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Clinical Relevance of Epidural Steroid Injections on Lumbosacral Radicular Syndrome-related Synptoms

Systematic Review and Meta-Analysis

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Objectives: Epidural steroid injections (ESIs) can be used to reduce lumbosacral radicular syndrome (LRS) related pain. The clinical relevance of ESIs are currently unknown. This systematic review and meta-analyses aims to assess whether ESIs are clinically relevant for patients with LRS.

Materials and Methods: Comprehensive literature searches for randomized controlled trials regarding steroid injections for LRS were conducted in PudMed, EMBASE, CINAHL, and CENTRAL from their inception to September 2018 (December 2019 for PubMed). For each homogenous comparison, the outcomes function, pain intensity and health-related quality of life at different follow-up intervals were pooled separately. The GRADE approach was used to determine the overall certainty of the evidence.

Results: Seventeen studies were included. Two different homogenous comparisons were identified for which the randomized controlled trials could be pooled. In 36 of the 40 analyses no clinically relevant effect was found. The certainty of evidence varied between very low to high. Four analyses found a clinically relevant effect, all on pain intensity and health-related quality of life, but the certainty of the evidence was either low or very low. Two of the 33 subgroup analyses showed a clinically relevant effect. However, according to the GRADE approach the certainty of these findings are low to very low.

Discussion: On the basis of the analyses we conclude there is insufficient evidence that ESIs for patients with LRS are clinically relevant at any follow-up moment. High-quality studies utilizing a predefined clinical success are necessary to identify potential clinically relevant effects of ESIs. Until the results of these studies are available, there is reason to consider whether the current daily practice of ESIs for patients with LRS should continue.

Key Words: lumbosacral radicular syndrome, sciatica, steroid, epidural steroid injection

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The International Association for the Study of Pain (IASP) defines radicular pain as pain perceived as arising in a limb or the trunk wall caused by ectopic activation of nociceptive afferent fibers in a spinal nerve or its roots or other neuropathic mechanisms. This pain is often stabbing or shooting with paresthesia and tingling or lancinating elements, but may well occur against a background of more dull aching pain.[1] Radicular pain can occur in any part of the spine, but it is most common in the lower back.[2] Lumbosacral radicular syndrome (LRS) is a disorder that causes (radicular) pain in the lower back that radiates down the back of the thigh into the leg. LRS is also known as sciatica, lumbosacral radiculopathy, nerve root pain, nerve root entrapment, or nerve root irritation.

The most frequent cause of LRS is a herniated intervertebral disc in the lumbar region where the nerve root is compressed by disc material that has ruptured through its surrounding annulus.[3–5] Other causes include lumbar spinal stenosis, spondylolisthesis, and malignancy.[3,4] In all causes the lumbar nerve root is compressed, which could result in inflammation.[5,6] Personal risk factors for LRS include age, stature, weight, smoking, and mental stress.[7,8] Some occupational risk factors for LRS are strenuous physical activity and continued exposure to whole body vibration.[9]

The guidelines of the Dutch General Practitioners Society (GPS) advise a conservative approach in the first 6 to 8 weeks of LRS, since ~75% of the patients recover spontaneously.[8] Conservative treatment consists of consultation and adjusted daily activities, with the option of oral analgesics and exercise therapy.[8] When symptoms persist after 6 to 8 weeks, surgical intervention is an option.[8] Although surgical discectomy is effective in the short-term, its long-term effectiveness in comparison to conservative treatment has not been proven.[8,10–13]

The GPS' guidelines advise steroid injections if the patient has severe pain but does not respond to opiates in the first 6 to 8 weeks, is not eligible for surgery and/or has multiple herniated discs.[8] The primary aim of steroid injections is pain reduction. Usually the steroid is injected in

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the epidural space of the corresponding segmental level of the herniated disc or surrounding tissues of the affected nerve root.[14]

Several systematic reviews and meta-analyses regarding the effectiveness of epidural steroid injections (ESIs) have been conducted over the last decade.[15–23] All reviews conclude ESIs provide short-term relief and some report long-term relief as well. Three of these reviews report on the clinical relevance of ESIs, stating the found effects were below predefined minimum clinically important difference thresholds.[15,20,21]

In most of the aforementioned systematic reviews saline injections and local anesthetic agents were lumped together in the same comparator group. Although normal saline is commonly used as a placebo and epidural saline injections show a lack of effectiveness for managing LRS in general,[24] individual cases are known in which saline injections provide a relief of symptoms.[22,25] Saline does not provide an anti-inflammatory effect, but because of possible washout effects of inflammatory mediator exiting the epidural space a patient can experience small benefits. Washout effects can also happen when injecting a local anesthetic agent. However, contrary to saline injections, local anesthetic agents are also known to have some anti-inflammatory effects.[26,27] Thus, in order to assess the clinically relevant effectiveness of ESIs compared with other injectates, the comparator group should consist of a homogeneous injectate.

Therefore, this systematic review aims to assess the clinically relevant effectiveness of ESIs as compared with saline injections or noninvasive usual care in adults suffering from LRS caused by a herniated disc or lumbar spinal stenosis.

MATERIALS AND METHODS

The recommendations of the updated Method Guidelines for Systematic Reviews in the Cochrane Back and Neck Group were followed for this review.[28] The PRISMA checklist was used to structure the review.[29] The protocol of this review is registered in PROSPERO under CRD42018115779.

Eligibility Criteria for Studies in This Review

To be eligible for inclusion in this review the comparator must consist of saline injections or noninvasive usual care. Noninvasive usual care was defined as either oral analgesics, bed rest, counseling, or exercise therapy, or a combination thereof.

Further eligibility criteria are:

- Published randomized controlled trials (RCTs) and disclosed results of unpublished RCTs, in English, Dutch, German, or French.
- Adults (18 y and older) with LRS with or without sensory deficits or muscular paresis, caused by a herniated intervertebral disc or lumbar spinal stenosis. RCTs including patients with LRS presumably caused by a herniated intervertebral disc or lumbar spinal stenosis based on clinical symptoms were also included. When studies included patients with low back pain with and without radicular signs, but did not analyze the LRS-subgroup separately, at least 80% of the patients must experience radicular symptoms. Studies with an unspecified proportion of patients with radicular symptoms were excluded.
- Interventions consisting of an ESI with or without a local anesthetic agent.
- RCTs must report on one or more of the following crucial outcomes for effectiveness: function, pain intensity and health-related quality of life (HRQOL).

There was no restriction with regard to the follow-up period. Treatment effects were classified as post-treatment (within 1 wk after the last treatment session), short-term (between 1 wk and 3 mo after the last treatment session), medium-term (between 3 mo and < 1 year after the last treatment session) and long-term (1 y or longer after the last treatment session). If 1 study had multiple measurements within one of these follow-up periods, the measurement nearest to the cut-off point was used. For measurements classified as long-term, the latest measurement was used.

Exclusion criteria were: crossover studies, RCTs with surgery as comparator, RCTs with surgery as part of the trial protocol, RCTs including pregnant or postpartum women, RCTs with patients whose symptoms related to facet joint or sacroiliac joint conditions. RCTs including patients with the cauda equina syndrome, degenerative disc disease, vascular intermittent claudication, prior back surgery, tumors or cancer were also excluded.

