

Systematic Review

Comparative Systematic Review and Meta-Analysis of Cochrane Review of Epidural Injections for Lumbar Radiculopathy or Sciatica

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Background: Epidural injections are among the most commonly performed procedures for managing low back and lower extremity pain. Pinto et al and Chou et al previously performed systematic reviews and meta-analyses, which, along with a recent update from Oliveira et al showing the lack of effectiveness of epidural steroid injections in managing lumbar disc herniation, spinal stenosis, and radiculopathy. In contrast to these papers, multiple other systematic reviews and meta-analyses have supported the effectiveness and use of epidural injections utilizing fluoroscopically guided techniques. A major flaw in the review can be related to attributing active-controlled trials to placebo-controlled trials. The assumption that local anesthetics do not provide sustained benefit, despite extensive evidence that local anesthetics provide long-term relief, similar to a combination of local anesthetic with steroids is flawed.

Study Design: The Cochrane Review of randomized controlled trials (RCTs) of epidural injections in managing chronic low back and lower extremity pain with sciatica or lumbar radiculopathy were reanalyzed using systematic methodology and meta-analysis.

Objectives: To re-evaluate Cochrane data on RCTs of epidural injections in managing chronic low back and lower extremity pain with sciatica or lumbar radiculopathy utilizing qualitative and quantitative techniques with dual-arm and single-arm analysis.

Methods: In this systematic review, we have used the same RCTs from the Cochrane Review of a minimum of 20% change in pain scale or significant pain relief of $\geq 50\%$. The outcome measures were pain relief and functional status improvement. Significant improvement was defined as 50% or greater pain relief and functional status improvement.

Our review was performed utilizing the Cochrane Review methodologic quality assessment and the Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB). Evidence was summarized utilizing the principles of best evidence synthesis and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. Clinical relevance of the pragmatic nature of each study was assessed.

Results: In evaluating the RCTs in the Cochrane Review, 10 trials were performed with fluoroscopic guidance. Utilizing conventional dual-arm and single-arm meta-analysis, the evidence is vastly different from the interpretation of the data within the Cochrane Review. The overall combined evidence is Level I, or strong evidence, at one and 3 months, and Level II, or moderate evidence, at 6 and 12 months.

Limitations: The limitation of this study is that only data contained in the Cochrane Review were analyzed

Conclusion: A comparative systematic review and meta-analysis of the Cochrane Review of randomized controlled trials (RCTs) of epidural injections in managing chronic low back and

lower extremity pain with sciatica or lumbar radiculopathy yielded different results. This review, based on the evidence derived from placebo-controlled trials and active-controlled trials showed Level I, or strong evidence, at one and 3 months and Level II at 6 and 12 months. This review once again emphasizes the importance of the allocation of studies to placebo-control and active-control groups, utilizing standards of practice with inclusion of only the studies performed under fluoroscopic guidance.

Key words: Chronic low back pain, lumbar radiculopathy, sciatica, epidural injections, local anesthetic, steroids, caudal epidural injections, interlaminar epidural injections, transforaminal epidural injections

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The goal of evidence-based-medicine is that one should use the best available evidence in determining clinical care for an individual patient or population. In order to do this, one needs to provide reliable information from research on the benefits and harms of specific interventions, actions, or strategies. It is expected that systematic reviews and meta-analyses provide information from high quality research (1). The uncovering of inappropriate research continues to be an important role for systematic reviews in demonstrating poor quality studies (2). Multiple organizations provide assessment of the literature in the form of systematic reviews, meta-analyses, and more recently, comparative effectiveness research (CER).

Bias is the inherent tendency of a process to support particular outcomes. A distinction may be drawn between systemic and systematic bias corresponding to that between unplanned and planned or to that arising from the characteristics of a system versus that from an individual or group (3). Consequently, systematic bias stems from a concerted effort by an individual or group to favor certain outcomes. Bias within systematic and non-systematic literature reviews has been extensively discussed (4-15). Petticrew and Roberts (16) in 2006, described biased data results as being either an over or under estimation. In 2012, Booth et al (14) referred to bias as the systematic error within a study or a review of multiple studies which lead to faulty conclusions about interventions, programs, or policies. Consequently, bias can occur when selecting studies for a literature review and bias when interpreting the results of the selected studies. Song et al (15) and Booth et al (14) presented a taxonomy for different kinds of bias affecting literature reviews. Among multiple biases described, publication bias, outcome reporting bias, multiple publication bias, place of publication bias, citation bias, and interpretation bias, appear to be crucial and relevant to systematic reviews in interventional pain management.

Publication bias refers to the bias that occurs when only studies with a significant result in a preferred direction are published (4,14,15). Outcome reporting bias refers to publication bias within a study, when multiple outcomes are measured, but only the significant ones are reported (14,15). Multiple publication bias refers to studies where significant results that are more likely to generate multiple publications, which can lead to an over-representation of one study within a literature review (4,14,15). Place of publication bias refers to studies where more significant results in a preferable direction are more likely to be published in more popular journals because of the editorial choices of the journal or the readers preferences (15). Citation bias occurs when a study being cited because the direction or significance of the results support the hypothesis of the researcher. It makes scanning through the reference list of a study less reliable since supportive studies are over represented, skewing the literature review (14,15). Finally, interpretation bias refers to the researchers or reviewers' abilities to synthesize, objectively judge and weigh the results found in a study. Therefore, 2 researchers of different backgrounds might look at the same result in a different way, thus, drawing different conclusions based on their own background. This happens when the data are debatable or qualitative, leading to some conclusions being overstated while others are understated (4). Another issue is the erroneous classification of trials as "pragmatic" and "real world." A genuinely pragmatic RCT should fulfill at least 2 fundamental features, including conduct of the study which should resemble usual clinical practice, and the applicability of the results to multiple other settings (i.e., "real world"), not only the one where the trial was conducted (17). Dal-Ré et al (17) stated that some randomized controlled trials (RCTs) overtly deviate from usual clinical care and pragmatism, yet many RCTs are classified as pragmatic for purposes of convenience since pragmatic trials are said to represent real world evidence.

