Meta-Analysis

Is Epidural Injection of Sodium Chloride Solution a True Placebo or an Active Control Agent? A Systematic Review and Meta-Analysis

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Background: Epidural injections have been extensively used since their description in 1901, and steroids since their first utilization in 1952. Multiple randomized controlled trials and systematic reviews have reached discordant conclusions regarding the effectiveness of sodium chloride solution and steroids in managing spinal pain.

True placebo-controlled trials with the injection of an inactive substance to unrelated structures have been nonexistent. Consequently, the discussions continue to escalate, seemingly without proper discourse.

In this review, we sought to assess the true placebo nature of saline and the effectiveness of steroids.

Objectives: This assessment of sodium chloride solution is undertaken to assess if it is a true placebo when injected into the epidural space, is effective alone, and whether steroids are effective when injected with sodium chloride solution rather than local anesthetic in managing spinal pain.

Study Design: A systematic review of randomized controlled trials utilizing sodium chloride solution alone, steroids alone, or sodium chloride solution with steroids in managing spinal pain secondary to disc herniation or spinal stenosis.

Methods: The systematic review was performed utilizing Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Cochrane review criteria and Interventional Pain Management techniques--Quality Appraisal of Reliability and Risk of Bias Assessment (IPM–QRB) was used to assess the methodological quality assessment. Qualitative analysis was performed by utilizing best evidence synthesis principles, and quantitative analysis was performed utilizing meta-analysis with conventional methodology and single-arm meta-analysis.

PubMed, Cochrane Library, US National Guideline Clearinghouse, Google Scholar, and prior systematic reviews and reference lists were utilized in the literature search from 1966 through December 2018. The evidence was summarized utilizing principles of best evidence synthesis on a scale of 1 to 5.

Outcome measures for the present analysis, 20% improvement from the baseline pain scores or disability scores was considered clinically significant. Effectiveness was determined short-term if it was less than 6 months, whereas longer than 6 months was considered to be long-term.

Results: Of the 8 trials meeting inclusion criteria, 2 trials utilized fluoroscopic imaging and one study utilized ultrasound. All other studies performed the procedure without fluoroscopy.

With dual-arm meta-analysis, there was no significant difference between epidural sodium chloride solution and epidural steroids with sodium chloride solution. Utilizing single-arm analysis, both epidural saline and epidural steroids with saline were effective in reducing 20% of pain, however, only reducing disability scores by 10% to 12%.

Based on the qualitative analysis, epidural saline and epidural steroids with saline showed effect beyond placebo and showed level I, or strong evidence, that neither epidural saline, nor epidural steroids with saline are placebo and that both are effective.

Limitations: Despite 8 randomized controlled trials, only 2 of them utilized fluoroscopy. Overall evidence is considered less than optimal and further studies elucidating these actions are strongly recommended.

Conclusions: The findings of this systematic review and meta-analysis show that epidurally administered sodium chloride solution and sodium chloride solution with steroids may be effective in managing low back and lower extremity pain. Consequently, the findings of this review provide information that epidurally administered sodium chloride solution is not a true placebo.

Key words: Chronic low back pain, epidural injections, local anesthetic, sodium chloride solution, steroids, placebo effect

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Low back and neck pain continue to be the most frequently encountered disabling spinal conditions with an annual expenditure of $134.5 billion in 2016 increased from $89.2 billion in 2013 in the United States (1,2). Opioids and epidural injections are the most commonly utilized nonsurgical modalities in managing chronic spinal pain (3-11). The utilization patterns of epidural injections have shown significant increases over the years, even though a decline with reversal of growth patterns has been noted from 2009 to 2016 (3-9). Epidural injections with local anesthetics have been extensively utilized since 1901 (12-18), whereas steroids were not used until 1952 (12,19,20).

Multiple systematic reviews and other types of analyses have reached discordant conclusions in reference to the effectiveness of steroids in managing spinal pain (12,15,18,21-33). Discordant conclusions are based on various challenges faced in the performance of systematic reviews of randomized controlled trials, with seeming lack of understanding of placebo control and the differences between active- and placebo-controlled studies, misinterpretation of evidence, and finally, conflicts and confluence of interest (12,21,26,27,34-39). Conflicts and confluence of interest have been reported extensively including conversion of facts in a systematic review (12,21). The major tenet of evidence-based medicine is that clinical decisions should be influenced by all relevant high-quality evidence, as opposed to select studies or analysis. Systematic reviews and meta-analyses are aimed at acquiring all available evidence to address a specific research question and must involve a reproducible and thorough search of the literature with critical assessment of the methodological quality of the studies (39). Further, evidence must be presented as intended by the authors of the individual studies.

Analyses by Pinto et al (26) and Chou et al (21) converted all active controls to placebo controls creating lack of validity to these systematic reviews. Chou et al (21) in a protocol and subsequent manuscripts developed for the Agency for Healthcare Research and Quality (AHRQ) defined "placebo interventions" as epidural, saline, or local anesthetic injections without corticosteroid. This was based on the presumption that therapeutic effects in the epidural space are primarily related to the corticosteroids. Notably, some of the same authors had previously described that epidural steroids were ineffective (21,26).

Since the discovery of steroids in the 1940s by Phillip Hench (40) as potent anti-inflammatory agents, steroids have been injected for numerous chronic painful conditions (41). Although most steroid injections in clinical practice are combined with local anesthetics, they are also combined with sodium chloride solution in experimental settings and occasionally in clinical settings (41), with the presumption that the addition of steroid can increase the duration of the treatment effect (42-46). Except for inflammatory conditions such as rheumatoid arthritis, there is no evidence that steroid injections are disease-modifying agents (43,45,46). Thus any direct effect of steroids on pain generation or transmission continues to be hypothetical. Although there is some experimental evidence demonstrating suppression of ectopic discharge in neuromas by steroids (47), and although preclinical experiments suggest that steroids may reduce neuropathic pain in some, whereas increasing it in others (44), there is no significant evidence of any direct effect on pain generation or transmission. The rationale for epidural steroids is thus a post hoc argument. Bogduk (45) described that because steroids are anti-inflammatory and because they work for sciatica,

they have been assumed to work by reducing nerve root inflammation. Additionally, some authors have adduced circumstantial evidence from postmortem studies and operative experience showing that lumbar nerve roots can be inflamed and have argued by inference that this must be the pathology they treat with epidural steroids. However, there are no clinical studies demonstrating how inflammatory radiculopathies are distinguished from noninflammatory radiculopathies prior to administering epidural steroids, as well as the differences in effectiveness based on inflammation (45). The only favorable basis has been that epidural steroids were more effective in patients with increased cerebrospinal fluid protein levels (46), even though this criterion, like other putative criteria of inflammatory radiculopathy, has never been applied prospectively (45). It also has been described that proponents of epidural steroids continue to overlook that most commonly used agent, methylprednisolone, may be effective, based on a reversible, local anesthetic effect (48). Thus extensive mechanisms of long-lasting effects of local anesthetics based on neural blockade altering nociceptive input, the reflex mechanism of afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities have been proposed (49-58). Additionally, studies also have shown that corticosteroid failed to provide any additional significant benefit in nerve infiltration for lumbar disc herniation (54).