Study Search

A comprehensive search with controlled vocabulary and free text search terms for LRS, steroid injections and respective synonyms was conducted in MEDLINE through PubMed, EMBASE, CINAHL, and CENTRAL on September 24, 2018. Disclosed results of unpublished RCTs were also searched through the US National Library of Medicine (https://clinicaltrials.gov/) on the same day. An update of the PubMed search was conducted on December 4, 2019. The full search strategy for all databases is provided in Supplemental Digital Content 1 (http://links.lww.com/CJP/A760). Additional references were sourced through references from existing systematic reviews and meta-analyses focusing on low back pain, as well as references from the selected studies.

Data Selection and Extraction

After removing duplicates, the titles and abstracts of all studies were independently screened for eligibility by pairs of 2 reviewers. T.M.dB. screened all references while H.S.M. and I.B.dG. screened a half (separate halves). Disagreements were discussed between the reviewers until consensus was reached. If consensus was not reached, a third reviewer (either I.B.dG. or H.S.M.) made the final decision. This was followed by independent thorough scanning of the full-text of the eligible studies. Again, T.M.dB. reviewed all texts and the second assessor was either H.S.M. or I.B.dG. Disagreement was handled in a similar manner. Once full-text selection was completed, data relevant to the outcomes were extracted from the selected studies. If the results presented in the original study were not applicable in a meta-analysis (eg, no SD and confidence interval [CI] were reported, only median and range were reported, or results were reported in a figure), the authors were contacted and disclosure of original data was requested.

Measurement Instruments

Studies using the Oswestry Disability Index (ODI),[30] Quebec Back Pain Disability Questionnaire (QBDQ)[31] or Roland-Morris Disability Questionnaire (RMDQ)[32] were eligible for this review for the outcome function. The numeric rating scale (NRS)[33] or Visual Analog Scale (VAS)[34] had to be used for pain intensity. When assessing HRQOL, the EuroQol 5D (EQ-5D),[35] Health Utilities Index (HUI),[36] RAND 36-item Health Survey (RAND-36),[37] Medical Outcomes Study 12-Item[38] and 36-Item Short Form Health

Survey (SF-12; SF-36)[39] or the Sickness Impact Profile (SIP)[40] had to be reported. Other instruments for measuring function, pain or HRQOL could be included as well. However, these were handled on a case by case basis and judged on comparability with the aforementioned instruments.

Risk of Bias in Individual Studies

All articles were independently assessed for Risk of Bias (RoB) by T.M.dB. and I.B.dG. The 7 RoB-items were: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Items were scored as low, unclear or high RoB based on a consensus meeting between the reviewers and, if necessary, a third review author, H.S.M.

Data Analysis

Pooling of Data

Studies featuring patients with LRS because of a herniated disc or lumbar spinal stenosis were analyzed separately. Meta-analyses with an inverse variance method were performed in Review Manager 5.3 (RevMan).[41] Pooling of the data was only performed if studies had similar treatment arms, similar outcome variables and similar follow-ups. If available, data from adjusted analyses were used. Otherwise data from crude analyses were used. All data were presented with their respective 95% CI.

For dichotomous data, a risk ratio (RR) was calculated with the Mantel-Haenszel statistical method.[42] For continuous data, regarding the same instrument and scale, a mean difference (MD) was calculated. Otherwise a standardized mean difference (SMD) was used.[42] If studies utilizing a different instrument could not be pooled in an SMD because they presented their results in a different manner (eg, change score instead of post score), a separate MD analyses was conducted which could include those specific studies. If necessary, mean values were multiplied by −1 to ensure that the severity of symptoms measured by each scale was aligned.[42] If a 0 to 10 scale was used for the NRS and VAS, the results of these instruments were converted into a 0 to 100 scale.

Sensitivity analyses were performed based on the overall RoB of individual studies. Studies with an unclear or high overall RoB assessment in the selection bias, performance bias or detection bias domains were classified as a study with a high overall RoB. Studies with a maximum of one high RoB and one unclear RoB assessments in the attrition bias, reporting bias or other bias domains were classified as a "low overall RoB". The same overall RoB classification was given to studies that contained a maximum of 2 unclear RoB assessments in these domains. In case a study contained 2 or more high RoB or 3 unclear RoB assessments in the attrition bias, reporting bias or other bias domains the study was classified "high overall RoB".

Where applicable, subgroup analyses were performed on duration of symptoms (≤ 3 mo is acute, > 3 mo is chronic), epidural injection approach (caudal, transforaminal, or interlaminar), if the patient received repeat injections or just a single injection, and if the steroid was mixed with a local anesthetic agent (eg, lidocaine) before injection. Eligibility of studies to a subgroup was judged by J.H. A subgroup analysis was only performed if there were at least 2 studies with a combined total minimum of 100 patients.

A random-effects model was used if the number of eligible studies exceeded 5.[43,44] A fixed-effects model was used when < 6 studies in a meta-analysis showed no statistical heterogeneity according to the I^2 test ($< 40\%$ = no heterogeneity; 40% to 70% = moderate heterogeneity; and $\geq 70\%$ = substantial heterogeneity).[42,43,45] A random-effects model was used when < 6 studies in the meta-analysis showed moderate or substantial heterogeneity.

In the event of multiple similar treatment arms being compared within one study, similar arms where combined according to the Cochrane Handbook of Systematic Reviews of Interventions in Section 7.7.3.8.[42] When results were presented in medians and/or ranges, and contacting the authors did not result in the required data, the original data were either recalculated to obtain the required data (eg, from median, range and sample size to mean and SD), described in qualitative synthesis, or the study was excluded.[46]

Publication Bias

Publication bias was checked when 10 or more studies were eligible for a meta-analysis, by creating a funnel plot and by a formal statistical test of asymmetry, the Egger test, performed in RevMan.[47]

Clinically Relevant Differences

To define whether or not a significant ($P \leq 0.05$) result of a meta-analysis is a clinically relevant effect, boundaries for minimal clinical differences were established before performing the meta-analyses. For outcomes regarding function, the MD between the intervention group and comparator group should be 10 points on the ODI, 20 points on the QBPQ and 5 points on the RMDQ.[48] With regard to pain intensity, the MD must be 15 points.[48] For meta-analyses with an SMD we regarded an effect size of ≥ 0.5 as clinically relevant. For instruments without a preset minimal clinical difference, the SMD effect size was calculated and ≥ 0.5 was regarded as clinically relevant. For RR a clinically relevant effect size was either ≤ 0.75 or ≥ 1.25.[42]

GRADE

The GRADE approach was used to determine the certainty of evidence and strength of recommendations, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions and the Cochrane Back and Neck Review Group.[28,42] All 5 domains were graded in GRADEpro.[49] Inconsistency was downgraded by 1 level if the (pooled) effect size of low (overall) RoB studies was in the opposite direction than the (pooled) effect size of high (overall) RoB studies. Otherwise, inconsistency was downgraded by 1 or 2 levels when a meta-analysis showed unexplained moderate or substantial heterogeneity respectively. For the imprecision domain, pooled outcomes were downgraded by 1 level if the 95% CI crossed the clinically relevant boundary. If this was not the case, imprecision was downgraded by 1 level if the optimal information size was not reached (400 participants for continuous outcomes and 300 events for dichotomous outcomes). Both criteria were used for analyses with a single study, which could thus be downgraded by 2 levels. Grading was separately executed by T.M.dB. and I.B.dG., a consensus meeting was held afterwards, including R.W.J.G.O.