Cochrane Collaboration is a British international charitable group formed to organize medical research findings to facilitate evidence-based choices regarding interventions involving health professionals, patients, and policymakers (18). While Cochrane Collaboration has provided numerous reviews over the years, their presence in the United States was reignited recently with the launch of the Cochrane U.S. Network (19). However, multiple controversies have arisen with regards to the value of the Cochrane Collaboration, their systematic reviews, and their existing bias (13,20-22). Among the multiple systematic reviews published over the years on interventional techniques (23-28), the recent systematic review by Oliveira et al (27,28) on epidural injections elicited multiple controversies in relation to potential systematic bias, erroneous estimation of an effect, bias in selecting the studies for literature review, and bias when interpreting the results of the selected studies (29-31). Publications from the Agency for Healthcare Research and Quality (AHRQ) (32), as well as by Pinto et al (33) have been similarly criticized (34).

Based on the present clinical practice patterns in the United States, many of the studies utilized in previous systematic reviews lack clinical relevance and are not useful for medical practice in the United States.

The first epidural was a caudal injection of a local anesthetic for low back pain in 1901 (35-37). Epidural injections have evolved to include interlaminar and transforaminal epidural injections with steroid administration (38-41). Despite their long use, controversy remains as to the efficacy of epidural injections (23-34,41-61). Kepes and Duncalf (54) in a 1985 review article, concluded that the rationale for the use of epidural steroid injections had not been scientifically proven. One year later, Benzon (55) evaluated the same literature and concluded that low back pain of mechanical origin, especially if accompanied by signs of nerve root irritation, may respond to epidural injections. Nine years later 2 systematic reviews concerning the management of sciatica reported conflicting results (46,47). Watts and Silagy (46) concluded that present quantitative evidence from meta-analysis of pooled data from RCTs of epidural administration of corticosteroids showed effectiveness in the management of lumbosacral radicular pain. In contrast, Koes et al (47) in their systematic review without meta-analysis published the same year concluded that the best studies showed inconsistent results of epidural steroid injections, and the efficacy of epidural steroid injections

has not yet been established. They also stated that the benefits of epidural steroid injections, if any, seem to be of short duration only. These differing conclusions left general practitioners questioning which study was correct Hopayian and Mugford (45) raised multiple issues, indicating that the 2 reviews had the same overall aims and met the criteria for review methods, but they differed in their choice of methods, including the judgment of quality of studies for inclusion and for deriving conclusions. This emphasized that the choice of methods for systematic review may alter the perception of the current status of evidence. They warned that, "Users should be aware that systematic reviews include an element of judgment, whatever method is used." Despite 60 systematic reviews, a multitude of RCTs, and several published guidelines, the same questions regarding epidural injections persist (23-34,41-61).

The issue of a lidocaine injection as an active-control or placebo-control originated in the first systematic review by Koes et al (47). They discussed the role of an injection of local anesthetic and opined that the use of lidocaine as placebo was not clear since there were no studies at the time, which compared an injection of sodium chloride solution to an injection of lidocaine. They addressed the possibility that an injection of a local anesthetic may result in specific effects, such as the "interruption of sustained neural activity that produced and perpetuated the pain, relaxation of paraspinal muscle spasm, and resolution of accompanying reflex sympathetic dystrophy" (47). They concluded that using an injection of local anesthetic instead of saline may lead to less contrast between study groups in a controlled trial. Obviously, this has significant effects on the interpretation of the studies, the repercussions of which may alter access to effective treatments. As discussed in multiple manuscripts and now the evidence is solid that any substance injected into the epidural space is active, rather than inert, including sodium chloride solution and dextrose (43).

In a systematic review assessing whether sodium chloride solution is a true placebo or an active-control agent, Manchikanti et al (43) showed that sodium chloride solution may not be a true placebo and may exert significant therapeutic effects when injected into the epidural space. Multiple studies have demonstrated similar of varying degree (42) between epidural local anesthetic injections versus epidural local anesthetic combined with steroids (34,41,42,51,53,57,62). In a recent systematic review, Shanthanna et al (41) clearly showed that the addition of corticosteroids to local

anesthetics for chronic non-cancer pain injections provided only short-term additional relief for short-term. There is extensive preclinical and clinical evidence (63-65) showing the anti-inflammatory actions of local anesthetics and the lack of any further significant effect with the addition of steroids.

Oliveira et al performed a Cochrane systematic review followed by an abridged Cochrane systematic review and meta-analysis (27,28), concluding that 20 placebo-controlled trials provided moderate quality evidence that epidural corticosteroid injections are effective, although the effects are small and short-term. This was based on their assumption that a substance acting as a placebo injected either into the epidural space or adjacent spinal tissue is considered inert (i.e., no pharmacological activity), innocuous (e.g., normal saline), or pharmacologically active but does not provide sustained benefit (e.g., local anesthetic). However, multiple authors have shown that an epidural injection of a local anesthetic does provide extensive anti-inflammatory effects, long-term response, and improved outcomes. Because Oliveira et al (27,28) believed that epidural lidocaine did not provide sustained benefits, they considered it an appropriate placebo and misinterpreted the Cochrane reviews. Many authors have demonstrated with experimental and clinical evidence that there is no significant difference in patient response between epidural steroids and local anesthetic, indicating that local anesthetics do provide sustained benefits (34,41,42,51,53,57).

Our recent systematic review and meta-analysis (29) assessed the evidence for epidural injections in comparison to the Cochrane review by Oliveira et al (27,28). However, by using stricter, clinically relevant inclusion criteria, we showed that only 6 of the 25 clinical trials from 29 publications used by Oliveira et al met the standards for in our review and meta-analysis (29). The results of our review (29) were contrary to the reviews by Oliveira et al (27,28), with Level I, or strong evidence, using local anesthetic and steroids and Level II, or moderate evidence, utilizing local anesthetic alone.