To complicate the understanding of placebo, there is also emerging literature showing that a small volume of local anesthetic or normal saline abolishes a motor response induced by a weak current (59-61). In addition, epidural administration of 5% dextrose (D5W) has shown a lack of electrophysiologic effect (62,63) but showed long-term postinjection analgesia and clinically significant improvement in pain and disability through 12 months in a significant proportion of patients with repeat epidural injections (64,65). Further, transforaminal hypertonic sodium chloride solution has also shown to increase the duration of the effect of epidural steroid injection compared with steroid with local anesthetic alone without hypertonic sodium chloride solution (66,67).

Thus there is more than a theoretical probability that sodium chloride solution placed into the epidural space is not a true placebo, exerting significant effects on nerve conduction providing pain relief and improvement in functional status with epidural administration (68-74). Conversely, the evidence of efficacy is lacking for epidural steroids without the addition of local anesthetic (15,25,27-30).

To resolve these issues and understand the effect of sodium chloride solution in the epidural space, as well as epidural steroid injection without local anesthetic administered through interlaminar, caudal, or transforaminal approaches in the lumbar spine, but also to avoid inappropriate conversions of local anesthetic solutions as placebos, we have undertaken this systematic review and meta-analysis to assess the effectiveness of sodium chloride alone and steroids with sodium chloride solution or alone.

Methods

The present systematic review was performed based on the methodological and reporting quality of systematic reviews as described by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (75).

This review focuses on the effectiveness of epidural sodium chloride solution with or without corticosteroid injections for all types of low back pain.

Eligibility Criteria

Types of Trials

Randomized controlled trials.

Types of Patients

Patients in chosen trials had been suffering with chronic low back pain secondary to disc herniation, discogenic pathology without disc herniation or radiculitis or facet joint arthropathy, spinal stenosis, and postsurgery syndrome.

Types of Interventions

Caudal, interlaminar, and transforaminal epidural injections in the lumbar spine with saline or steroids or combination.

Types of Outcome Measures

- The primary outcome parameter was pain relief.
- The secondary outcome measure was functional status improvement.

Data Sources

All available trials, in all languages, from all countries, providing appropriate management with outcome evaluations were considered for inclusion. Searches were performed from the following sources

without language restrictions:

1. PubMed from 1966
   www.ncbi.nlm.nih.gov/pubmed
2. Cochrane Library
   www.thecochranelibrary.com
3. US National Guideline Clearinghouse (NGC)
   www.guideline.gov/
4. Previous systematic reviews and cross references
5. Clinical Trials
   www.clinicaltrials.gov/
6. All other sources including nonindexed journals and abstracts.

The search period was from 1966 through December 2018.

Search Strategy

The search strategy emphasized chronic spinal pain treated with epidural injections.

The search terminology was as follows:

((((((((((((((((chronic low back pain) OR chronic mid back OR upper back pain) OR chronic neck pain) OR disc herniation) OR discogenic pain) OR herniated lumbar discs) OR nerve root compression) OR lumbosciatic pain) OR postlaminectomy) OR lumbar surgery syndrome) OR radicular pain) OR radiculitis) OR sciatica) OR spinal fibrosis) OR spinal stenosis) AND ((((((((((epidural injection) OR epidural steroid) OR epidural perineural injection) OR interlaminar epidural) OR intraarticular corticosteroid) OR nerve root blocks) OR periradicular infiltration) OR transforaminal injection) OR corticosteroid) OR methylprednisolone OR lidocaine) OR bupivacaine))) AND ((meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp]).

Data Collection and Analyses

The review focused only on randomized trials. Only epidural injections with saline with or without steroids were evaluated. All of the studies providing appropriate management and with outcome evaluations and statistical evaluations were reviewed. Reports without appropriate diagnosis, nonsystematic reviews, book chapters, and case reports were excluded.

Data Items

The population of interest was patients suffering with chronic spinal pain. Patients with acute trauma, fractures, malignancies, and inflammatory diseases were excluded.

Data Collection Process

Two review authors independently, in an unblinded, standardized manner, developed the search criteria, searched for relevant literature, selected the manuscripts, and extracted the data from the included studies. Disagreements were resolved by discussion between the 2 reviewers; if no consensus could be reached, a third author was called in to break the impasse. If there was a conflict of interest with a reviewed manuscript (concerning authorship), or if the reviewer was also one of the authors or had any type of conflict, the involved reviewer did not review the manuscript for methodological quality assessment.

Data Syntheses and Analyses

Data syntheses and analyses were performed with assessment of risk of bias or quality of individual studies, outcomes assessment, qualitative and quantitative analyses.

Risk of Bias of Individual Studies

The quality of each individual article used in this analysis was assessed by Cochrane review (76) criteria and Interventional Pain Management techniques--Quality Appraisal of Reliability and Risk of Bias Assessment (IPM–QRB) for randomized trials (77).

Methodological quality assessment was performed by 2 authors. The assessment was carried out independently in an unblinded, standardized manner to assess the methodological quality and internal validity of all the studies considered for inclusion. Reviewers performed their methodological quality assessment so as to prevent any discrepancies. If discrepancies occurred, a third reviewer performed an assessment, and a consensus was reached. Issues beyond that were discussed by all reviewers and then resolved.

Outcome of the Studies

For the present analysis, either 20% improvement from the baseline pain scores or functionality scores was considered clinically significant.

Analysis of Evidence

The analysis of the evidence was performed based

on the best evidence synthesis, modified and collated from multiple available criteria, including Cochrane review criteria and US Preventive Task Force (USPSTF) criteria as illustrated in Table 1 (78). The analysis was conducted using 5 levels of evidence ranging from strong to opinion- or consensus-based. The results of best evidence as per grading were utilized.

At least 2 of the review authors independently, in an unblinded, standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus. If there were any conflicts of interest (e.g., authorship), those reviewers were recused from assessment and analysis.

Meta-Analysis

For this meta-analysis, software Review Manager (Rev Man 5.3) was used (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008). For pain and functionality improvement data, the studies were reported as the standardized mean differences (SMD) with 95% confidence intervals (CI). Data were plotted using forest plots to evaluate treatment effects using random-effects model. Heterogeneity was interpreted through I^2 statistics.

We also performed single-arm meta-analyses to assess net changes in the same outcome variables (79,80). For this meta-analysis, Comprehensive Meta-Analysis version 3.0 software was used (Biostat Inc., Englewood, NJ). For pain and functionality improvement data, the studies were reported as the mean differences with 95% CI. Data were plotted using forest plots to evaluate treatment effects. Heterogeneity was interpreted through I^2 statistics.