RESULTS

The literature search resulted in 2809 unique records (Fig. 1). After screening for eligibility, 17 studies (reported in 18 articles) about ESIs fulfilled the inclusion criteria (Table 1). One of the excluded studies did fulfill the inclusion criteria, but was eventually excluded because it was unclear if patients were randomized. Thus, we did not consider this study to be a true RCT.[68]

Full-text assessment revealed that pain intensity was reported in different ways between and within studies. Measurements were of back pain intensity and/or leg pain intensity and/or total (or global) pain intensity. Consequently, in this manuscript the predetermined pain intensity outcome was stratified into pain intensity (total pain intensity), back pain intensity, and leg pain intensity and these outcomes were analyzed separately.

All studies featured patients with LRS because of a herniated disc confirmed by medical imaging or LRS presumably caused by a herniated disc based on clinical symptoms. One of these studies also included patients with radicular pain because of a spinal stenosis.[56] However, the number of patients with radicular pain because of a spinal stenosis was < 15% in both study arms and outcomes were not reported separately. Therefore, in this review all patients were classified as radicular pain because of a herniated disc.

Two different groups were identified based on the application method of the steroid injection and/or comparator: ESIs versus saline injections and ESIs versus usual care. These groups were analyzed separately. The comparator group in one study received saline injections in the posterior ligaments proximal to the epidural space and gabapentin capsules.[56] This group was classified as receiving usual care, since gabapentin was prescribed for pain management and saline was not injected in the epidural space and, thus, washout effects could not happen.

In none of the meta-analyses 10 or more studies were included. Therefore, publication bias was not checked. Table 2 summarizes the results of all analyses for all comparisons including all outcomes and follow-up periods. The GRADE assessments can be found in Supplemental Digital Content 2, http://links.lww.com/CJP/A761 (for ESIs vs. saline injections) and Supplemental Digital Content 3, http://links.lww.com/CJP/A762 (for ESIs vs. usual care). The forest plots of all comparisons can be found in Supplemental Digital Contents 4 through 13, http://links.lww.com/CJP/A763, http://links.lww.com/CJP/A764, http://links.lww.com/CJP/A765, http://links.lww.com/CJP/A766, http://links.lww.com/CJP/A767, http://links.lww.com/CJP/A768, http://links.lww.com/CJP/A769, http://links.lww.com/CJP/A770, http://links.lww.com/CJP/A771, http://links.lww.com/

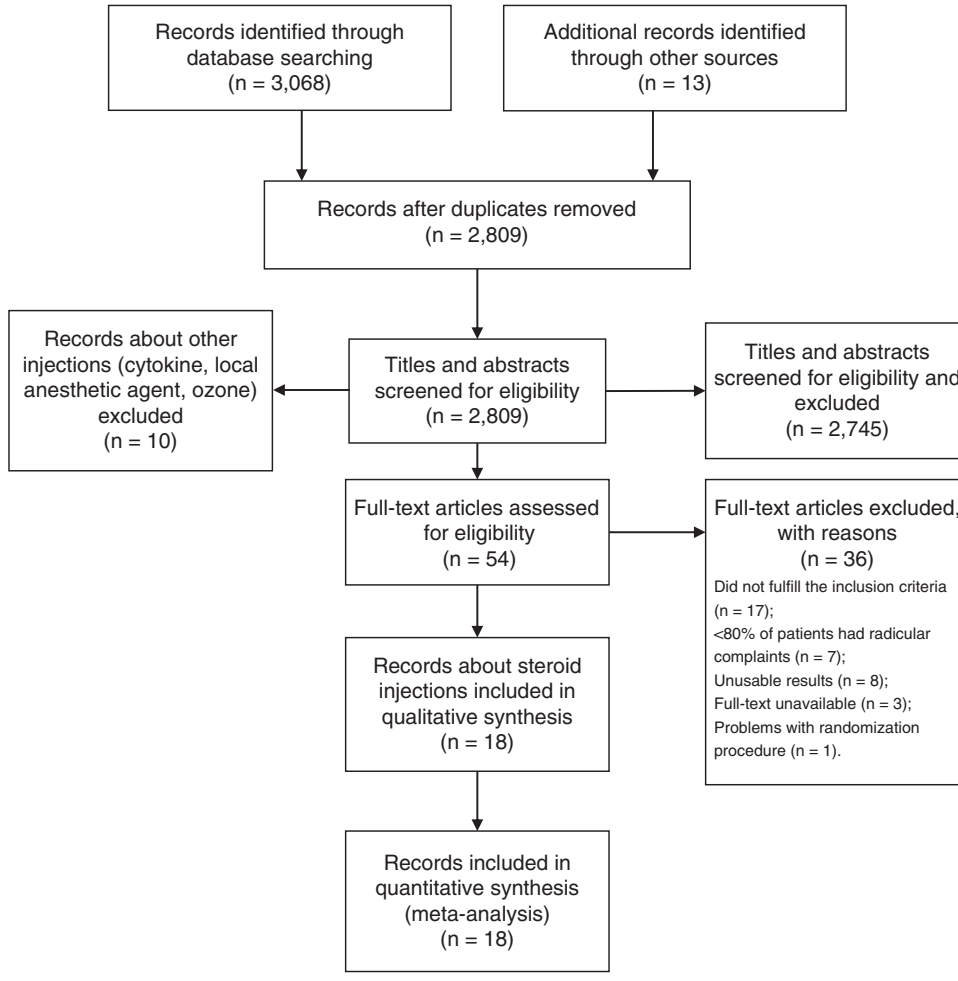

FIGURE 1. PRISMA flow diagram of the study search and selection process.