Consequently, our systematic re-review and meta-analysis of the findings of the Cochrane review by Oliveira et al (27,28) was undertaken to assess the efficacy or lack thereof of epidural injections with saline, local anesthetic alone, or local anesthetic with steroids, utilizing the same trials from the Cochrane review by Oliveira et al (27,28).

METHODS

This systematic review and meta-analysis was performed based on the methodological and reporting criteria of systematic reviews as described by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (66,67). Additionally, the Institute of Medicine (IOM) standards for systematic reviews and (CER) (29,68,69) and other publications relevant to systematic reviews were utilized. There was no external funding in preparation of this manuscript and there are no undisclosed conflicts.

Based on the Cochrane review, this present manuscript focuses on the effectiveness of epidural injections for radiculopathy or sciatica when utilizing sodium chloride solution or with local anesthetic in placebo-controlled trials. In this manuscript, however, we will analyze true placebo trials (explanatory or efficacy trials) versus active-controlled trials (pragmatic or effectiveness trials). Appropriate conventional dual-arm and single-arm analysis will be performed to assess the effect of each modality of treatment with either non-inferiority or lack of superiority and assessment of local anesthetics with or without steroids.

In contrast to Oliveira et al (27,28), we defined placebo injections as the administration of an inert substance into the epidural space, over the nerve root, or in remote tissues. All local anesthetic injections into the epidural space or over the nerve root were considered to be active controls.

Data Sources, Search Criteria, and Study Selection

Data sources, search criteria, and study selection were omitted and all the studies utilized in the Cochrane review were utilized in this assessment (27,28).

Methodologic Quality Assessment

At least 2 of the review authors, in an unblinded standardized manner, independently acquired the literature, performed the methodological quality assessment, and analyzed the evidence. Any disagreements between reviewers were resolved by a third author and by consensus. If there were any conflicts of interest with a manuscript, e.g., authorship, the review author(s) was/were recused from assessment and analysis.

The quality assessment of each individual article used in this analysis was performed by comparing the analysis performed by Oliveira et al (27,28) with an independent assessment using Cochrane review criteria (70) and Interventional Pain Management Techniques

- Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) criteria (71).

Utilizing Cochrane review criteria (70) or IPM-QRB (71), studies meeting the inclusion criteria with a score of 9 to 13 or 32 to 48, respectively, were considered high quality and 4 to 7 or 16 to 31, respectively, were considered moderate quality. All of these were included in the review. Those with a score of less than 4 or 16 were considered low quality.

Data Synthesis and Analysis

Data were synthesized utilizing qualitative and quantitative measurements.

Qualitative Evidence Synthesis

Evidence was assessed based on best evidence synthesis for qualitative analysis as shown in Table 1 (72). Each trial was evaluated using 5 levels of evidence ranging from strong to opinion or consensus-based. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to determine the best level of evidence (73,74). Clinical relevance and pragmatism of RCTs was assessed (17). GRADE assessment was based on 5 factors: 1) Methodological limitations, 2) Consistency, 3) Indirectness, 4) Imprecision, and 5) Publication bias. They were graded high, moderate, low, or very low. Based on the study evaluation of methodologic quality, grading was applied as no change, downgraded, or upgraded.

Quantitative Evidence Synthesis

Quantitative evidence synthesis was performed utilizing a dual arm meta-analysis for all placebo-controlled trials and a single-arm meta-analysis for active-controlled trials.

Dual-Arm Meta-Analysis

For dual-arm meta-analysis, software RevMan 5.4 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark), The Cochrane Collaboration, 2020 was used. For pain and functionality improvement data, the studies were reported as the standardized mean differences (SMD) with 95% confidence interval (CI). Data were plotted using forest plots to evaluate treatment effects using random-effects model. Heterogeneity was interpreted through I^2 statistics.

Single-Arm Meta-Analysis

For single-arm meta-analysis, software Compre-

Table 1. Qualitative modified approach to grading of evidence of therapeutic effectiveness studies.

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 trial or Evidence obtained from at least one relevant high-quality non-randomized 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

Modified from: Manchikanti L, et al. A modified approach to grading of evidence. Pain Physician 2014; 17:E319-E325 (72).

hensive Meta-Analysis version 3.0 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.

Evidence Synthesis

Qualitative and quantitative measurements were assessed which indicated the direction of a treatment's effect and the magnitude of a treatment's effect. For placebo-controlled trials, the net effect between 2 treatments was utilized; however, for active-controlled trials, the differences between baseline and at the follow-up period were utilized. This is in contrast to Oliveira et al who utilized differences between 2 active-controlled trials and also considered a larger number of studies as placebo-controlled, even though these studies were active-controlled (27,28). We believe that in both of their papers (27,28), Oliveira et al made errors in methodology.

Outcome Measures

Even though a minimum change of 20% in pain scales is widely accepted, the evolving concepts of minimal clinically important differences (MCID) have shown to be patient centered and practical. Multiple publications have alluded clinically relevant outcome

measures defined as significant improvement with at least 50% improvement in pain and functional status (34,50-53,68,73,74). When comparing 2 groups in an active-controlled trial, there is ample literature documenting the necessity to use changes from baseline to follow up, instead of absolute changes between groups (29,34,42,43,50-53,68).

Consequently, in this report, we have utilized either $\geq 50\%$ relief from the baseline pain score or at minimum a change in pain scales of $\geq 30\%$ or ≥ 2 -point change on an 11-point pain scale. A net change of ≥ 2 points, $\geq 30\%$ or 50% decrease from baseline of disability scores was considered clinically significant.

RESULTS

Literature Search

We adapted the results of Oliveira et al's search from the Cochrane review (27,28).

Overall, 25 trials from 29 articles were included in the qualitative synthesis (75-99), and 19 trials (75,79,82-93,95-99) were included in the dual-arm conventional meta-analysis (27,28). However, in a recent comparative systematic review and meta-analysis, Manchikanti et al (29) included 15 additional trials (100-115).