Results

Study Selection

Figure 1 shows a flow diagram of the study selection as recommended by PRISMA (75).

Following the search criteria, with identification of numerous manuscripts and consideration of inclusion, 13 manuscripts (68-74,81-86) were identified. Of these, 8 manuscripts (68-71,73,74,82,83) met inclusion criteria, with 2 manuscripts utilizing caudal epidural (71,74), 4 manuscripts with interlaminar epidural (68,73,82,83), and 2 manuscripts with transforaminal epidural (69,70). One study of transforaminal epidural without fluoroscopy was excluded (86). A trial by Cohen et al (72) was excluded because all patients received bupivacaine prior to administration of sodium chloride solution. Two other studies by Cohen et al (84,85) were excluded as gabapentin was the subject of the study. A study by Revel et al (81) describing forceful injection was excluded.

Study Characteristics

A description of the various studies included is shown in Table 2.

Of the 8 trials meeting inclusion criteria (68-71,73,74,82,83), 2 trials utilized fluoroscopic imaging (69,70) and one study utilized ultrasound (71). All other studies performed the procedures without fluoroscopy. Of these, caudal epidural saline alone was injected in 2 trials (71,74), with interlaminar approach in 3 trials (68,73,83), and with transforaminal approach in 2 trials (69,70). In reference to steroids, epidural saline with steroids was utilized in 3 trials with caudal (71,74) and in 2 trials with interlaminar approach (68,73,82).

Table 1. *Qualitative modified approach to grading of evidence.*

Level I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials
Level II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate- or low-quality randomized controlled trials
Level III	Fair	Evidence obtained from at least one relevant moderate- or low-quality randomized controlled trial with multiple relevant observational studies or Evidence obtained from at least one relevant high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate- or low-quality relevant observational studies
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists

Adapted from Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (78).

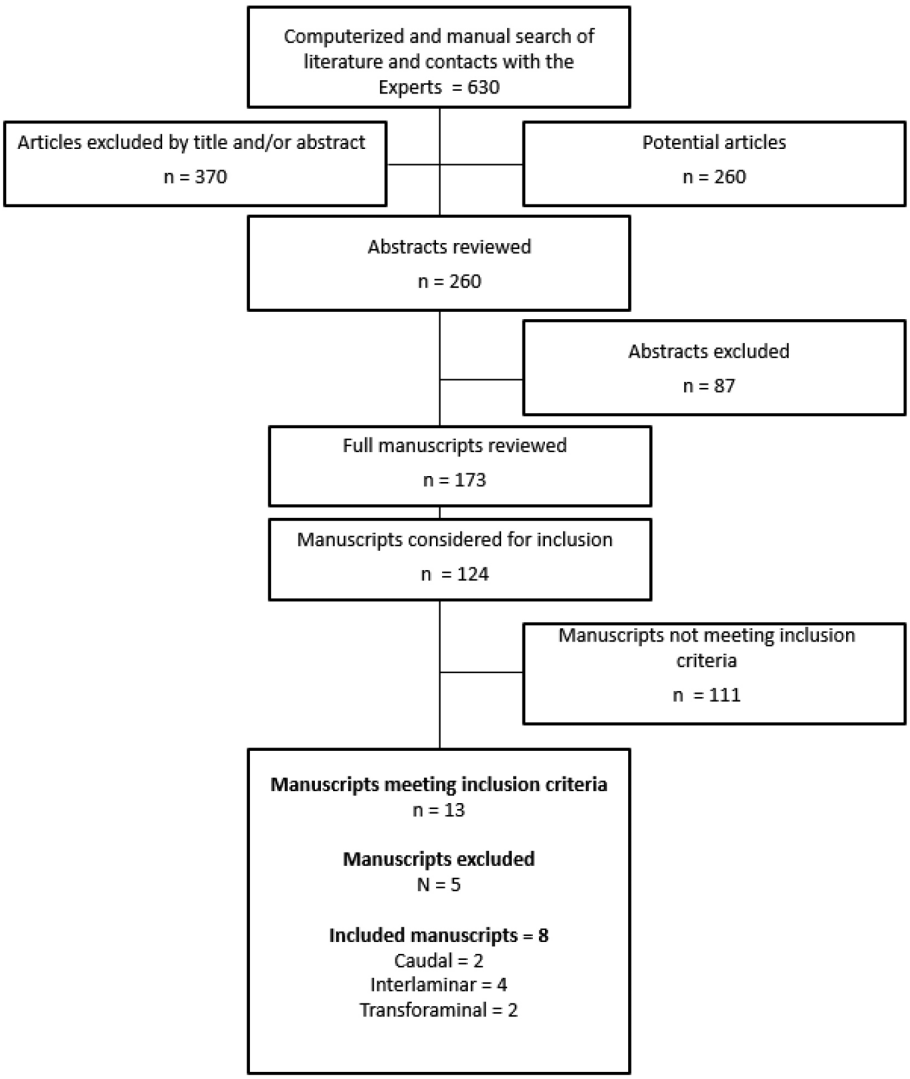

Fig. 1. *Flow diagram illustrating published literature evaluating epidural injections in managing spinal pain.*

Methodological Quality Assessment

A methodological quality assessment of the randomized controlled trials meeting inclusion criteria was carried out utilizing Cochrane review (76) criteria and IPM–QRB (77) criteria as shown in Tables 3 and 4.

Methodological quality assessment showed 6 of the 8 trials as high quality (score of 9–13) as shown in Table 3 (68-70,73,74,82), with 2 trials showing moderate quality with a score of 5 to 8 (71,83) based on Cochrane Review criteria. In contrast, based on IPM–QRB criteria (Table 4), 2 trials were of high quality with a score above 32 (69,70), whereas the remaining trials were considered to be of moderate quality with a score of 16 to 31 (68,71,73,74,82,83).

Results Based on Injected Solution(s)

As shown in Table 5, results of individual studies showed that epidural sodium chloride solution was administered in 5 of 9 studies (68-71,83). Overall, 341 patients were studied in the epidural saline group, whereas 254 patients were studied with epidural saline with steroids.

Table 6 shows results of effectiveness of epidural injections.

Qualitative Analysis

Among the 5 studies as shown in Tables 2 and 5, which provided appropriate data with the proportion of patients with significant improvement either with pain relief or functional status improvement (68,69,73,74,83), a total of 221 patients were included. Forty percent of them, or 89 patients, showed improvement. In contrast, in patients receiving sodium chloride with steroids, there were 4 studies with appropriate data available (68,73,74,82), which included a total of 218 patients with 52%, or 113 patients, showing appropriate improvement in parameters of pain or functional status.