TABLE 1. Characteristics of Included Studies

References	Participants	Intervention	Comparator	Outcome*	Notes
Abedini et al[50] Iran	56 patients with radicular chronic LBP because of a herniated disc diagnosed by radiologic evidence or CT scan. Onset of back pain was during the last 6 wk and patients were nonresponsive to systematic pharmacotherapy. 31 women. Mean age in years: I 42.0, C 42.6	Fluoroscopic guided epidural injection of 80 mg methylprednisolone (n = 28)	Fluoroscopic guided epidural injection of normal saline solution of equal volume (n = 28)	ODI Post-treatment: I 34.2 (10.8)/C 29.8 (8.4) Short-term: I 6.2 (1.9)/C 7.8 (1.8) VAS (0-10) for pain Post-treatment: I 6.2 (1.2)/C 6.6 (0.8) Short-term: I 1.6 (0.6)/C 2.0 (0.7)	Dropouts not mentioned Received financial support from the Trabriz University of Medical Sciences
Arden et al[51] UK	228 patients with a clinical diagnosis of unilateral sciatica for at least 4 wk to 18 mo. 108 women. Mean age in years: I 43, C 44	Three lumbar injections of, 3 weeks apart, 80 mg triamcinolone acetonide and 10 mL of 0.25% bupivacaine (n = 120)	Three injections, 3 weeks apart, in the interspinous ligament of 2 mL of normal saline (n = 108)	ODI (change score) Short-term: I −12 (19)/C −12 (21) Medium-term: I -16 (23)/C −14 (24) **VAS (0-100) for back pain (change score)** Short-term: I −4 (28)/C −7 (32) Medium-term: I -8 (31)/C −9 (33) **VAS (0-100) for leg pain (change score)** Short-term: I -13 (33)/C −18 (33) Medium-term: I −17 (36)/C −20 (34)	Dropouts: I 28, C 26 Injections at week 3 or 6 were dropped if the ODI improved by 75% beforehand Received financial support from the National Health Service Research and Development program, the UK
Buchner et al[52] Germany	36 patients with radicular pain and MRI-confirmed disc herniation with a median pain duration of 8 wk. 13 women. Mean age in years: I 37, C 32	Three lumbar epidural injections within 14 d of hospitalization, of 100 mg methylprednisolone in 10 mL 0.25% bupivacaine in combination with the control treatment (n = 17)	Initially standardized conservative treatment consisting of bed rest, oral analgesics, and NSAIDs. Followed by a standard program of graded rehabilitation of hydrotherapy, electroanalgesia, back school, and/or spinal mobilizing physiotherapy (n = 19)	HFAQ‡ Post-treatment: I 63.7 (33-88)/ C 57.5 (21-88) Short-term: I 61.5 (25-88)/ C 58.3 (13-100) Medium-term: I 61.8 (25-83)/ C 57.2 (17-83) **VAS (0-100) for pain‡** Post-treatment: I 30.8 (0-80)/ C 37.1 (0-70) Short-term: I 32.9 (0-85)/ C 38.1 (0-100) Medium-term: I 32.9 (0-85)/ C 39.2 (0-100)	No dropouts
Bush & Hillier[53] UK	23 patients with lumbar nerve root compression signs and unilateral sciatica for 5 wk to 13 mo. 8 women. Mean age in years: I 38.2, C 37.3	Two caudal injections, 2 weeks apart, of 80 mg triamcinolone acetonide in 25 mL normal saline with 0.5% procaine hydrochloride (n = 12)	Two caudal injections, 2 weeks apart, of 25 mL normal saline (n = 11)	VAS (0-100) for pain Short-term: I 16 (15.74)/C 45 (32.18) Long-term: I 14.2 (28.47)/ C 29.6 (39.88)	Dropouts: I 1, C 4.
Carette et al[54] Canada	158 patients with radicular pain and CT scan-confirmed disc herniation, for 4 wk to 1 y with a score higher than 20 on the ODI. 69 women. Mean age in years: I 39.0, C 40.6	Epidural injection of 80 mg (2 mL) methylprednisolone acetate in 8 mL isotonic saline (n = 78). Injection was repeated after 3 and/or 6 wk if the patient did not show improvement. Mean number of injections was 2.1	Epidural injection of 1 mL isotonic saline (n = 80). Injection was repeated after 3 and/or 6 wk if the patient did not show improvement. Mean number of injections was 2.1	ODI (change score) Short-term: I 17.3 (20.6)/ C 15.4 (25.5) SIP (change score) Short-term: I 9.2 (10.8)/C 8.0 (14.1) VAS (0-100) for leg pain (change score) Short-term: I 26.5 (36.0)/C 22.5 (34.4)	Dropouts: I 13, C 22 Received financial support from the Medical Research Council of Canada and the Canadian Arthritis Society
Cohen et al[55] USA	58 patients with lumbosacral radiculopathy for 4 wk to 6 mo and MRI-confirmed pathologic disc	Two fluoroscopic guided epidural injections, 2 weeks apart, with a total volume	Two fluoroscopic guided epidural injections, 2	NRS (0-10) for back pain Short-term: I 3.49 (2.60)/ C 4.01 (2.49)	No dropouts 6 patients (I 4, C 2) received one injection

	conditions correlating with the symptoms. 17 women. Mean age in years: I 41.5, C 42.3	of 2 mL consisting of 60 mg methylprednisolone acetate and 0.5 mL saline (n = 28)	weeks apart, 2 mL normal saline (n = 30)	NRS (0-10) for leg pain Short-term: I 2.54 (3.04)/ C 3.78 (2.84) ODI Short-term: I 24.10 (19.24)/ C 30.00 (18.21) Success Rate defined as complete relief of leg pain (NRS 0-10) or ≥ 50% improvement in leg pain 1 month after treatment plus a positive GPE: Short-term: I 21 of 28/C 15 of 30	Received financial support from the John P. Murtha Neuroscience and Pain Institute, International Spinal Intervention Society, and Center for Rehabilitation Sciences Research
Cohen et al[56] USA and Europe	145 patients with radicular pain because of either an MRI-confirmed herniated disc (I 86%, C 90%) or spinal stenosis (I 14%, C 10%) for 6 wk to 4 y and an NRS for leg pain ≥ 3. 38 women. Mean age in years: I 43.8, C 41.7	Either a fluoroscopic guided transforaminal epidural injection (total volume 3 mL) for patients with unilateral pain (n = 62) or a fluoroscopic guided interlaminar epidural injection (total volume 4 mL) for patients with bilateral pain (n = 11) of 60 mg depomethylprednisolone and 1 mL of 0.25% bupivacaine plus thrice daily over-capsulated placebo pills ranging from 1800 mg/d to 3600 mg/d for 15 to 24 d (n = 73). Tramadol and NSAIDs could be prescribed when needed as rescue medications	Fluoroscopic guided injection of just over 3 mL saline in the posterior ligaments 1-2 cm proximal to the epidural space plus thrice daily over-capsulated 300 mg gabapentin ranging from 1800 mg/d to 3600 mg/d for 15 to 24 d (n = 72). Tramadol and NSAIDs could be prescribed when needed as rescue medications	NRS (0-10) for average back pain Short-term: I 3.9 (2.7)/C 3.7 (2.5) NRS (0-10) for average leg pain Short-term: I 3.4 (2.7)/3.7 (2.8) ODI Short-term: I 33.6 (19.4)/C 29.6 (16.3) Success Rate defined as a ≥ 2 points decrease in average leg pain (NRS 0-10) coupled with a positive GPE Short-term: I 27 of 73/C 21 of 72	Dropouts: I 2, C 1 Received financial support from the Center for Rehabilitation Sciences Research, Bethesda, MD
Dincer et al[57] Turkey	64 patients with LBP and radicular pain diagnosis based on history, clinical findings and MRI. Pain lasting from 1 to 12 mo with a VAS higher than 40. Patients with protruded lumbar disc herniation were eligible. Patients with extruded or sequestered lumbar disc herniation were excluded. 18 women. Mean age in years: I 28, C 28	Single caudal injection (20 mL) of 40 mg methylprednisolone acetate, 8 mg dexamethasone phosphate, 7 mL 2% prilocaine hydrochloride and 10 mL normal saline plus therapeutic exercise (n = 34)	Twice daily, with 12 h intervals, diclophenac sodium 75 mg for 14 consecutive days plus therapeutic exercise (n = 30)	ODI Short-term: I 16.2 (9.4)/C 20.3 (10.1) VAS (0-10) for pain Short-term: I 3.3 (1.3)/C 4.1 (1.5)	No dropouts
Ghahreman et al†[58] Australia	65 patients with radicular pain because of CT scan or MRI-confirmed disc herniation with a median pain duration of 6 to 96 wk. 29 women. Median age in years: I 49, C 44	Single fluoroscopic guided transforaminal injection of 1.75 mL triamcinolone acetonide 40 mg/ mL and 0.75 mL 0.5% bupivacaine (n = 28)	Single fluoroscopic guided transforaminal injection of 2 mL normal saline (n = 37)	NRS (0-10) for leg pain Short-term: I 4.1 (3.0)/C 5.5 (2.6) Success Rate defined as a complete relief of leg pain (NRS 0-10) or ≥ 50% improvement in leg pain 1 month after treatment Short-term: I 15 of 28/C 7 of 37	No dropouts. Up to 3 injections were allowed for patients who felt they only benefitted partially from one injection