Among the included trials in the Cochrane review (27,28), 6 trials used the caudal approach (76,79,82,86,88,95). However, Oliveira et al (27,28) miscategorized an interlaminar trial as caudal (81), showing 7 caudal trials. Six trials used the transforaminal approach (78,80,93,94,97,99), and 13 trials used the interlaminar approach (75,77,81,83-85,87,89-92,96,98). As shown above, the miscategorized trial (81) was included instead as interlaminar.

Types of Studies

Oliveira et al's (27,28) inclusion of placebo interventions varied among included trials; sodium chloride solution was used in 12 trials (75,78,82-84,87,88,91,92,97-99). Two trials used a variety of intramuscular injections, including paravertebral muscles, at points of maximum back muscle tenderness, or over the sacral hiatus (86,90). Additionally, 2 studies investigated 2 types of epidural injectates, saline solution alone or a combination of saline and anesthetic (95,97). Multiple trials have utilized a local anesthetic or a combination of saline and local anesthetic (76,77,79-81,86,97,90). We separated studies into 2 different groups based on placebo-controlled trials and active-controlled trials.

Among the 25 included articles, 10 trials employed

fluoroscopic guidance (76-78,80,81,90,93,94,97,99). Of these 6 used a transforaminal approach (78,80,93,94,97,99), 3 used an interlaminar approach (77,81,90), and one was performed as a caudal epidural injection (76). One study using a caudal approach was performed with ultrasound guidance (95). The remaining 14 trials were performed without image guidance as shown in Appendix Table 1 (75,79,82-89,91,92,96,98).

Timing of Trials Performed

Oliveira et al (27,28) included 7 of the studies (83-88,96) originally found in the 1995 systematic review and meta-analysis by Koes et al (47) and Watts and Silagy (46). Additionally, the authors utilized 2 trials published prior to 1980 (83,84), 5 trials published between 1981 and 1990 (85-87,96,98), 4 trials published from 1991 to 2000 (75,88-90), 6 trials published from 2001 to 2010 (78,91-94,99), and 8 trials published from 2011 to 2020 (76,77,79-82,95,97) (Appendix Table 2). However, 16 trials (100-115) were excluded by Oliveira et al (27,28), even though they were of high quality with a long-term follow-up. These trials met criteria for a subsequent review manuscript in 2021 (29). Appendix Table 3 shows the trials (75-119) included in the 4 systematic reviews (27-29,32,33).

Methodological Quality Assessment

Appendix Tables 4 and 5 show the scoring for methodological quality assessment of all RCTs utilizing the Cochrane review criteria (70) and the IPM-QRB criteria (71).

Table 2 shows the scoring for the methodological quality assessment of lumbar epidural RCTs with a comparison between the Cochrane review criteria (70), and the IPM-QRB criteria (71), along with the results of the Cochrane review (27,28).

This assessment as found in Table 2 shows the importance of using the interventional pain management-specific scoring criteria IPM-QRB, which has shown results that differ from those of the Cochrane review derived data (27,28). There was agreement between the Cochrane review scoring and the IPM-QRB scoring in 11 of the 25 trials (76-81,93-95,97,99). The IPM-QRB scoring showed lower grading than the Cochrane review criteria in 14 trials as shown in Table 2 (75,82-92,96,98).

Effectiveness of Epidural Injections

Descriptive characteristics of included studies are shown in Appendix Tables 6 and 7.

Evidence Synthesis

Evidence synthesis was performed by qualitative and quantitative analysis.

Qualitative Analysis

Qualitative analysis of the evidence included all 25 studies (75-99) with 16 placebo-controlled trials meeting the inclusion criteria (75,78,82-88,90-92,95,96,98,99). There were 9 trials utilizing active-controlled design (76,77,79-81,89,93,94,97). Tables 3 and 4 show qualitative analysis of the effectiveness of epidural injections based on RCTs and active-controlled trials.

Qualitative results were determined based on multiple factors including the application of an ap-

propriate treatment regimen where 3 injections versus one injection were performed, with monitoring the patient throughout the year. Factors analyzed included the clinical applicability, pragmatism, fluoroscopic usage (standard of care in the United States), the number of patients, the dosage of the steroid, successful outcomes, and the clinical utility. In addition, GRADE criteria were applied with downgrading, upgrading, or no change in the study quality.

Placebo-Controlled Trials

Qualitative analysis was performed utilizing 16 placebo-controlled trials as shown in Table 3 (75,78,82-88,90-92,95,96,98,99). Because the standard of care for

Table 2. Methodological quality assessment and pragmatic nature of epidural injections with caudal, interlaminar, and transforaminal approaches in lumbar radiculopathy or sciatica.

Trial	Type of Trial	Imaging	Cochrane Criteria	IPM-QRB Criteria	Quality Grading (high, moderate, low) Cochrane/IPM-QRB	Clinical Relevance and Pragmatism	GRADE Assessment
Manchikanti et al (76)	AC	F	12/13	44/48	High / High	Y	H
Manchikanti et al (77)	AC	F	11/13	44/48	High / High	Y	H
Ghai et al (81)	AC	F	10/13	39/48	High / High	Y	H
Karppinen et al (78)	PC	F	13/13	34/48	High / High	N	M
Manchikanti et al (80)	AC	F	11/13	44/48	High / High	Y	H
Tafazal et al (94)	AC	F	11/13	32/48	High / High	Y	M
Datta & Upadhyay (79)	AC	B	6/13	18/48	Moderate / Moderate	Y	M
Dilke et al (83)	PC	B	9/13	28/48	High / Moderate	N	L
Snoek et al (84)	PC	B	9/13	10/48	High / Low	N	L
Klenerman et al (85)	PC	B	12/13	13/48	High / Low	N	L
Mathews et al (86)	PC	B	10/13	12/48	High / Low	N	L
Ridley et al (87)	PC	B	9/13	10/48	High / Low	N	L
Bush & Hillier (88)	PC	B	11/13	14/48	High / Low	N	L
Rogers et al (89)	AC	B	12/13	12/48	High / Low	N	L
Kraemer et al (90)	PC	B	6/13	7/48	Moderate/ Low	N	L
Valat et al (91)	PC	B	12/13	28/48	High / Moderate	N	M
Arden et al (92)	PC	B	10/13	31/48	High / Moderate	N	M
Ng et al (93)	AC	F	12/13	37/48	High / High	N	M
Iversen et al (95)	PC	U	5/13	24/48	Moderate / Moderate	N	L
Cuckler et al (96)	PC	B	10/13	13/48	High / Low	N	L
Carette et al (75)	PC	B	12/13	27/48	High / Moderate	N	M
Cohen et al (97)	AC	F	13/13	38/48	High / High	Y	L
Helliwell et al (98)	PC	B	12/13	18/48	High / Moderate	N	L
Ghahreman et al (99)	PC	F	12/13	37/48	High / High	Y	H
Nandi & Chowdhery (82)	PC	B	12/13	20/48	High / Moderate	N	M