Quantitative Analysis

Both dual-arm and single-arm meta-analysis was performed. In the performance of meta-analysis, the following issues were noted applicable to both dual-arm and single-arm analysis:

Table 2. *Characteristics of included studies utilizing epidural sodium chloride solution with or without steroids.*

Study Study Characteristics Methodological Quality Scoring	Patients and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
								Long-Term		
			≥ 3 wks.	3 mos.	6 mos.	12 mos.	Short-term ≤ 3 mos.	> 6 mos.	≥ 12 mos.	
CAUDAL EPIDURAL INJECTIONS										
Iversen et al., 2011 (71) RA, PC, UL Disc herniation or radiculopathy Quality scores: Cochrane = 8/13 IPM–QRB = 28/48	Total = 116 Sham = 40 Epidural saline = 39 Epidural saline with steroids = 37 Number of injections = 2 for 1 year	ODI, EQLS, VAS Follow-up: 12 months with only initial procedures	No significant difference with leg pain or ODI	No significant difference with leg pain or ODI	No significant difference with leg pain or ODI	No significant difference with leg pain or ODI	Lack of efficacy with leg pain or ODI	Lack of efficacy with leg pain or ODI	Lack of efficacy with leg pain or ODI	• Negative results for both epidural saline and epidural steroids. • There were no significant differences between epidural saline and epidural saline with steroids.
Nandi and Chowdhery, 2017 (74) RA, PC, B Lumbosacral sciatica Quality scores: Cochrane = 12/13 IPM–QRB = 28/48	Total = 98 Caudal saline group = 49 Caudal steroid = 49 With 80 mg of methylprednisolone and 18 mL of isotonic saline solution Placebo = 49 20 mL of isotonic saline Number of injections = 1	Pain (VAS), Straight Leg Raising, Schober's test, Roland-Morris Index, ODI, marked improvement, slight improvement, and worse Recovery and marked improvement, slight improvement, failure, or worse	Steroid group showed significant improvement 17% in the placebo group and 68% in the steroid group were considered as success	At the end of the study (week 12), there was no significant difference in primary outcome between the groups with 48% patients in the placebo group and 60% in the steroid group considered as success	NA	NA	There was no significant difference in caudal saline or steroid. However, successful outcome was seen in 48% of the patients with saline and 60% of the patients with steroids	NA	NA	• Positive results for steroids with short-term improvement for 4 weeks with 68% in the successful group and 17% for the placebo successful group. • By week 12, there was no significant difference in primary outcome between the groups: 48% of the patients in the placebo group and 60% in the steroid group were considered as success. • This study shows a strong effect of sodium chloride solution at 12-week follow-up rather than 1-week follow-up with a change of 17% to 48% success rate, with steroid effect declining from 68% to 60%.
LUMBAR INTERLAMINAR EPIDURAL INJECTIONS										
Dilke et al., 1973 (82) RA, B, PC Disc herniation or radiculopathy Quality scores: Cochrane = 9/13 IPM–QRB = 28/48	Total = 100 Epidural = 50 Interspinous = 50 Methylprednisolone in normal saline or interspinous ligament injection of saline Number of injections = 1–2	Pain relief, analgesic consumption, changes in straight leg raising, or neurologic signs Follow-up: 3 months	Steroids: Clear relief = 32% Some relief = 48% Placebo: Clear relief = 11% Some relief = 29%	Placebo: Clear relief = 22% Some relief = 74% Steroids: Clear relief = 36% Some relief = 90%	NA	NA	No significant effect of steroid	NA	NA	• A true placebo control trial with interspinous injection of saline with no difference at 3 months.

Table 2. *Characteristics of included studies utilizing epidural sodium chloride solution with or without steroids. (continued)*

Study Study Characteristics Methodological Quality Scoring	Patients and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
								Long-Term		
			≥ 3 wks.	3 mos.	6 mos.	12 mos.	Short-term ≤ 3 mos.	> 6 mos.	≥ 12 mos.	
Carette et al., 1997 (68) RA, B, PC Disc herniation or radiculopathy Quality scores: Cochrane = 12/13 IPM–QRB = 27/48	Total = 158 Methylprednisolone 80 mg mixed with 8 mL of saline epidural = 78 Placebo = 80 2 mL of epidural saline Number of injections = 1–3	VAS and ODI Follow-up: 3 weeks, 6 weeks, 3 months	Marked improvement ODI Placebo = 30% Steroids = 33%	Marked improvement ODI Placebo = 56% Steroids = 55%	NA	NA	Similar improvement in placebo and steroids	N	N	• Methylprednisolone with epidural saline was somewhat better at 3 weeks with function. • Overall, there was no significant difference between sodium chloride solution alone or sodium chloride solution with steroids.
Valat et al., 2003 (73) RA, PC, B Sciatica Quality scores: Cochrane = 12/13 IPM–QRB = 28/48	Steroid group, 50 mg prednisolone by lumbar interlaminar approach. Number of patients = 43 Placebo group, 2 mL isotonic saline by lumbar interlaminar approach. Number of patients = 42 3 epidural injections 2 days apart	VAS, Schober test, Straight Leg Raising test, Dallas Pain questionnaire, Roland-Morris Index Slight improvement or worse = failure Recovery or marked improvement = success	Successful group: 34% in epidural saline group 56% in steroid group	NA	NA	NA	NA	NA	NA	• This is a short study for 35 days without fluoroscopy with 3 injections consecutively with short-term follow-up. • At 35-day follow-up with 3 epidural injections, steroids were shown to be effective in 56% compared with 34% in the epidural saline group. • Authors concluded that the efficacy of saline administered epidurally for sciatica cannot be excluded and that epidural steroid injections provided no additional improvement.
Fukusaki et al., 1998 (83) RA, B, AC, PC Spinal stenosis Quality scores: Cochrane = 6/13 IPM–QRB = 18/48	Total = 53 Epidural saline = 16 Mepivacaine = 18 Mepivacaine and methylprednisolone = 19 Saline or mepivacaine or a combination of mepivacaine and methylprednisolone Number of injections = 1–3	Walking distance Excellent >100 m Good 20–100 m Outcomes: 1 week, 2 weeks, 1 month, 3 months	Saline 6.5% Local anesthetic 16.7% Local anesthetic with steroid 15.8%	Saline 6.3% Local anesthetic = 5.6% Local anesthetic with steroid 5.3%	NA	NA	Lack of effectiveness of epidural steroid with saline	NA	NA	• In this assessment, steroid patients showed better improvement after 1 week; however, this started dissipating at 2 weeks, and completely dissipated at the end of 3 months. All 3 groups provided lack of significant improvement. • There was no difference between saline and local anesthetic and steroids with lack of effectiveness with all 3 solutions. • Very low placebo response.

