
Nam and Park[68]	+	?	–	–	+	+	3	6
Ng[69]	+	+	+	+	+	+	5	7
Price[98]	+	+	+	+	+	+	5	7
Ridley[99]	+	?	+	+	+	–	5	2
Rocco[100]	?	+	+	+	+	?	4	0
Rogers[101]	?	?	+	+	+	+	4	1
Sayegh[102]	?	?	+	+	?	–	4	4
Snoek[103]	?	?	+	+	?	?	4	7
Stav[104]	+	?	–	–	?	?	3	3
Tafazal[105]	+	?	+	+	+	+	5	7
Vad[106]	–	–	–	–	–	–	2	7
Valat[107]	+	+	+	+	+	+	5	10
Wilson–MacDonald[108]	+	+	+	+	+	–	4	3

For Kraemer *et al.*,[84] the numbers in parentheses designate separate studies within a single article.
"+" = low risk; "?" = unclear risk; "–" = high risk; ESI = epidural steroid injection.

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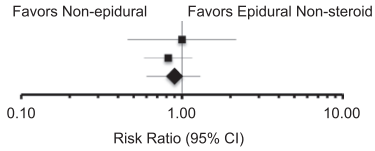
A Direct comparison of epidural non-steroid to non-epidural injections

Study	Epidural Non-steroid Injection Events	Total	Non-epidural Injection Events	Total	Weight, %	Risk Ratio (95% CI)	Risk of Bias	Technical Quality Score
Ghahreman 2010[81]	11	64	10	58	41.9	1.00 (0.46, 2.17)	1	8
Klenerman 1984[83]	22	32	10	12	58.1	0.82 (0.58, 1.16)	0	4
Total (95% CI)	**33**	**96**	**20**	**70**	**100.0**	**0.90 (0.60, 1.33)**		

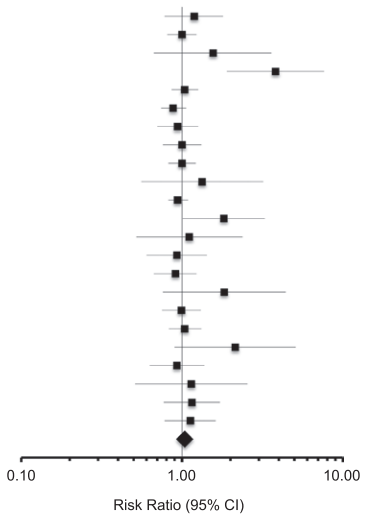
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



B Direct comparison of epidural steroid to epidural non-steroid injections

Study	Epidural Steroid Injection Events	Total	Epidural Non-steroid Injection Events	Total	Weight, %	Risk Ratio (95% CI)	Risk of Bias	Technical Quality Score
Cohen 2012[37]	32	54	15	30	3.2	1.19 (0.78, 1.80)	1	11
Manchikanti 2008[85]	34	42	34	42	8.0	1.00 (0.81, 1.23)	1	9
Cohen 2009[78]	14	18	3	6	0.9	1.56 (0.67, 3.59)	1	8
Ghahreman 2010[81]	15	28	9	64	1.3	3.81 (1.90, 7.65)	1	8
Manchikanti 2012[89]	48	60	46	60	8.8	1.04 (0.86, 1.26)	1	8
Manchikanti 2012[94]	45	60	51	60	9.1	0.88 (0.74, 1.06)	1	8
Manchikanti 2012[90]	31	50	33	50	5.4	0.94 (0.70, 1.26)	1	7
Manchikanti 2012[91]	23	30	23	30	5.7	1.00 (0.76, 1.32)	1	7
Manchikanti 2012[92]	26	30	26	30	8.4	1.00 (0.82, 1.22)	1	7
Snoek 1977[103]	9	27	6	24	0.9	1.33 (0.56, 3.20)	1	7
Manchikanti 2012[93]	50	60	53	60	10.7	0.94 (0.82, 1.09)	1	6
Nam & Park 2011[68]	13	17	8	19	1.8	1.82 (1.01, 3.27)	1	6
Cuckler 1985[79]	12	42	8	31	1.1	1.11 (0.52, 2.38)	1	5
Manchikanti 2008[86]	13	20	14	20	3.1	0.93 (0.60, 1.43)	1	5
Manchikanti 2012[88]	20	28	22	28	5.1	0.91 (0.67, 1.23)	1	5
Bush 1991[77]	8	12	4	11	0.9	1.83 (0.76, 4.41)	1	4
Kraemer 1997[84] (2)	19	24	20	25	5.6	0.99 (0.75, 1.31)	1	4
Manchikanti 2012[95]	48	70	46	70	7.2	1.04 (0.83, 1.32)	1	4
Breivik 1976[76]	9	16	5	19	0.9	2.14 (0.90, 5.09)	1	1
Rocco 1989[100]	12	15	6	7	3.5	0.93 (0.63, 1.38)	1	0
Anderberg 2007[52]	8	20	7	20	1.0	1.14 (0.51, 2.55)	0	4
Klenerman 1984[83]	15	19	11	16	3.4	1.15 (0.77, 1.72)	0	4
Beliveau 1971[75]	18	24	16	24	4.0	1.13 (0.78, 1.62)	0	1
Total (95% CI)	**522**	**766**	**466**	**746**	**100.0**	**1.04 (0.96, 1.13)**		