AC = Active control; PC = Placebo control; F = Fluoroscopy; B = Blind; U = Ultrasound; Y = Yes; N = No
 GRADE criteria: H = high; M = moderate; L = low; VL = very low

Table 3. Qualitative analysis of effectiveness of epidural injections based on randomized controlled trials.

Study Characteristics Methodological Quality Scoring	Number of Participants & Interventions	Results of Pain Relief and Function					Comments	Clinical Relevance and Pragmatism	GRADE Criteria
		1 month	3 months	6 months	1 year				
Carette et al, 1997 (75)	Total = 158 Treatment = 78 Number of injections = 1 to 3	NSD	NA	NA	NA	NA	Negative trial	Low	Moderate Downgraded
Karppinen et al, 2001 (78)	Total=160 Treatment = 80 Saline = 80 Number of injections = 1	NA	NA	NA	NA	NA	Negative trial	Low	Moderate No change
Nandi & Chowdhery, 2017 (82)	Total = 93 Placebo = 46 Treatment = 47 Number of Injections = 1	Positive	N	NA	NA	NA	Positive short-term	Low	Moderate No change
Dilke et al, 1973 (83)	Total = 100 Epidural = 50 Interspinous = 50 Number of injections = 1-2	NA	N	NA	NA	NA	Negative trial	Moderate	Low No change
Snoek et al, 1977 (84)	Total = 51 Placebo = 24 Treatment = 27 Number of injections = 1	NA	NSD	NA	NA	NA	Negative trial	Low	Low No change
Mathews et al, 1987 (86)	Total = 57 Placebo control group = 34 Treatment group = 23 Number of procedures = 1 to 3 at 2-week intervals	Positive	Positive	NA	NA	NA	Positive trial - short term	Low	Low No change
Ridley et al, 1988 (87)	Total = 35 Placebo group = 16 Treatment group = 19 Injection was repeated weekly for 3 times if there was no improvement	Positive	Positive	NSD	NA	NA	Positive trial - short-term	Moderate	Low No change
Bush & Hillier, 1991 (88)	Total = 54 Placebo group = 11 Treatment group: 12 Number of procedures = 2 at 2 weeks apart	Positive	NA	NA	Positive	Positive	Positive trial - short-term and long-term	Moderate	Low No change
Kraemer et al, 1997 (90)	Total = 136 Placebo group = 46 Conventional epidural injection = 40 Interlaminar epidural perineural injection = 47	NA	Perineural more effective than interlaminar	NA	NA	NA	Indeterminate	Low	Low No change

Table 3 cont. Qualitative analysis of effectiveness of epidural injections based on randomized controlled trials.

Study Characteristics Methodological Quality Scoring	Number of Participants & Interventions	Results of Pain Relief and Function					Comments	Clinical Relevance and Pragmatism	GRADE Criteria
		1 month	3 months	6 months	1 year				
Valat et al, 2003 (91)	Total = 85 Control group = 42 Treatment group = 43 3 epidural injections at 2-day intervals	NSD	NA	NA	NA	NA	Negative trial	Low	Moderate Downgraded
Arden et al, 2005 (92)	Total = 228 Steroid group = 120 Placebo group = 108 Number of injections = 1	NSD	NSD	NSD	NSD	NSD	Negative trial	Low	Moderate Downgraded
Iversen et al, 2011 (95)	Sham group = 40 Subcutaneous placebo = 40 Caudal epidural placebo = 39 Epidural steroid group = 37 patients Number of injections = 2	NA	N	NA	N	N	Negative trial	Low	Low No change
Helliwell et al, 1985 (98)	Total = 39 Control (placebo) = 19 Treatment (steroid) = 20 Number of injections = 1	NA	Positive	NA	NA	NA	Positive trial – short-term	Moderate	Low Downgraded
Ghahreman et al, 2010 (99)	Total = 150 5 groups with 28, 37, 27, 28, 30 Number of injections: 1 to 3 for 12 months	Effectiveness only in steroids with local anesthetic Positive	NA	NA	NA	NA	Positive trial – short-term	Moderate	High No change
Klenerman et al, 1984 (85)	Total = 63 Placebo group = 16 Local anesthetic group = 16 Steroid group = 19	NA	NSD	NA	NA	NA	Negative trial	Low	Low Downgraded
Cuckler et al, 1985 (96)	Total = 73 Placebo group = 14 patients Steroid with local anesthetic = 22 patients	NA	NA	NA	NSD	NSD	Negative trial	Low	Low Downgraded

NA = Not Applicable; N = Negative; NSD = No Significant Difference

Table 4. Qualitative analysis of effectiveness of epidural injections based on active controlled trials.