Table 2. *Characteristics of included studies utilizing epidural sodium chloride solution with or without steroids.*

Study Study Characteristics Methodological Quality Scoring	Patients and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
			≥ 3 wks.	3 mos.	6 mos.	12 mos.	Short-term ≤ 3 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	
LUMBAR TRANSFORAMINAL EPIDURAL INJECTIONS										
Ghahreman et al., 2010 (69) RA, PC, F Disc herniation or radiculopathy Quality scores: Cochrane = 12/13 IPM–QRB = 37/48	Total = 150 5 groups with 28, 37, 27, 28, 30 Transforaminal saline = 37 Transforaminal injection of 2 mL of 0.5% bupivacaine = 27 Transforaminal local anesthetic with steroid, 40 mg per mL or 70 mg of triamcinolone = 28 Intramuscular injection of saline = 28 Number of injections = 1–3 for 12 months	At least 50% pain relief at least 1 month after treatment, SF-36, Roland-Morris Follow-up: 1–3 months	At 1 month follow-up: Transforaminal local anesthetic = 7% Transforaminal epidural with steroids = 54% Intramuscular steroids = 21% Intramuscular saline = 13% Transforaminal saline = 19%	NA	NA	Transforaminal local anesthetic = 7%, duration 7 months Transforaminal epidural with steroids = 54%, duration 6 months Intramuscular steroids = 21%, duration 12 months Intramuscular saline = 13%, duration 12 months Transforaminal saline = 19%, duration 6 months	Effectiveness only in steroids with local anesthetic	NA	Effectiveness only in steroids with local anesthetic	• In this short-term assessment, high-dose transforaminal steroids (70 mg of triamcinolone) with local anesthetic were superior to local anesthetic and saline. • They described worst outcomes with transforaminal bupivacaine, even worse than intramuscular saline.
Karppinen et al., 2001 (70) RA, PC, F Disc herniation or radiculopathy Quality scores: Cochrane = 13/13 IPM–QRB = 34/48	Total = 160 Methylprednisolone-bupivacaine = 80 Saline = 80 Sodium chloride solution or methylprednisolone (40 mg) and bupivacaine (5 mg) Number of injections = 1	VAS, ODI, Nottingham Health Profile, cost, physical examination Follow-up: 2 weeks to 12 months with only initial procedures	NA	A significant treatment effect in favor of saline treatment for back pain	The treatment effects in both leg pain and back pain favored the saline treatment	There were no treatment effects in favor of either treatment	Saline superior	Lack of effectiveness of steroid with bupivacaine	Lack of effectiveness of steroid with bupivacaine	• Overall, saline appears to have been superior at 3 months and 6 months, but no significant difference at 1 year between both groups. • Leg pain decreased on average by 65% in both groups. • Surgery was avoided in the majority of the patients with 18 patients in the steroid group and 15 in the saline group undergoing surgery. • Transforaminal saline was superior to steroids at 3 and 6 months.

RA = randomized; AC = active control; F = fluoroscopy; B = blind; PC = placebo control; UL = ultrasound; NA = not applicable; ODI = Oswestry Disability Index; EQLS = European Quality of Life Scale; VAS = Visual Analog Scale; SF-36 = 36-Item Short-Form; IPM–QRB = Interventional Pain Management techniques–Quality Appraisal of Reliability and Risk of Bias Assessment

Table 3. *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Iversen et al 2011 (71)	Dilke et al 1973 (82)	Carette et al 1997 (68)	Fukusaki et al 1998 (83)	Ghahreman et al 2010 (69)	Karppinen et al 2001 (70)	Valat et al 2003 (73)	Nandi and Chowdhery 2017 (74)
Randomization adequate	Y	N	Y	N	Y	Y	Y	Y
Concealed treatment allocation	Y	N	Y	N	Y	Y	Y	Y
Patient blinded	Y	Y	Y	N	Y	Y	Y	Y
Care provider blinded	N	N	N	N	Y	Y	N	N
Outcome assessor blinded	U	Y	Y	U	Y	Y	Y	Y
Drop-out rate described	Y	Y	Y	N	Y	Y	Y	Y
All randomized participants analyzed in the group	N	Y	Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	N	N	Y	Y	N	Y	Y	Y
Cointerventions avoided or similar	Y	Y	Y	N	Y	Y	Y	Y
Compliance acceptable in all groups	N	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias likely	Y	Y	Y	Y	Y	Y	Y	Y
Score	8/13	9/13	12/13	6/13	12/13	13/13	12/13	12/13

Y = Yes; N = No; U = Unclear

Source: Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, Bronfort G, van Tulder MW; Editorial Board of the Cochrane Back, Neck Group. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. Spine (Phila Pa 1976) 2015; 40:1660-1673 (76).

In the study by Dilke et al (82) we could not extract any data because there were no scales for pain or functionality. Fukusaki et al (83) just measured functionality with walking distance and because it was the only study that used this, subsequently, we could not use it for meta-analysis. Ghahreman et al (69) used median and interquartile range; the pain level was measured for the leg, and not the back. Consequently, we could not use it because it was the only study using leg pain. Karppinen et al (70) did not provide crude change of each group, only the difference between groups, therefore we could not identify the individual change with these data.

Dual-Arm Meta-Analysis

Figure 2 shows change in the pain level using Visual Analog Scale (VAS) from baseline at 3 months (Fig. 2A) and functional level (Fig. 2B). There were 3 studies with

Table 4. *Methodological quality assessment of randomized trials utilizing IPM–QRB.*

		Iversen et al 2011 (71)	Dilke et al 1973 (82)	Carette et al 1997 (68)	Fukusaki et al 1998 (83)	Ghahreman et al 2010 (69)	Karppinen et al 2001 (70)	Valat et al 2003 (73)	Nandi and Chowdhery 2017 (74)
I.	TRIAL DESIGN AND GUIDANCE REPORTING								
1.	CONSORT or SPIRIT	2	0	1	0	3	2	1	1
II.	DESIGN FACTORS								
2.	Type and Design of Trial	2	3	2	2	2	2	2	2
3.	Setting/Physician	1	2	2	1	2	1	1	1
4.	Imaging	1	0	0	0	3	3	0	0
5.	Sample Size	2	3	3	0	2	3	2	2
6.	Statistical Methodology	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS								
7.	Inclusiveness of Population	2	2	2	2	2	2	2	2
8.	Duration of Pain	1	0	0	1	1	0	0	0
9.	Previous Treatments	0	0	0	0	0	0	0	0
10.	Duration of Follow-Up with Appropriate Interventions	1	1	0	1	0	1	0	0
IV.	OUTCOMES								
11.	Outcomes Assessment Criteria for Significant Improvement	0	2	0	1	4	2	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	1	2	2	2	2
13.	Description of Drop-Out Rate	1	2	1	1	2	1	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	2	1	1	1	2	2	2
15.	Role of Cointerventions	1	1	0	0	0	0	0	0
V.	RANDOMIZATION								
16.	Method of Randomization	2	1	2	1	2	2	2	0
VI.	ALLOCATION CONCEALMENT								
17.	Concealed Treatment Allocation	2	1	2	0	2	2	2	2
VII.	BLINDING								
18.	Patient Blinding	1	1	1	0	1	1	1	1
19.	Care Provider Blinding	0	0	0	0	1	1	0	0
20.	Outcome Assessor Blinding	0	1	1	0	1	1	1	1
VIII.	CONFLICTS OF INTEREST								
21.	Funding and Sponsorship	3	0	3	2	2	2	2	2
22.	Conflicts of Interest	3	3	3	3	3	3	3	3
TOTAL		28	28	27	18	37	34	28	28

Source: Manchikanti L, Hirsch JA, Cohen SP, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (77).