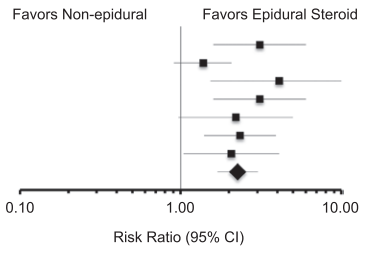
Heterogeneity: Tau² = 0.01; Chi² = 32.75, df = 22 (P = 0.07); I² = 33%
Test for overall effect: Z = 0.93 (P = 0.35)



C Direct comparison of epidural steroid to non-epidural injections

Study	Epidural Steroid Injection Events	Total	Non-epidural Injection Events	Total	Weight, %	Risk Ratio (95% CI)	Risk of Bias	Technical Quality Score
Ghahreman 2010[81]	15	28	10	58	13.6	3.11 (1.60, 6.02)	1	8
Price 2005[98]	40	113	27	105	24.2	1.38 (0.91, 2.07)	1	7
Dilke 1973[80]	16	35	4	36	7.2	4.11 (1.53, 11.09)	1	5
Mathews 1987[96]	15	28	10	58	13.6	3.11 (1.60, 6.02)	1	4
Hesla 1979[96]	12	15	4	11	9.8	2.20 (0.97, 5.00)	1	0
Kraemer 1997[84] (1)	53	87	12	46	18.9	2.34 (1.40, 3.91)	0	5
Stav 1993[104]	19	26	6	17	12.9	2.07 (1.04, 4.11)	0	3
Total (95% CI)	**170**	**332**	**73**	**331**	**100.0**	**2.26 (1.70, 3.02)**		

Heterogeneity: Tau² = 0.01; Chi² = 12.24, df = 6 (P = 0.06); I² = 51%
Test for overall effect: Z = 5.55 (P < 0.001)



D Indirect comparison of epidural non-steroid to non-epidural injections

Indirect comparison of injections used the formulas
$\log(RR_{ESI\ vs\ NEI}) - \log(RR_{ESI\ vs\ ENSI}) = \log(RR_{ENSI\ vs\ NEI})$ and
$SE_{ESI\ vs\ NEI}^{2} + SE_{ESI\ vs\ ENSI}^{2} = SE_{ENSI\ vs\ NEI}^{2}$

Risk Ratio (95% CI)
2.17 (1.87, 2.53)

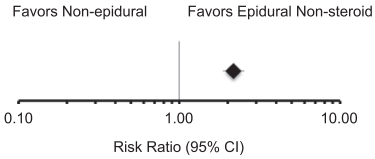


Fig. 4. (*A-D*) Forest plots comparing positive response to injection for epidural nonsteroid and nonepidural injections. Two studies included treatment injections besides steroid (etanercept [Cohen[78] and Cohen[37]]). For risk of bias ratings, "0" = low methodological quality whereas "1" = adequate methodological quality. ENSI = epidural nonsteroid injection; ESI = epidural steroid injection; NEI = nonepidural injection; RR = risk ratio.

comparison. Examination of funnel plots for studies comparing ESI and ENSIs for both primary outcomes revealed small study effects for only the pain score reduction outcome. The Egger test confirmed the presence of possible publication bias ($P < 0.001$). *Post hoc* sensitivity analysis to identify and correct for funnel plot asymmetry arising from publication bias included the "trim and fill" method. This method estimated eight studies were needed to account for possible publication bias, and provided a corrected pain score reduction estimate that was not significant.