(*Continued*)

TABLE 1. (*continued*)

References	Participants	Intervention	Comparator	Outcome*	Notes
Iversen et al[59] Norway	77 patients with clinically confirmed radiating unilateral lumbar radiculopathy for more than 12 wk. All included patients were subjected to an MRI or CT scan; final inclusion was not dependent on the results. All patients either had disc herniation (n = 49), disc sequestration (n = 25) or recess stenosis (n = 1), 33 women. Mean age in years: I 40.1, C 42.8	Two ultrasound guided caudal epidural injections, 2 weeks apart, of 40 mg triamcinolone acetonide in 29 mL normal saline (n = 37)	Two subcutaneous injections, 2 weeks apart, of 2 mL normal saline (n = 40)	EQ-5D (between group difference)§ Short-term: −0.11 (95% CI: −0.22 to 0.00) Long-term: −0.05 (95% CI: −0.16 to 0.07) ODI (between group difference)§ Short-term: 3.7 (95% CI: −2.3 to 9.7) Long-term 1.7 (95% CI: −4.5 to 7.8) VAS (0-100) for back pain (between group difference)§ Short-term: 5.1 (95% CI: −6.5 to 16.8) Long-term: −1.4 (95% CI: −13.6 to 10.8) VAS (0-100) for leg pain (between group difference)§ Short-term: 10.0 (95% CI: −2.2 to 22.3) Long-term: −1.4 (95% CI: −14.1 to 11.4)	Dropouts: I 3, C 8. Two of 3 treatment arms included in this study. Received financial support from the North Norway Regional Health Authority and Health Region Nord-Trøndelag, Norway
Karppinen et al[60] Finland	160 patients with unilateral sciatica and MRI-confirmed herniated disc, lasting for 1 to 6 mo. 63 women. Mean age in years: I 43.8, C 43.7	Fluoroscopic guided periradicular injection of either 2 mL or 3 mL combination of methylprednisone (40 mg/mL) and bupivacaine (5 mg/mL) (n = 80)	Fluoroscopic guided periradicular injection of either 2 mL or 3 mL isotonic saline (n = 80)	ODI (between group difference)§ Short-term: 1.3 (95% CI: −6.1 to 8.6) Medium-term: 5.9 (95% CI: −0.7 to 12.4) Long-term: 0.4 (95% CI: −6.2 to 7.0) VAS (0-100) for back pain (between group difference)§ Short-term: 12.2 (95% CI: 1.0 to 23.5) Medium-term: 13.5 (95% CI: 2.4 to 24.6) Long-term: 8.4 (95% CI: −2.1 to 18.9) VAS (0-100) for leg pain (between group difference)§ Short-term: 0.5 (95% CI: −11.0 to 12.0) Medium-term: 16.2 (95% CI: 5.6 to 26.8) Long-term: 5.3 (95% CI: −5.0 to 15.97)	Dropouts: I 2, C 0. Received financial support from the Yrjö Jahnsson Foundation, the Finnish Office for Health Technology Assessment, the Finnish Work Environment Fund, and the International Spinal Injection Society
Kotb et al[61] Egypt	48 patients with LBP and radicular symptoms of < 6 wk duration because of lumbar disc herniation diagnosed by history, clinical examination and	Three CT-guided transforaminal injections of 40 mg triamcinolone acetonide in 1 mL lidocaine 0.02% over a period of	Medical treatment in the form of muscle relaxants, NSAIDs and vitamin B complex preparations	ODI Short-term: I 36.1 (5.6)/ C 55 (5.1) VAS (0-10) for back pain	Dropouts not mentioned. Two of 4 treatment arms did not fulfill inclusion criteria. Characteristics not described

	MRI. 4 women. Mean age in years: I 39.1, C 39	1 month at 10-day intervals (n = 12)	over a period of 1 month (n = 12).	Short-term: I 1.0 (0.8)/ C 4.8 (1.5)	
Laiq et al[62] Pakistan	52 patients with lumbar radicular pain or radicular pain caused by herniated intervertebral disc or single level disc herniation diagnosed by symptoms and/ or MRI. All with a VAS higher than 60 mm 2 wk before treatment. Excluding dropouts: 18 women, mean age in years: I 40, C 42	Single injection of 80 mg methylprednisolone in combination with 3 mL 2% plain xylocaine and 3 mL normal saline in the lumbar epidural space through a midline approach (n = 26)	Bed rest, NSAIDs, muscle relaxants, and opioids (n = 26)	VAS (0-10) for pain Short-term: I 4.5 (1.50)/C 5.0 (1.10) Medium-term: I 6.0 (1.45)/ C 6.5 (1.30)	Dropouts: I 1, C 1
Mondal et al[63] India	60 patients with clinically, radiologically and neurophysiologically diagnosed lumbar disc herniation and unilateral radiculopathy with chronic LBP of more than 3 mo with pain intensity limiting function and NRS score above 5. 13 women. Mean age in years: I 42.1, C 48.4	Single fluoroscopic guided transforaminal injection with methylprednisolone (20 mg) and 0.25% bupivacaine (total 2 mL to 3 mL) combined with control (n = 30)	Gabapentin (300 mg thrice daily orally) and amitriptyline (25 mg once daily orally), and spine extension exercises on day 0/visit 1 (n = 30)	NRS (0-10) for pain (change score) Short-term: I −4.19 (1.00)/ C −1.10 (0.77) ODI (change score) Short-term: I −27.58 (5.08)/ C −4.65 (4.49)	Dropouts: I 3, C 1 All patients were industrial workers
Nandi & Chowdhery[64] India	98 patients with MRI-confirmed prolapsed lumbar disc and sciatic pain for 1 to 6 mo. All with a VAS higher than 40mm. Excluding dropouts: 39 women, mean age in years: I 43.0, C 42.9	Single lumbar caudal injection of 80 mg methylprednisolone in 18 mL isotonic saline (20 mL in total) (n = 49)	Single lumbar caudal injection of 20 mL isotonic saline (n = 49)	ODI Short-term: I 35.15 (10.19)/ C 40.20 (8.41) RMDQ Short-term: I 11.51 (5.03)/ C 13.96 (4.09) VAS (0-100) for pain Short-term: I 34.83 (20.34)/ C 45.78 (23.60)	Dropouts: I 2, C 3
Spijker-Huiges et al[65,66] Netherlands	73 patients with LRS, as established by the GP, of at least 2 wk and no more than 4 wk. Equal sex distributions in the analyzed group (n = 63) with a mean age of 43.7 y for all patients	Lumbar interlaminar epidural injection of 80 mg triamcinolone acetonide in 10 mL of normal saline in combination with control treatment (n = 37; analyzed: n = 33; SF-36 analyses: n = 22)	Unstandardized usual care based on treatment decided by the patient and their GPS (n = 36; analyzed: n = 30; SF-36 analyses: n = 22)	NRS (0-10) for back pain Short-term: I 2.1 (2.5)/C 3.0 (3.0) Medium-term: I 1.9 (2.5)/C 2.0 (2.4) Long-term: I 1.3 (1.9)/C 2.0 (2.9) NRS (0-10) for leg pain Short-term: I 1.6 (2.5)/C 2.7 (2.8) Medium-term: I 1.6 (2.4)/C 1.9 (2.5) Long-term: I 1.0 (2.0)/C 1.4 (2.2) NRS (0-10) for (total) pain Short-term: I 2.5 (2.5)/C 3.2 (2.8) Medium-term: I 2.3 (2.5)/C 2.3 (2.4) Long-term: I 1.3 (2.0)/C 2.1 (3.0) RMDQ Short-term: I 5.3 (5.9)/C 7.6 (6.3) Medium-term: I 3.0 (4.5)/C 5.4 (6.5) Long-term: I 2.3 (3.7)/C 4.1 (6.2) SF-36 MCS Short-term: I 65.0 (10.60)/C 61.2 (11.05) Medium-term: I 67.3 (11.05)/ C 64.1 (11.28) Long-term: I 67.0 (11.05)/C 65.2 (11.50) SF-36 PCS Short-term: I 68.9 (11.95)/ C 59.4 (12.18)	No dropouts in the analyzed group. SF-36 analyses included a subgroup of participants. Received financial support from the University Medical Center Groningen