318 patients (68,71,74) that provided results for eligible analysis of back pain improvement using VAS and functional status utilizing Oswestry Disability Index (ODI) after 3 months of epidural injection. Analysis showed no statistically significant difference in pain improvement between saline and steroids groups at 3 months follow-up (SMD 0.11 [–0.42, 0.65], $P = 0.68$) or function (SMD 0.15 [0.24, 0.55], $P = 0.45$).

Single-Arm Meta-Analysis

Figure 3 shows the results of single-arm analysis utilizing epidural saline. Three studies (68,71,74) were used to assess back pain score after 3 months of treatment using VAS and ODI in patients who underwent epidural saline injections. As shown in Fig. 3A, the pooled mean difference of pain score from baseline to 3 months of follow-up was decreased by 21.83 points (95% CI, –26.137 to –17.540, $P < 0.001$, $I^2 = 0.00\%$). As shown in Fig. 3B, the pooled mean difference in ODI score from baseline to 3 months of follow-up was decreased by 9.85 points (95% CI, –14.10 to –5.612, $P < 0.001$, $I^2 = 82.01\%$).

Figure 4 shows changes at 3 months with epidural steroids with single-arm analysis. Three studies (68,71,74) were used to assess pain scores and function after 3 months of treatment using VAS and ODI in patients who underwent epidural steroid injections. The pooled mean difference of pain score from baseline to 3 months of follow-up was decreased by 23.17 points (95% CI, –37.48 to –8.8, $P < 0.005$, $I^2 = 89.70\%$), as shown in Fig. 4A. The pooled mean difference in ODI score from baseline to 3 months of follow-up was decreased by 12.12 points (95% CI, –17.03 to –7.21, $P < 0.001$, $I^2 = 74.77\%$), as shown in Fig. 4B.

Overall, there was no significant difference in pain improvement between sodium chloride solution and steroids groups at 3 months follow-up with dual-arm analysis. In contrast, with a single-arm analysis, as shown in Fig. 3A, the pooled mean difference of pain scores from baseline to 3 months follow-up was decreased by 21.83 points. However, ODI scores decreased by 9.85 points (Fig. 3B).

In contrast, assessment of steroids utilizing single-arm analysis, the pain was decreased by 23.17 points (Fig. 4A), however, ODI scores decreased by 12 points (Fig. 4B).

Thus as shown in dual-arm analysis in Fig. 2, there was no difference with changes in pain or function be-

Table 5. *Results of individual studies based on injected solution(s).*

Study	Epidural Saline	Epidural Saline with Steroids
Iversen et al 2011 (71)	39	37
Nandi and Chowdhery 2017 (74)	47	46
Dilke et al 1973 (82)	--	50
Carette et al 1997 (68)	80	78
Valat et al 2003 (73)	42	43
Fukusaki et al 1998 (83)	16	--
Ghahreman et al 2010 (69)	37	--
Karppinen et al 2001 (70)	80	--
TOTALS	341	254

Table 6. *Results of epidural injections at 3 months.*

	Sodium Chloride				Sodium Chloride with Steroids			
Study	No. of Injections	No. of Patients	Improved Patients	Improved Proportion	No. of Injections	No. of Patients	Improved Patients	Improved Proportion
Iversen et al 2011 (71)	2	39	--	--	2	37	--	--
Nandi and Chowdhery 2017 (74)	1	46	22	48%	1	47	28	60%
Dilke et al 1973 (82)*	--	--	--	--	2	50	18	36%*
Carette et al 1997 (68)	1–3	80	45	56%	1–3	78	43	55%
Valat et al 2003 (73)†	3	42	14	34%	3	43	24	56%
Fukusaki et al 1998 (83)	1–3	16	1	6.3%	--	--	--	--
Ghahreman et al 2010 (69)†	1–3	37	7	19%	--	--	--	--
Karppinen et al 2001 (70)	1	80	> better than steroid		--	--	--	--

*No significant difference with placebo injection of interspinous ligament (22% vs. 36%).
†3-month follow-up NA—only ≥ 3 weeks follow-up available.

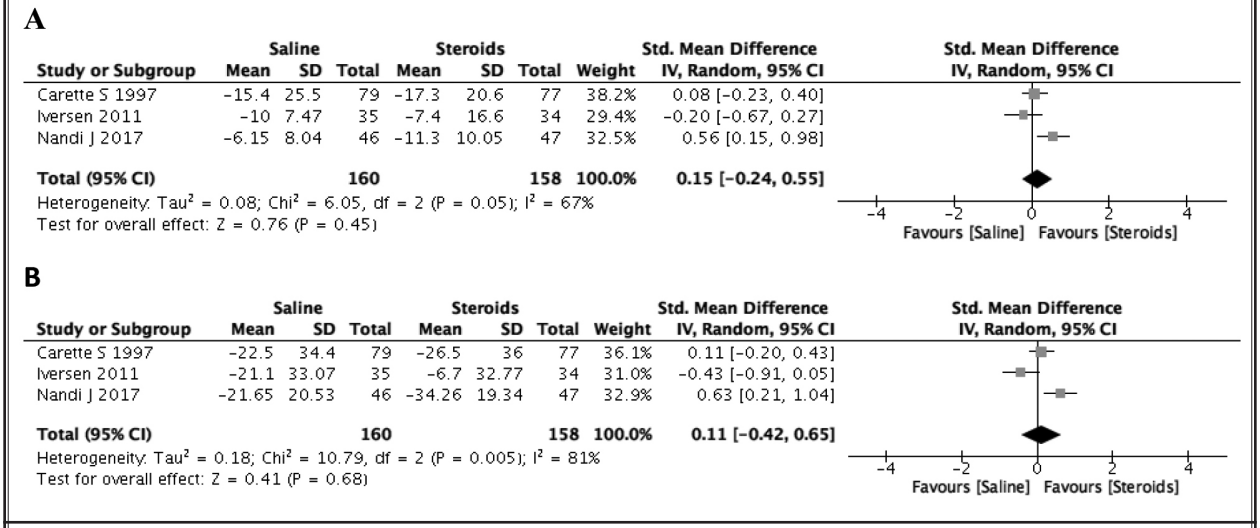

Fig. 2. *Change in pain and functional status level using VAS (A) and ODI (B) after 3 months of epidural injections with saline or steroids.*