Discussion

The findings in this systematic review and meta-analysis comparing epidural nonsteroid and nonepidural injections are mixed, with only one study of high quality directly comparing these treatments. Although no difference in direct

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Table 5. Effect Estimates for Positive Response to Injection

	Direct Comparison			Indirect Comparison
Effect estimate	ENSI *vs.* NEI	ESI *vs.* ENSI	ESI *vs.* NEI	ENSI *vs.* NEI
Risk ratio (95% CI)	0.90 (0.60–1.33)	1.04 (0.96–1.13)	2.26 (1.70–3.02)	2.17 (1.87–2.53)
Risk difference (95% CI)	–0.03 (–0.15 to 0.09)	0.04 (–0.01 to 0.10)	0.31 (0.20–0.42)	0.27 (0.15–0.39)
Odds ratio (95% CI)	0.81 (0.36–1.80)	1.28 (0.98–1.67)	4.07 (2.44–6.79)	3.18 (2.37–4.27)

Data are provided as effect estimate with 95% CI.

ENSI = epidural nonsteroid injection; ESI = epidural steroid injection; NEI = nonepidural injection.

outcomes between the two "control" injections was demonstrated, the larger number of studies providing indirect comparisons suggests ENSIs may provide greater benefit for spinal pain than nonepidural injections. This conclusion is based on the significant but small difference found between the two treatments when examining the positive response outcome. For this outcome, the benefit favoring epidural nonsteroid over nonepidural injections is actually greater (risk difference [95% CI], 0.27 [0.15–0.39]) than the difference between ESI and epidural nonsteroid, suggesting that, at least in the short term, most of the benefit of epidural injections may derive from the solution itself, rather than the steroid. ENSIs also showed a nonsignificant trend toward greater relief when examining pain score reduction with indirect comparisons. A single binary outcome measure may represent a better reflection of global perceived effect than reduction in pain score, which is only one of many core domain outcome measures,[109] and in most studies analyzed signified only the pain rating at a single cross-section in time.

Although several review articles[9,31,36] and clinical trials[67,81] have alluded to the possibility of a therapeutic effect for epidural nonsteroid solutions, this assertion has never been systematically examined. In addition to the evidence presented here, several other randomized studies indirectly bolster this assertion. Randomized, double-blind studies comparing high doses of steroid with lower doses in which the steroid was replaced by saline[110,111] or local anesthetic[112] have consistently failed to demonstrate any significant differences between treatment groups. A systematic review by Rabinovitch *et al.*[113] found a statistically significant benefit for larger epidural injectate volumes irrespective of the contents, suggesting that the beneficial effect of nonsteroid solutions may counterbalance dilution of steroids.

There are several possible explanations for our findings. The most likely is that nonsteroid solutions injected epidurally may provide benefit comparable with that of steroids *via* a host of different mechanisms, to include the suppression of ectopic discharges from inflamed nerves, enhancing blood flow to ischemic nerve roots, lysis of iatrogenic and inflammatory adhesions, the washout of proinflammatory cytokines, and reversing peripheral and central sensitization.[9,31–34] A second possible reason involves the placebo effect. Epidural injections, especially those administered *via* the transforaminal approach, often elicit a reproduction of radicular symptoms,[114,115] which is not observed with soft-tissue injections, and may undermine the effectiveness of blinding. When this occurs, it may lead to a greater placebo response with ENSIs, as patients mistakenly believe they received epidural steroids.[116]