(*Continued*)

TABLE 1. (*continued*)

References	Participants	Intervention	Comparator	Outcome*	Notes
				Medium-term: I 77.7 (12.18)/ C 63.1 (12.41)	
				Long-term: I 79.5 (11.50)/C 67.6 (12.86)	
Valat et al[67] France	85 patients with sciatica and radicular symptoms, presumably caused by a herniated disc, lasting 15-180 d. At least one nerve root compression sign had to be present. All with a VAS higher than 30 mm. 33 women. Mean age in years: I 43.5, C 38.4	Three interlaminar injections (at 2-day intervals) of 2 mL prednisolone acetate (50 mg) (n = 43). NSAIDs were allowed after 20 d of the first injection	Three interlaminar injections (at 2-day intervals) of 2 mL normal saline (n = 42). NSAIDs were allowed after 20 d of the first injection	RMDQ Post-treatment: I 12.6 (5.2)/C 12.8 (4.3) Short-term: I 8.5 (5.4)/C 9.1 (5.4) VAS (0-100) for pain Post-treatment: I 31.0 (20.8)/C 34.5 (19.8) Short-term: I 22.1 (20.1)/C 24.8 (25.7)	Dropouts: I 2, C 3. Received financial support from the PHRC 1995, Ministry of Health, France

*Mean (SD), based on results presented in the study stratified by follow-up definition used in this report.
†Other outcomes were reported, but results were unusable for this review.
‡Mean (range).
§Negative values indicate a positive intervention effect.
C indicates comparator group; CT scan, computed tomography scan; EQ-5D, EuroQol 5D; GP, general practitioner; GPE, global perceived effect; HFAQ, Hannover Functional Ability Questionnaire; HNP, herniated nucleus pulposus; I, intervention group; LBP, low back pain; LRS, lumbosacral radicular syndrome; MCS, mental component summary; MRI, magnetic resonance imaging; n, sample size; NRS, Numeric Rating Scale; NSAID, nonsteroidal anti-inflammatory drug; ODI, Oswestry Disability Index; PCS, Physical Component Summary; RMDQ, Roland-Morris Disability Questionnaire; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; SIP, Sickness Impact Profile; VAS, visual analog scale.

CJP/A772, the forest plots of all subgroup analyses can be found in Supplemental Digital Contents 14 through 20, http://links.lww.com/CJP/A773, http://links.lww.com/CJP/A774, http://links.lww.com/CJP/A775, http://links.lww.com/CJP/A776, http://links.lww.com/CJP/A777, http://links.lww.com/CJP/A778, http://links.lww.com/CJP/A779.

ESIs Versus Saline Injections

Ten studies[50,51,53–55,58–60,64,67] compared the epidural administration of steroids versus saline injections. Four studies had a high (overall) RoB.[53,58,59,64] The remaining had a low RoB (see RoB summary, Supplemental Digital Content 21, http://links.lww.com/CJP/A780). Eighteen comparisons were identified (see forest plots, Supplemental Digital Contents 4 through 8, http://links.lww.com/CJP/A763, http://links.lww.com/CJP/A764, http://links.lww.com/CJP/A765, http://links.lww.com/CJP/A766, http://links.lww.com/CJP/A767), of which 16 could be pooled (Table 2). One meta-analysis (see forest plot, Supplemental Digital Content 7, comparison B, http://links.lww.com/CJP/A766) including 2 studies (total n = 123) showed a clinically relevant effect—in favor of the intervention group—on the proportion of responders who experienced > 50% reduction in short-term leg pain intensity (RR = 1.92; 95% CI = 1.02-3.61). However, certainty of evidence was very low. Of all other analyses only 2 of them showed a statistically significant effect, both in favor of the intervention group (see forest plots, Supplemental Digital Content 4, comparison D, http://links.lww.com/CJP/A763 and Supplemental Digital Content 5, comparison B, http://links.lww.com/CJP/A764). However, these effects were not clinically relevant and the certainty of evidence was low: function short-term (RMDQ) (MD = −1.72; 95% CI = −3.16 to −0.27) and pain intensity short-term (MD = −7.63; 95% CI = −14.51 to −0.76).

There was 1 meta-analysis graded as high certainty of evidence: back pain intensity short-term. This analyses (see forest plot, Supplemental Digital Content 6, comparison A, http://links.lww.com/CJP/A765) did not show a clinically relevant nor a statistically significant effect (MD = 4.14; 95% CI = −1.04 to 9.32). Four meta-analyses were graded as moderate certainty of evidence, all of the effects were not clinically relevant nor statistically significant: function short-term (ODI) (see forest plot, Supplemental Digital Content 4, comparison C, http://links.lww.com/CJP/A763), pain intensity post-treatment (see forest plot, Supplemental Digital Content 5, comparison A, http://links.lww.com/CJP/A764), leg pain intensity short-term (see forest plot, Supplemental Digital Content 7, comparison A, http://links.lww.com/CJP/A766) and leg pain intensity medium-term (see forest plot, Supplemental Digital Content 7, comparison C, http://links.lww.com/CJP/A766). All remaining analyses either had a low or very low certainty of evidence (Table 2).

Two of the 19 subgroup analyses showed clinically relevant effects. These were the single injection subgroup in function short-term (see forest plot, Supplemental Digital Content 14, comparison C, http://links.lww.com/CJP/A773) and the caudal approach in pain intensity short-term (see forest plot, Supplemental Digital Content 15, comparison B, http://links.lww.com/CJP/A774). The found clinically relevant effect of the single injection subgroup (SMD = −0.65; 95% CI = −0.98 to −0.32) would be graded as low certainty of evidence because of downgrading for high (overall) RoB and imprecision. The clinically relevant effect of the caudal approach subgroup (MD = −17.41; 95% CI = −34.37 to