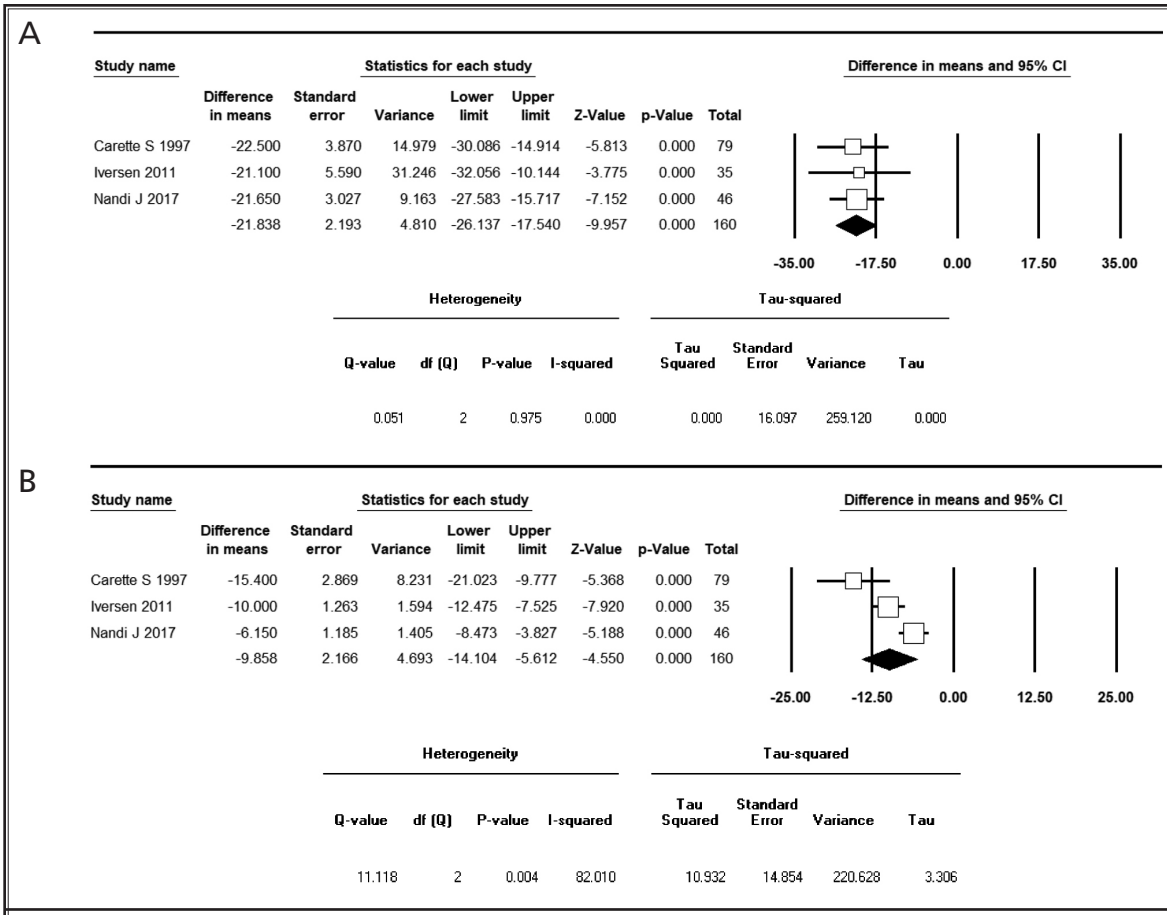

Fig. 3. *Changes in pain and functional level using VAS (A) and ODI (B) from baseline at 3 months in patients treated with epidural saline utilizing a single-arm analysis.*

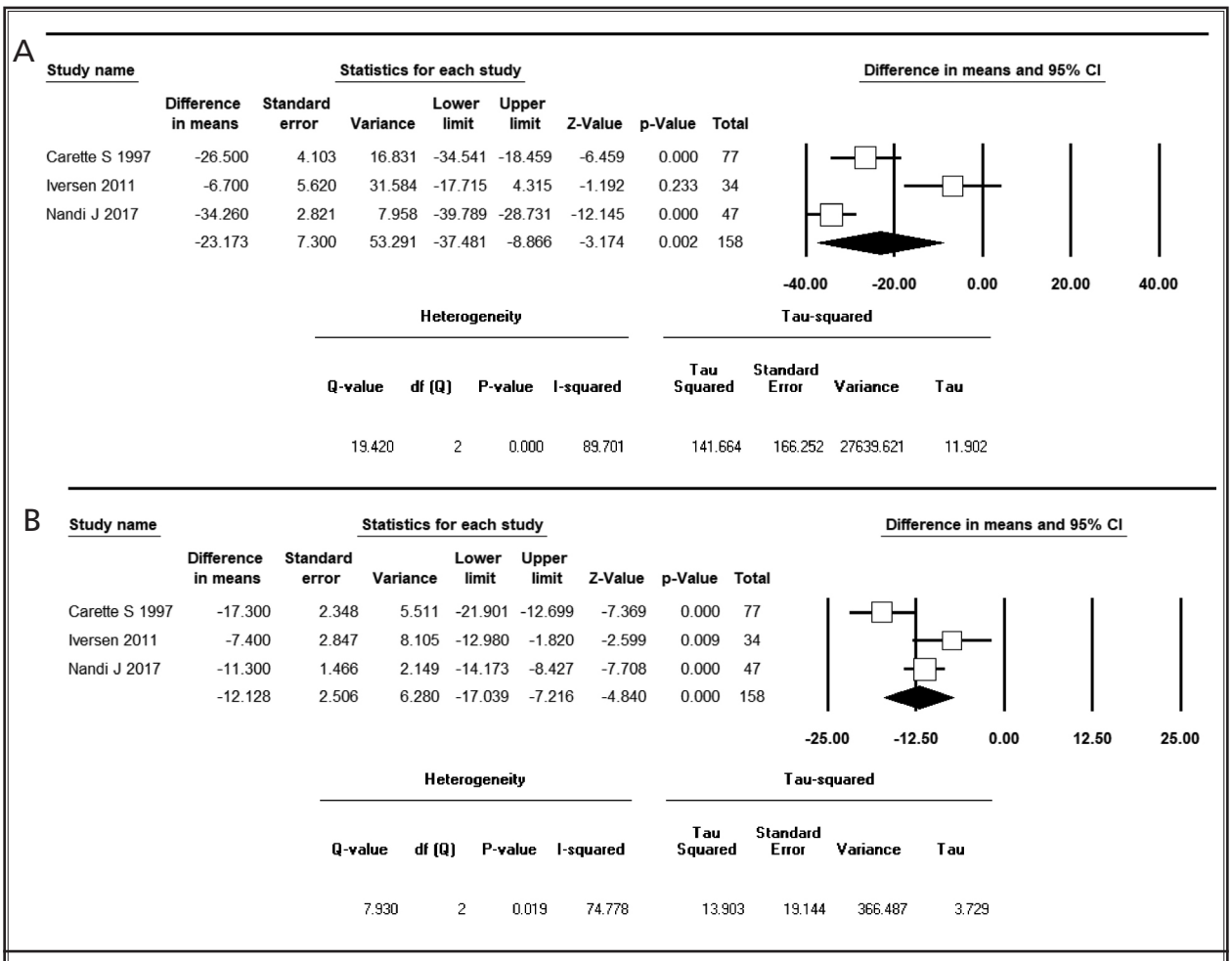

Fig. 4. *Changes in pain and functional status using VAS (A) and ODI (B) in patients treated with epidural steroids at 3-month follow-up utilizing a single-arm analysis.*

tween sodium chloride solution and steroids in a dual-arm analysis.