Study Characteristics Methodological Quality Scoring	Number of Participants & Interventions	Results of Pain Relief and Function				Comments	Clinical Relevance and Pragmatism	GRADE Criteria
		1 month	3 months	6 months	1 year			
Manchikanti et al, 2012 (76)	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Number of injections = 1 to 5	NA	Lidocaine alone or with steroids effective Positive	Lidocaine alone or with steroids effective Positive	Lidocaine alone or with steroids effective Positive	Positive trial short- and long-term	High	High No change
Manchikanti et al, 2014 (77)	Total = 120 Local anesthetic = 60 Local anesthetic and steroids = 60 Average number of injections = 5 to 6 for 2 years	NA	Lidocaine alone or with steroids effective Positive	Lidocaine alone or with steroids effective Positive	Lidocaine alone or with steroids effective Positive	Positive trial short- and long-term	High	High No change
Datta & Upadhyay, 2011 (79)	Total = 163 Bupivacaine = 55 Methylprednisolone = 50 Bupivacaine and triamcinolone = 52 Bupivacaine and dexamethasone = 50 Number of injections = 1 to 3	Similar improvement in all groups Positive	Bupivacaine and bupivacaine with steroids effective. Bupivacaine with steroids superior to bupivacaine alone. Positive	NA	NA	Positive trial short-term	Moderate	Moderate No change
Manchikanti et al, 2014 (80)	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Average number of injections = 5 to 6 for 2 years	NA	Lidocaine alone or with steroids effective Positive	Lidocaine alone or with steroids effective Positive	Lidocaine alone or with steroids effective Positive	Positive trial short- and long-term	High	High No change
Ghai et al, 2015 (81)	Total = 69 Lidocaine = 34 Lidocaine + methylprednisolone = 35 Average procedures = 2	NA	Both arms effective. Steroids superior Positive	Both arms effective. Steroids superior Positive	Both arms effective. Steroids superior Positive	Positive trial short- and long-term	High	High No change
Rogers et al, 1992 (89)	Total = 30 Local anesthetic group = 15 Lidocaine with steroid group = 15	Steroids effective Positive	NA	NA	NA	Positive trial short-term	Low	Low Downgraded
Ng et al, 2005 (93)	Total = 86 Bupivacaine only = 41 Bupivacaine + steroid = 40 Number of injections = 1	Bupivacaine alone and bupivacaine plus steroid were equally effective Positive	Bupivacaine alone and bupivacaine plus steroid were equally effective Positive	NA	NA	Positive trial short-term	Low	Moderate Downgraded
Tafazal et al, 2009 (94)	Total: 150 Local anesthetic = 34 Local anesthetic with steroid = 42 Number of injections = 1 to 3	NA	Positive	NA	NA	Positive trial short- and long-term	Moderate	Moderate No change
Cohen et al, 2012 (97)	Total number of patients = 84 adults Bupivacaine + saline = 30 Bupivacaine + steroid = 28 Bupivacaine + etanercept = 26	Positive for steroids Positive	NA	NA	NA	Positive trial - short-term	Low	Low Downgraded

NA = Not Applicable; NSD = No Significant Difference

epidural procedures in the United States is with image guidance (primary fluoroscopy) except in cases of pregnancy and where fluoroscopy is contraindicated, we have considered all fluoroscopic studies and one ultrasound study in our review (95). As shown in Table 3, of the 16 placebo-controlled trials, 6 trials (82,86-88,98,99) were shown to be positive in the short-term and one trial (88) was positive in the long term at one-year. Among the positive trials, 2 trials (82,86) showed low clinical relevance and pragmatism, 4 trials (87,88,98,99) showed moderate clinical relevance and pragmatism, and none of the trials showed high clinical relevance and pragmatism. GRADE criteria also showed no change in 5 of 6 trials (82,86-88,99) and downgrading in one trial (98).

Based on this analysis, the evidence is Level I, or strong, evidence at one month and 3 months.

Active-Controlled Trials

There were 9 active-controlled trials (76,77,79-81,89,93,94,97). Of these, 7 studies (76,77,80,81,93,94,97) utilized fluoroscopy. Table 4 shows a qualitative analysis of the effectiveness of randomized active-controlled trials in re-evaluation of the Cochrane review of epidural injections for lumbar radiculopathy or sciatica.

As shown in Table 4, of the 9 active-controlled trials, 4 trials (79,89,93,97) were shown to be positive in short-term and 5 trials (76,77,80,81,94) were positive in long-term. Two trials (89,93) showed low clinical relevance and pragmatism, 3 trials (79,94,97) showed moderate clinical relevance and pragmatism, and 4 trials (76,77,80,81) showed high clinical relevance and pragmatism. GRADE criteria also showed no change in 6 trials (76,77,79-81,94) and downgrading in 3 trials (89,93,97).

Based on this analysis, the evidence is Level I, or strong, at one month, 3 months, and 12 months.

Quantitative Analysis

Quantitative analysis was performed utilizing both conventional dual-arm analysis and single-arm analysis for placebo-controlled trials and active-controlled trials.

Placebo-Controlled Trials

There was a total of 16 trials utilizing placebo control design (75,78,82-88,90-92,95,96,98,99). These included epidural and extra-epidural sodium chloride injections. We analyzed all placebo-controlled trials.

One-Month Follow-Up

Figures 1 and 2 show the change in pain level using the Numeric Rating Scale (NRS) or Visual Analog Scale (VAS) and functionality changes using Oswestry Disability Index (ODI) or Roland-Morris Disability Questionnaire (RMDQ) at one month.

There were 6 trials (78,82,88,91,98,99) with 463 patients that compared the placebo group versus the epidural steroid group in a dual-arm meta-analysis. Results showed a statistically significant difference in pain levels between these 2 groups [SMD 0.63 (0.23, 1.02), $P = 0.002$] (Fig. 1).

There were 3 trials (78,82,91) with 336 patients that compared the functionality between placebo and epidural steroid group in a dual-arm meta-analysis. Results showed no statistically significant difference in functionality between these 2 groups [SMD 0.44 (-0.05, 0.94), $P = 0.08$] (Fig. 2).