The implications of these findings are widespread and protean. Investigators designing clinical trials, and specialty organizations, patient advocate groups, and third-party payers evaluating studies, should consider these results when evaluating the efficacy of ESI. Specifically, trials that include an epidural nonsteroid "placebo" group may be less likely to demonstrate a difference in pain outcomes compared with nonepidural injections. In high-risk patients (*e.g.*, patients with previous surgery) and procedures (*e.g.*, cervical and thoracic transforaminal ESI) in which the inadvertent intravascular injection of depo-steroids can have catastrophic consequences such as paralysis and death,[117–119] physicians might consider removing steroids from the injectate and using nonsteroid solutions as a first-line treatment. Using nonsteroid solutions may also reduce the risk of rare but potentially fatal complications such as meningitis, which has recently been attributed to a contaminated steroid batch.# On the basis of these results and the results of other clinical trials demonstrating no differences between high- and low-dose ESI[110–112,120] the dose of steroids may be considerably reduced or even eliminated in high-risk patient populations. Examples of these patients might include individuals at high risk for avascular necrosis,[121] and those with diabetes,[122] at high risk for infection,[123] poor wound healing, or in whom the temporary suppression of the adrenocortical axis could adversely affect outcomes (*e.g.*, those scheduled for major surgery).[124]

These results should be interpreted in the context of some limitations. First, direct comparisons of the different types of controlled injections were only present in a limited number of low-quality randomized clinical trials. Although no standard guidelines exist regarding the minimum number of

Centers for Disease Control and Prevention. Meningitis and Stroke Associated with Potentially Contaminated Product. Atlanta, GA: Centers for Disease Control and Prevention, 2012. Available at: http://emergency.cdc.gov/HAN/han00327.asp. Accessed April 23, 2013.

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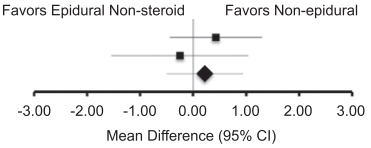
A Direct comparison of epidural non-steroid to non-epidural injections

Study	Epidural Non-steroid Injection Mean	SD	Total	Non-epidural Injection Mean	SD	Total	Weight, %	Mean Difference (95% CI)	Risk of Bias	Technical Quality Score
Ghahreman 2010[81]	-0.93	2.44	58	-1.36	2.47	64	68.70%	0.43 (-0.44, 1.30)	1	8
Iversen 2011[67]	-1.34	2.96	39	-1.09	2.89	40	31.30%	-0.25 (-1.54, 1.04)	0	6
Total (95% CI)			**97**			**104**	**100.00%**	**0.22 (-0.50, 0.94)**		

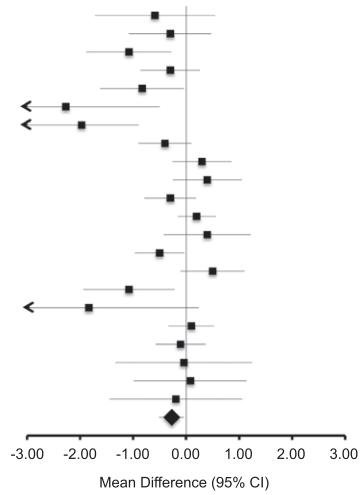
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)