However, utilizing single-arm analysis, as shown in Figs. 3B and 4B, there was a decrease of 9.85 from the baseline ODI scores in the epidural saline group and a 12-point decrease in the epidural steroids group, which is 10% to 12% decrease in functional scores utilizing sodium chloride solution and epidural steroid injections, demonstrating lack of effectiveness of steroids and lack of true placebo effect with epidural sodium chloride solution.

In contrast, as described earlier, the single-arm analysis of effect of epidural saline and steroids showed an approximately 22% decrease with saline and 23% decrease with steroids, showing above threshold difference and considered as significant in some studies and indicating lack of true placebo effect of epidurally injected saline and mild effect of epidural steroids, although the results are similar as shown in Figs. 3A and 4A.

Summary of Evidence

With dual-arm meta-analysis, there was no significant difference between epidural sodium chloride solution and epidural steroids with sodium chloride solution. However, utilizing single-arm analysis both epidural saline and epidural steroids with saline were effective in reducing 20% of pain; however, only reducing 10% to 12% of disability scores.

Based on the qualitative analysis, epidural saline and epidural steroids with saline showed effect beyond placebo and showed level I, or strong evidence, that neither epidural saline, nor epidural steroids with saline are placebo and that both are effective.

Discussion

The present systematic review utilizing qualitative analysis and meta-analysis utilizing single-arm analysis showed level II, or moderate evidence, regarding the effectiveness of epidural saline and epidural steroids with saline with pain score reductions greater than 20% at 3 months, showing lack of true placebo effect with saline and limited effectiveness of steroids. However, this analysis also showed lack of significant difference between epidural saline and epidural steroids with dual-arm analysis, and lack of effectiveness in improving function with single-arm analysis. Further, qualitative analysis showed that epidural saline injections are effective in 40% of the patients, whereas epidural steroids with saline are effective in 52% of patients at 3-month follow-up. Thus the evidence is based on qualitative and quantitative analysis with a combination of high-quality and moderate-quality randomized controlled trials. Epidural saline, even in extremely low doses of 1 mL, administered without fluoroscopy was also shown to be effective indicating lack of true placebo effect when injected into the epidural space. Further, the effectiveness of epidural steroids with saline was also demonstrated indicating that steroids are not placebo either. This analysis confirms that epidural saline injection is not a true placebo. A true placebo must be an inert substance injected into an inert structure. Consequently, neither is the epidural space an inert structure, nor is epidurally injected saline an inert solution. This raises numerous questions to experts utilizing all types of epidural injections with saline, but also with local anesthetic injections without corticosteroids; considering them as placebo interventions is based on misconceptions and leads to inaccurate conclusions affecting access to modalities, which are effective.

Steroids, since their application in the epidural space in 1952 (19,20), have been the subject of controversy in reference to their effectiveness (21,26). Multiple experts (21,26,59,87) have advanced their opinions that epidurally administered sodium chloride solutions, as well as local anesthetic injections, are placebo interventions. Investigators have used the theory that the therapeutic effects in the epidural space are primarily related to the corticosteroids and other drugs are considered as placebo (21,26). The effectiveness of sodium chloride solution or steroids with sodium chloride solution indicates that there are other effects separate from the anti-inflammatory effect described for steroids.

There are multiple additional issues to be considered when assessing the effectiveness of epidurally administered solutions. Local anesthetics have been shown to be equally effective to corticosteroid combined with local anesthetic in an overwhelming majority of patients. Extensive mechanisms have been proposed to describe the effects of epidural local anesthetic, as well as steroids with effects on nociceptive activity (49-58); to some extent that may also be exerted by sodium chloride solution, however, the literature is scant.

This review provides both researchers and interventional practitioners with evidence to consider the injection of an inert substance into an inert structure while performing epidural injection studies, rather than injection of sodium chloride solution, which may or may not be inert in the epidural space, which houses multiple active structures. In addition, all of the literature based on epidural saline and local anesthetics as placebo must either be discarded or reassessed based on the findings of this study with open mindedness and without bias.

To our knowledge, this systematic review is the first of its nature with a single-arm analysis showing the effectiveness of epidurally injected saline in reducing pain and improving function, showing that it is not a true placebo. This also explains multiple discordant conclusions reached in the past, which are based on various challenges, specifically the lack of understanding of placebo control, and consequently leading to the misinterpretation of evidence. Thus this analysis reinforces the major tenant of evidence-based medicine that clinical decisions should be influenced by all relevant high-quality evidence, as opposed to selective studies or selective analysis, as has been seen in many of the reports.

The results of this study, although in agreement with multiple systematic reviews (12,15,22-25,27-33) performed in the past showing positive results of epidural injections, are in conflict with other assessments (21,26). In recent years, multiple systematic reviews have been performed in interventional pain management, which have been described as appropriate with positive results, not only applying principles of placebo control and active control trials, and conventional meta-analysis and single-arm meta-analysis (10,12,18,22-25,28-33,80,87-96). Further, interventional techniques have been recommended by the authors and multiple agencies to utilize as a deterrent to the opioid epidemic (97,98).

Conclusions

This systematic review included high-quality methodological assessment, conventional dual-arm and single-arm meta-analysis. The results clearly showed that epidurally administered sodium chloride solution and sodium chloride solution with steroids may be effective in managing low back and lower extremity pain. Further, there was no significant difference between epidural sodium chloride solution and epidural steroids with sodium chloride solution with conventional dual-arm meta-analysis. A single-arm meta-analysis showed equal effectiveness in reducing pain of 20%, whereas disability scores by 10% to 12%, while both of the solutions were only weakly effective. This meta-analysis proves that epidurally administered sodium chloride solution is not a true placebo.

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Author Contributions

The study was designed by LM, NNK, and JH. Statistical analysis was performed by NNK. All authors contributed to preparation to the manuscript, reviewed, and approved the content with final version.

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