TABLE 2. Overview of All Results

Outcome	Instrument (Scale*)	Post-treatment	Short-term	Medium-term	Long-term
Epidural steroid injections vs. saline injections					
Function	ODI (0 to 100) & RMDQ (0 to 24)	SMD = 0.18[2] (−0.30 to 0.65) LOW	SMD = −0.29[5] (−0.66 to 0.07) LOW		
	ODI (0 to 100)		MD = −1.59[7]† (−3.42 to 0.24) MODERATE	MD = 1.85[2] (−5.89 to 9.59) LOW	MD = 1.09[2] (−3.43 to 5.61) LOW
	RMDQ (0 to 24)		*MD = −1.72[2]† (−3.16 to −0.27) LOW*		
Pain Intensity	NRS/VAS (0 to 100)	MD = −3.86[2] (−8.40 to 0.68) MODERATE	*MD = −7.63[4] (−14.51 to -0.76) LOW*		MD = −15.38[1] (−43.93 to 13.17) VERY LOW
Back Pain Intensity	NRS/VAS (0 to 100)		MD = 4.14[4] (−1.04 to 9.32) HIGH	MD = 6.69[2] (−5.51 to 18.89) LOW	MD = 4.23[2] (−3.73 to 12.19) LOW
Leg Pain Intensity	NRS/VAS (0 to 100)		MD = −1.69[6] (−8.77 to 5.39) MODERATE	MD = 9.31[2] (−3.62 to 22.23) MODERATE	MD = 2.64[2] (−5.36 to 10.64) LOW
	Success Rate (≥ 50% improvement)		***RR = 1.92[2] (1.02 to 3.61) VERY LOW***		
Health-Related Quality of Life	EQ-5D (−0.594 to 1) & SIP (0 to 100)		SMD = −0.21[2] (−0.47 to 0.06) LOW		
	EQ-5D (−0.594 to 1)				SMD = −0.22[1] (−0.70 to 0.27), translates to MD = −0.05[1] (−0.17 to 0.07) VERY LOW
Epidural steroid injections vs. usual care					
Function	HFAQ (0 to 100) & ODI‡ (0 to 100) & RMDQ (0 to 24)		SMD = −0.59[5] (−1.26 to 0.09) VERY LOW	SMD = −0.38[2] (−0.78 to 0.02) VERY LOW	
	HFAQ (0 to 100)	MD = −6.20[1] (−16.17 to 3.77) VERY LOW			
	ODI (0 to 100)		MD = −10.66[4]† (−22.52 to 1.20) VERY LOW		
	RMDQ (0 to 24)				MD = −1.80[1] (−4.35 to 0.75) VERY LOW
Pain Intensity	NRS/VAS (0 to 100)	MD = −6.30[1] (−18.64 to 6.04) VERY LOW	MD = −11.71[5] (−24.97 to 1.56) VERY LOW	MD = −4.00[3] (−9.94 to 1.94) VERY LOW	MD = −8.00[1] (−20.72 to 4.72) VERY LOW
Back Pain Intensity	NRS/VAS (0 to 100)		MD = −15.03[3] (−41.11 to 11.04) VERY LOW	MD = −1.00[1] (−13.10 to 11.10) VERY LOW	MD = −7.00[1] (−19.24 to 5.24) VERY LOW
Leg Pain Intensity	NRS/VAS (0 to 100)		MD = −5.53[2] (−12.94 to 1.87) LOW	MD = −3.00[1] (−15.13 to 9.13) VERY LOW	MD = −4.00[1] (−14.42 to 6.42) VERY LOW
	Success Rate (≥ 20 points improvement)		RR = 1.27[1] (0.79 to 2.03) VERY LOW		
Health-Related Quality of Life	SF-36 MCS (0 to 100)		SMD = 0.34[1] (−0.25 to 0.94), translates to MD = 3.80[1] (−2.60 to 10.20) VERY LOW	SMD = 0.28[1] (−0.31 to 0.88), translates to MD = 3.20[1] (−3.40 to 9.80) VERY LOW	SMD = 0.16[1] (−0.44 to 0.75), translate to MD = 1.80[1] (−4.87 to 8.47) VERY LOW

(*Continued*)

TABLE 2. (*continued*)

Outcome	Instrument (Scale*)	Post-treatment	Short-term	Medium-term	Long-term
	SF-36 PCS (0 to 100)		***SMD = 0.77 (0.16 to 1.39), translates to MD = 9.50(1) (2.37 to 16.63) VERY LOW***	***SMD = 1.17 (0.52 to 1.81), translates to MD = 14.60(1) (7.34 to 21.86) VERY LOW***	***SMD = 0.96 (0.33 to 1.59), translates to MD = 11.90(1) (4.69 to 19.11) VERY LOW***

Data reflect effect size(N studies), 95% CI, GRADE Certainty (VERY LOW, LOW, MODERATE, HIGH).
Italics indicate a significant difference; bold print signifies a clinically relevant difference.
Negative MD and SMD numbers favor the steroid group, except for Quality of Life. RR numbers > 1.00 favor the steroid group.
*Scale mentioned where applicable.
†In addition to the pooled SMD, a pooled outcome with just one instrument was performed because of being able to pool different studies.
‡ODI only included in the short-term analyses.
CI indicates confidence interval; EQ-5D, EuroQol 5D; HFAQ, Hannover Functional Ability Questionnaire; MCS, mental component summary; MD, mean difference; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; PCS, physical component summary; RMDQ, Roland-Morris Disability Questionnaire; RR, risk ratio; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; SIP, sickness impact profile; SMD, standardized mean difference; VAS, visual analog scale.

−0.45) was graded as very low certainty of evidence due high (overall) RoB, inconsistency, and imprecision.

ESI Versus Usual Care

Seven studies, published in 8 references,[52,56,57,61–63,65,66] compared ESIs with usual care. Only 1 study had a low (overall) RoB,[56] the other studies had a high RoB (see RoB summary, Supplemental Digital Content 22, http://links.lww.com/CJP/A781). Seven meta-analyses were performed and a further 15 comparisons of only 1 study were identified (see forest plots, Supplemental Digital Contents 9 through 13, http://links.lww.com/CJP/A768, http://links.lww.com/CJP/A769, http://links.lww.com/CJP/A770, http://links.lww.com/CJP/A771, http://links.lww.com/CJP/A772). All but 1 of these 22 comparisons yielded very low certainty of evidence (Table 2). Three comparisons, all based on the same study, showed a clinically relevant effect on the physical component scale of the SF-36 for HRQOL in the short-term (MD = 9.50; 95% CI = 2.37-16.63), medium-term (MD = 14.60; 95% CI = 7.34-21.86), and long-term (MD = 11.90; 95% CI = 4.69-19.11) follow-up. The leg pain intensity short-term comparison (see forest plot, Supplemental Digital Content 12, comparison A, http://links.lww.com/CJP/A771) was graded as low certainty of evidence. This analysis included two studies (one of these studies had low [overall] RoB), but did not show a significant effect (MD = −5.53; 95% CI = −12.94 to 1.87). None of the 14 subgroup analyses showed clinically relevant effects nor statistically significant effects (see forest plots, Supplemental Digital Contents 18 through 20, http://links.lww.com/CJP/A777, http://links.lww.com/CJP/A778, http://links.lww.com/CJP/A779).

DISCUSSION

This systematic review included 17 RCTs of ESIs for LRS, because of a herniateddisc (or presumably caused by a herniated disc), compared with saline injections or usual care. We did not find any study including mainly or only patients with LRS because of lumbar spinal stenosis. We were able to perform 23 meta-analyses regarding the outcomes function, pain intensity, back pain intensity, leg pain intensity, and HRQOL at post-treatment, short-term, medium-term, or long-term follow-up. The results suggest that there is currently insufficient evidence to support clinically relevant effects of ESIs compared with either saline injections or noninvasive usual care, in patients with LRS at any time point during follow-up.