B Direct comparison of epidural steroid to epidural non-steroid injections

Study	Epidural Steroid Injection Mean	SD	Total	Epidural Non-steroid Injection Mean	SD	Total	Weight, %	Mean Difference (95% CI)	Risk of Bias	Technical Quality Score
Cohen 2012[37]	-3.12	2.57	54	-2.53	2.53	30	2.90%	-0.59 (-1.72, 0.55)	1	11
Valat 2003[107]	-2.65	1.86	43	-2.35	1.82	42	4.40%	-0.30 (-1.08, 0.48)	1	10
Karppinen 2001[62]	-3.19	2.47	79	-2.11	2.64	79	4.40%	-1.08 (-1.88, -0.28)	1	9
Manchikanti 2008[85]	-4.50	1.37	42	-4.20	1.24	42	5.80%	-0.30 (-0.86, 0.26)	1	9
Carette 1997[65]	-2.07	2.57	77	-1.24	2.45	80	4.40%	-0.83 (-1.62, -0.04)	1	8
Cohen 2009[78]	-3.97	2.12	18	-1.70	1.84	6	1.50%	-2.27 (-4.03, -0.50)	1	8
Ghahreman 2010[81]	-2.90	2.44	28	-0.93	2.44	64	3.10%	-1.97 (-3.05, -0.89)	1	8
Manchikanti 2012[89]	-4.40	1.36	60	-4.00	1.42	60	6.30%	-0.40 (-0.90, 0.10)	1	8
Manchikanti 2012[90]	-3.50	1.46	50	-3.80	1.42	50	5.80%	0.30 (-0.26, 0.86)	1	7
Manchikanti 2012[91]	-4.00	1.49	30	-4.40	1.02	30	5.30%	0.40 (-0.25, 1.05)	1	7
Manchikanti 2012[92]	-4.50	0.90	30	-4.20	1.02	30	6.30%	-0.30 (-0.79, 0.19)	1	7
Manchikanti 2012[93]	-4.20	1.06	60	-4.40	0.95	60	7.20%	0.20 (-0.16, 0.56)	1	6
Manchikanti 2008[86]	-3.80	1.23	20	-4.20	1.42	20	4.20%	0.40 (-0.42, 1.22)	1	5
Manchikanti 2011[87]	-4.30	1.22	60	-3.80	1.40	60	6.50%	-0.50 (-0.97, -0.03)	1	5
Manchikanti 2012[88]	-3.80	1.06	28	-4.30	1.22	28	5.60%	0.50 (-0.10, 1.10)	1	5
Becker 2007[74]	-5.34	1.88	52	-4.26	1.99	32	4.00%	-1.08 (-1.94, -0.22)	1	4
Bush 1991[77]	-2.25	1.95	12	-0.42	2.96	11	1.10%	-1.83 (-3.90, 0.24)	1	4
Manchikanti 2012[94]	-4.10	1.18	60	-4.20	1.22	60	6.80%	0.10 (-0.33, 0.53)	1	4
Manchikanti 2012[95]	-3.70	1.36	70	-3.60	1.46	70	6.50%	-0.10 (-0.57, 0.37)	1	4
Meadeb 2001[97]	-0.50	1.82	31	-0.46	2.30	16	2.40%	-0.04 (-1.33, 1.25)	1	2
Ng 2005[69]	-1.80	2.70	43	-1.88	2.31	43	3.10%	0.08 (-0.99, 1.14)	0	7
Iversen 2011[67]	-1.53	2.61	37	-1.34	2.96	39	2.50%	-0.19 (-1.44, 1.06)	0	6
Total (95% CI)			**984**			**952**	**100.00%**	**-0.27 (-0.51, -0.04)**		

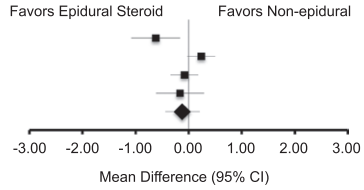
Heterogeneity: Tau² = 0.16; Chi² = 52.58, df = 21 (P = 0.0002); I² = 60%
Test for overall effect: Z = 2.26 (P = 0.02)



C Direct comparison of epidural steroid to non-epidural injections

Study	Epidural Steroid Injection Mean	SD	Total	Non-epidural Injection Mean	SD	Total	Weight, %	Mean Difference (95% CI)	Risk of Bias	Technical Quality Score
Ghahreman 2010[81]	-2.90	2.44	28	-1.36	2.47	58	20.70%	-0.62 (-1.08, -0.16)	1	8
Arden 2005[73]	-4.00	2.56	120	-4.60	2.52	108	29.10%	0.24 (-0.03, 0.50)	1	7
Price 2005[98]	-1.20	2.56	120	-1.00	2.52	108	29.10%	-0.08 (-0.34, 0.18)	1	7
Iversen 2011[67]	-1.53	2.61	37	-1.09	2.89	40	21.20%	-0.16 (-0.61, 0.29)	0	6
Total (95% CI)			**305**			**314**	**100.00%**	**-0.12 (-0.44, 0.21)**		

Heterogeneity: Tau² = 0.07; Chi² = 10.72, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 0.71 (P = 0.48)