3-Month Follow-Up

Figure 3 shows the change in pain level using VAS or NRS at 3 months.

Figure 4 shows the change in functionality status using ODI or RMDQ at 3 months.

There were 6 trials (75,78,82,92,95,98) with 683 patients that compared the placebo group versus the

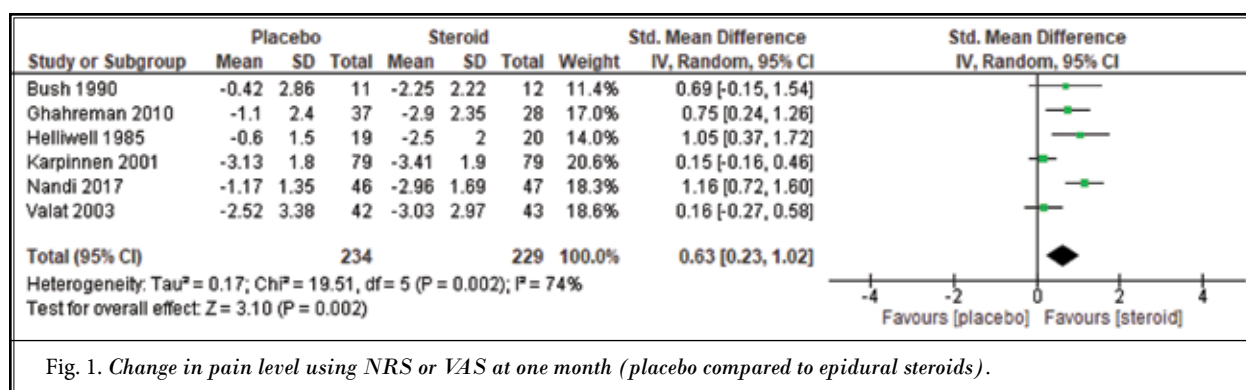


Fig. 1. Change in pain level using NRS or VAS at one month (placebo compared to epidural steroids).

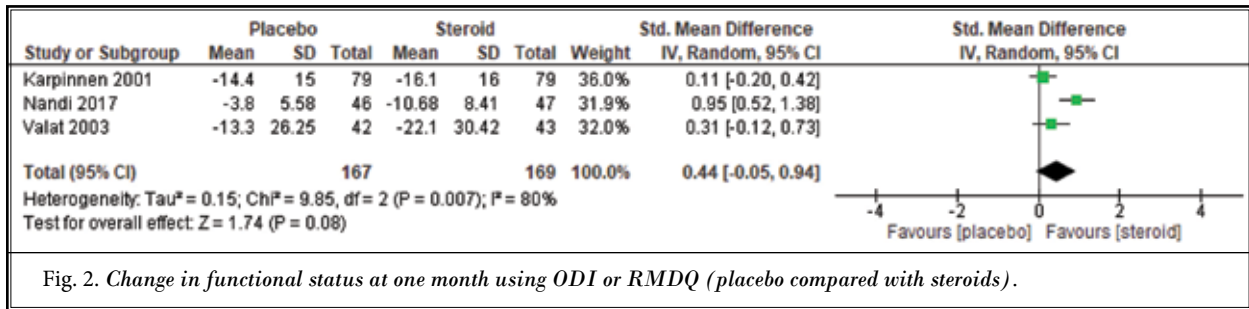


Fig. 2. Change in functional status at one month using ODI or RMDQ (placebo compared with steroids).

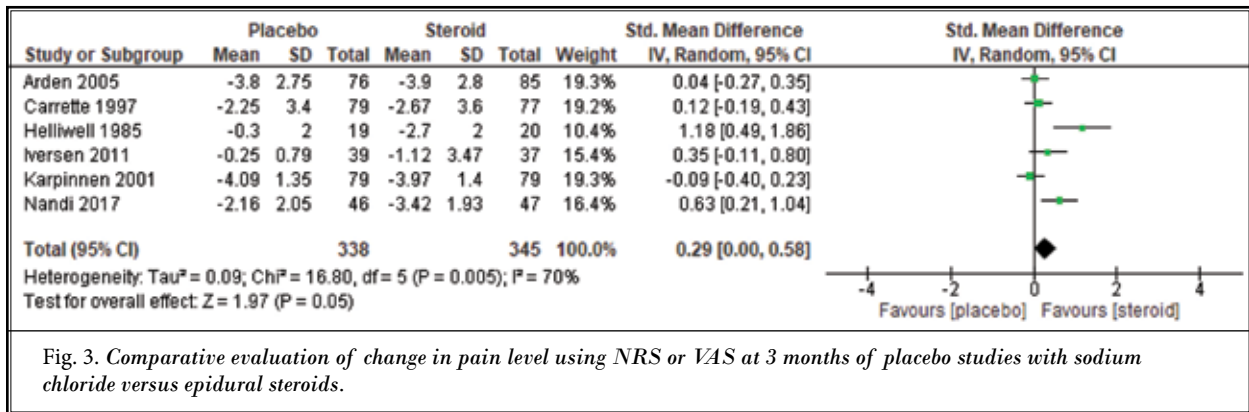


Fig. 3. Comparative evaluation of change in pain level using NRS or VAS at 3 months of placebo studies with sodium chloride versus epidural steroids.