Four of 40 comparisons showed a clinically relevant effect (Table 2). Three of these effects were based on single, small studies. The only clinically relevant meta-analysis (of 2 RCTs) was of very low certainty of evidence. Those RCTs studied responders with a > 50% reduction of leg pain after an ESI compared with saline injections at short-term follow-up. The other clinically relevant results regarded a MD in the physical component scale of the SF-36 (with very low certainty of evidence) at the short-term, medium-term, and long-term follow-up. These results were all because of a single, small study. In the same study, no significant effects were found with regard to function, pain intensity, back pain intensity, and leg pain intensity.

Moderate to high certainty of evidence was found in 5 meta-analyses which could not prove the clinical relevance of ESIs compared with saline injections (Table 2). These analyses included the results on function short-term (ODI), pain intensity post-treatment, back pain intensity short-term and leg pain intensity short-term and medium-term. On the basis of the certainty of evidence, these results are fairly robust. Thus, the clinically relevant effectiveness of ESIs, as compared with saline injections, has not been proven. The evidence of other comparisons to saline injections is too uncertain to make robust recommendations.

Only 1 meta-analysis of ESIs compared with usual care was graded as low certainty of evidence (Table 2). All other comparisons of ESIs compared with usual care were graded as very low certainty of evidence. This evidence is too uncertain to make robust recommendations.

We performed 33 subgroup analyses, of which only 2 showed a clinically relevant effect (see forest plots, Supplemental Digital Content 14, comparison C, http://links.lww.com/CJP/A773, and Supplemental Digital Content 15, comparison B, http://links.lww.com/CJP/A774). It appears to make a difference whether you receive a single injection or repeat injections and if the steroid was injected with the caudal approach instead of the transforaminal or interlaminar approach. However, according to the GRADE approach the certainty of these findings is only low to very low, thus, a cautious interpretation of the subgroup analyses is required.

No study regarding the effectiveness of ESIs for LRS caused by a lumbar spinal stenosis fulfilled the inclusion criteria. Thus, the clinically relevant effectiveness is currently

unknown. What is known is that ESIs combined with a local anesthetic agent does not provide better pain and functional improvement outcomes for patients with chronic low back pain secondary to lumbar spinal stenosis compared with local anesthetic agent injections alone.[69]

A strength of this review is the methodological rigor as we followed the Method Guidelines for Systematic Reviews in the Cochrane Back and Neck Group for this review.[28] Moreover we took into account the notion that application of a local anesthetic agent (ie, lidocaine injections) alone can be an effective treatment.[19] Studies in which local anesthetic agents were used as a comparator were excluded in this meta-analysis. This gives more detailed information about the effectiveness of ESIs.

In our analyses we did not take into account the possibility of washout effects when administering saline epidurally, even though individual patients can experience small benefits because of it. Two of the included studies administered saline in the surrounding tissues instead of epidurally.[51,59] Post hoc subgroup analyses based on epidural saline injections and saline injected in the surrounding tissues did not result in any clinically relevant outcomes (data not presented). Therefore, it is unlikely that possibility of washout effects affected our outcomes.

Nor did we take into account that the epidural administration of saline with or without steroids may be an effective intervention for managing spinal pain secondary to disc herniation or spinal stenosis, as mentioned in a recently conducted systematic review and meta-analysis.[70] Moreover, the authors of that systematic review did not find a significant difference in effectiveness between both interventions. They state that the epidural administration of saline is not a true placebo.[70] Even though our review included epidural saline injections as part of the comparator group and we assessed the clinical relevance of ESIs with or without saline for LRS compared with saline injections, our results are in line with the aforementioned systematic review. If there is no significant difference in effectiveness between the epidural administration of saline with or without steroids, there also will not be sufficient evidence to support clinically relevant effects of ESIs compared with saline injections, as is stated in this review.

A limitation of this review is the assumption that all meta-analyses included patients with LRS because of a herniated disc. However, just over a third of the studies included patients without MRI or CT-confirmed LRS, but based on clinical signs.[51,53,62,65–67,71] Although we cannot validate that all patients in these studies had LRS because of a herniated disc, it is highly likely that almost all patients suffered from LRS because of a herniated disc based on the inclusion of their clinical signs and the fact that the most common cause of LRS is a herniated disc.[3–5]

All noninvasive interventions for LRS were aggregated as usual care in this review, since all can be advised by GPS as initial treatment options, either alone or combined.[8] Although the treatment options within usual care can be quite different from one another, the meta-analyses showed that little to no statistical heterogeneity is present. Furthermore, the network meta-analysis performed by Lewis et al[16] displayed no effectiveness of interventions that could be classified as usual care compared with inactive control (eg, oral placebo, placebo injections, sham treatment, and no treatment). Moreover, our meta-analyses of ESIs compared with usual care did not yield substantially different results in comparison to saline injections. Therefore, to aggregate the various noninvasive interventions as usual care appears justified.

Another limitation of this review is that only 3 of the included studies reported on a predefined clinical success,[55,56,58] such as $\geq 50\%$ improvement in leg pain. Two of these studies could be pooled, resulting in the only clinically relevant effect found within this review. However, because of the very low certainty of evidence the evidence is insufficient to make robust recommendations. The US Food and Drug Administration states in their Guidance for Industry on patient-reported outcomes that the group average is not an appropriate measurement for individual change. However, if no other data are available, the mean group change is still the best estimate.[72] Therefore, more (high-quality) studies utilizing a predefined clinical success are necessary.

The predetermined boundaries for minimal clinical differences were based on a consensus statement regarding within-group improvements.[48] However, the clinical relevance in this review should be interpreted as between group differences. Therefore, exploring the robustness of our conclusion using somewhat different thresholds is warranted. To do so, we looked at a previously conducted systematic review that discussed minimal clinical differences thresholds of 10 to 30 points (on a scale of 0 to 100) of within-person improvements in pain intensity and function.[15] Applying this less stringent boundary of 10 points to outcomes with significant differences (Table 2) did not result in any additional clinically relevant outcomes. So, also when less stringent boundaries for minimal clinical differences were applied, still no clinically relevant results were found. Therefore, we consider our conclusions regarding the clinical relevance as robust.

Our results are in line with the pooled results of other recently conducted systematic reviews and meta-analyses.[15,18–21] Some of these reviews did report a significant pooled MD for some outcomes, but did not report a statement about clinical relevance. The effect sizes in these reviews did not exceed the boundaries for clinically relevant differences that we applied in this study.

CONCLUSION

On the basis of our primary analyses as well as post hoc sensitivity analyses with less stringent boundaries for minimal clinical differences, we conclude with low to high certainty there is insufficient evidence that ESIs compared with saline injections for patients with LRS are clinically relevant at any time point during follow-up. With regard to the comparison of ESIs to noninvasive usual care, we conclude that the quality of the available evidence is too uncertain to make robust recommendations. We found no evidence with regard to ESIs in patients with LRS because of lumbar spinal stenosis. High-quality studies utilizing a predefined clinical success for comparing ESIs to saline injections and noninvasive usual care are necessary to identify potential clinically relevant effects of ESIs. Furthermore, efforts should be made to identify important treatment predictors for nonresponse to ESIs in order to avoid unnecessary treatment. Until the results of these studies are available, there is reason to consider whether the current daily practice of ESIs for patients suffering from LRS should continue.

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