D Indirect comparison of epidural non-steroid to non-epidural injections

Indirect comparison of injections used the formulas
$MD_{ESI\ vs\ NEI} - MD_{ESI\ vs\ ENSI} = MD_{ENSI\ vs\ NEI}$ and
$SE_{ESI\ vs\ NEI}^2 + SE_{ESI\ vs\ ENSI}^2 = SE_{ENSI\ vs\ NEI}^2$

Mean Difference (95% CI)
-0.15 (-0.55, 0.25)

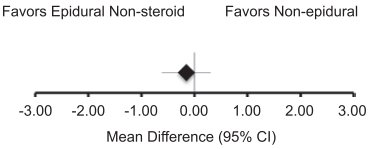


Fig. 5. (*A-D*) Forest plots comparing pain score reduction to injection for epidural nonsteroid and nonepidural injections. Three studies included treatment injections besides steroid (autologous conditioned serum [Becker[74]], etanercept [Cohen[78], Cohen[37]]). For risk of bias ratings, "0" = low methodological quality while "1" = adequate methodological quality. ENSI = epidural nonsteroid injection; ESI = epidural steroid injection; MD = mean difference; NEI = nonepidural injection.

studies needed to perform a meta-analysis, analyses of limited trials do exist[125] and generally agree with longer-term results.[126] Indirect comparisons do not qualify at the same level of evidence as randomized comparisons, because they represent mere observations of trials, may be subject to bias, and may inaccurately estimate treatment effect.[127] Yet, none of the three studies that directly compared the different types of "control" injections were designed or powered to detect a difference between nonsteroid groups (which would require significantly more patients than a study designed to detect a difference between ESI and a true placebo),[67,81,83] and two used excessively high injection volumes that resulted in a failure to detect a difference between the diluted steroid treatment (ESI) and any control group.[67,83] As the authors of the most robust study noted,[81] detecting a difference between two treatments (or control groups) with similar effect sizes would require between 1,000 and 2,000 patients, which is not practical. Consequently, indirect analyses evaluating numerous, well-designed studies may provide a better likelihood of detecting a difference between nonepidural injections and ENSIs in this context. Second, some analyses exhibited substantial heterogeneity, which is likely attributable to

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differences in methods or outcome assessments. Although the conversion of different pain-rating scales may result in increased heterogeneity and greater difficulty in detecting differences in outcomes, previous studies have consistently determined that there is a high correlation between pain-rating scales,[128–130] and scores derived from different scales are often combined in meta-analyses, including those evaluating ESI.[131] With regard to differences in treatment parameters (*e.g.*, region, number of injections, dose and type of steroid), recent reviews have concluded that minor variations in practice are likely to have no significant effect on outcome.[27,132] For example, increasing the depo-steroid dose of more than 40 mg appears to provide no added benefit, and there is little evidence that a series of ESI results in better outcomes than a single injection, or tailoring the number of injections to patient response.[27,110–112,120,132,133] However, the conglomeration of these different factors (*e.g.*, injection type and number, dose, volume) may have a cumulative effect, and hence limit the generalization of the meta-analyses. Third, publication bias may be present for studies that compared ESI and ENSIs, with modeling suggesting a nonsignificant outcome favoring ESI when a correction for small study effects was performed. Fourth, our technical rating scale remains formally unvalidated. If detecting a difference between a placebo and control requires between 50 and 150 patients, identifying outcome difference for different variables (*e.g.*, fluoroscopy *vs.* no fluoroscopy, disability *vs.* no disability) would require exponentially more patients, and be logistically challenging. Fifth, inherent to any meta-analysis are the biases contained in the included studies. Finally, to enhance generalization, we elected to include studies with follow-up periods varying from a few days to up to 3 months. Hence, this efficacy analysis was not designed to assess the long-term benefits of ESI or controlled injections.

In conclusion, the evidence comparing epidural nonsteroid with nonepidural injections is limited but suggests that ENSIs may not constitute a true placebo treatment. In light of these findings, opportunities exist for clinicians and investigators to modify their approach to these procedures, such as reducing[110–112,120] or even in some cases eliminating, the steroid component of epidural injections in high-risk scenarios, and performing high-quality RCTs that directly compare epidural nonsteroid and nonepidural injections.

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