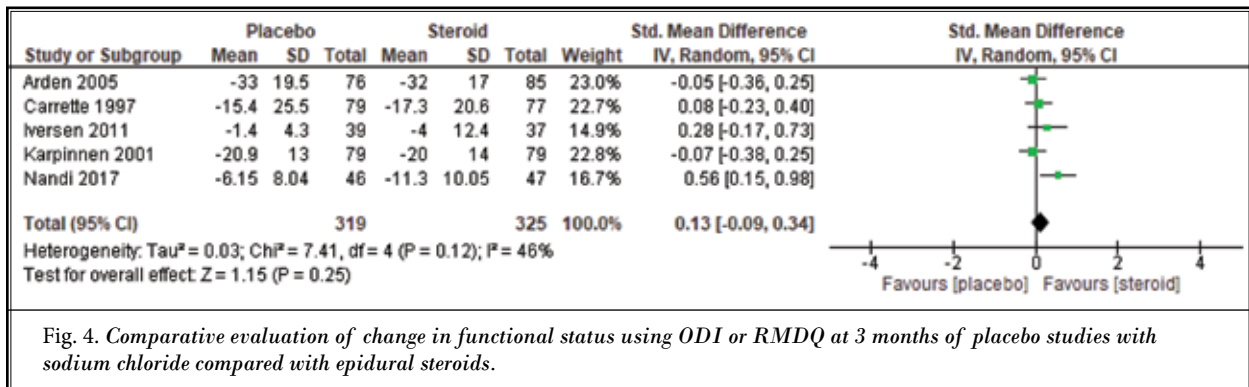


Fig. 4. Comparative evaluation of change in functional status using ODI or RMDQ at 3 months of placebo studies with sodium chloride compared with epidural steroids.

epidural steroid group in a dual-arm meta-analysis. Results showed a border line significant difference in pain levels between these 2 groups. [SMD 0.29 (0.00, 0.58), P = 0.05] (Fig. 3).

There were 5 trials (75,78,82,92,95) with 644 patients that compared the placebo group versus the steroid group in a dual-arm meta-analysis. Results showed no statistically significant difference in functionality between these 2 groups [SMD 0.13 (-0.09, 0.34), P = 0.25] (Fig. 4).

6-Month Follow-Up

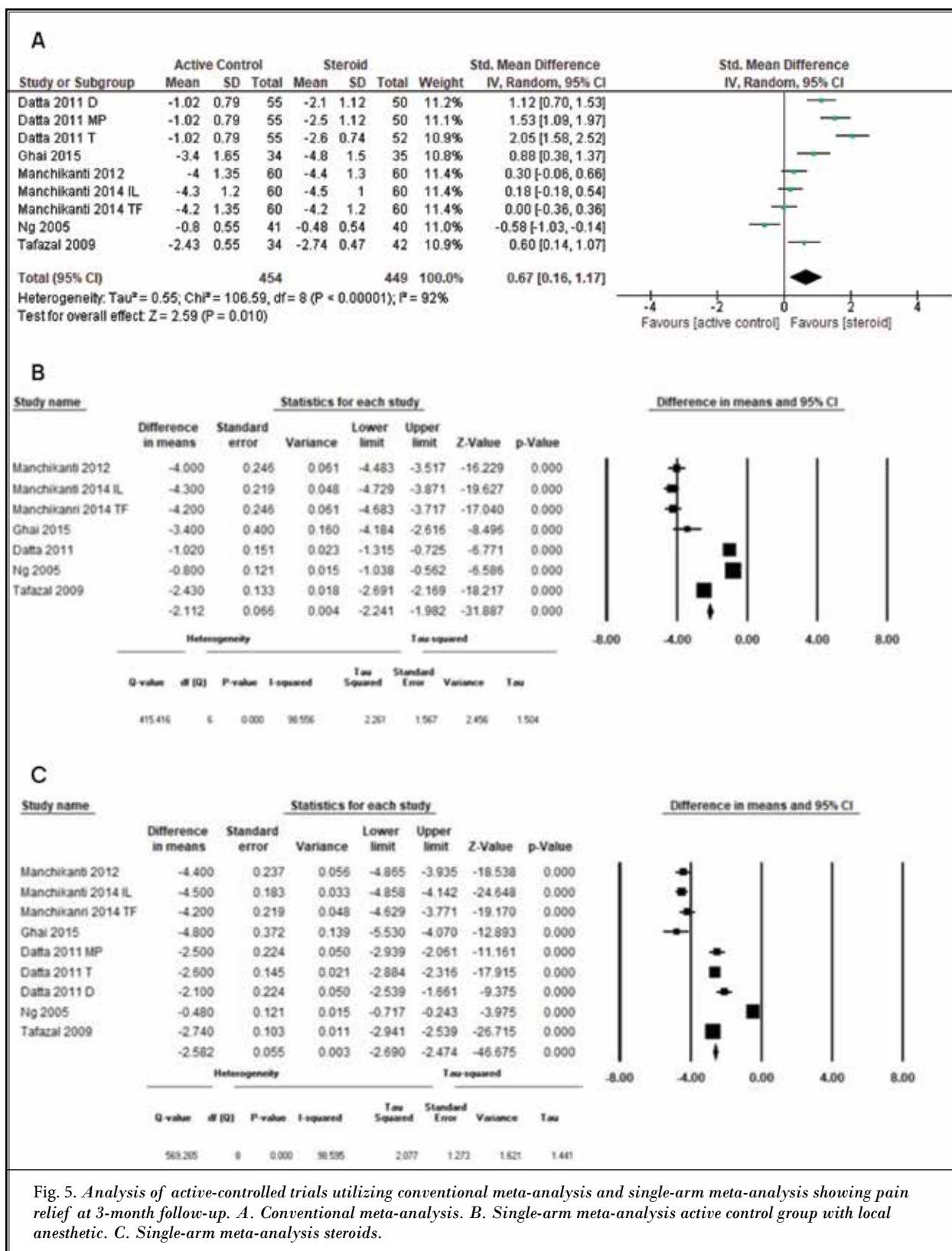
There were not enough studies to calculate changes in pain and functionality at 6 months.

Active-Controlled Trials

There was a total of 9 active-controlled trials meeting the inclusion criteria (76,77,79-81,89,93,94,97). Of these, fluoroscopy was used in 7 trials (76,77,80,81,93,94,97). All active-controlled trials were analyzed for pain relief and functional status assessment utilizing conventional meta-analysis, as well as single-arm meta-analysis. The analysis was carried out at 3, 6, and 12 months. Analysis at one month was felt to be inconclusive since multiple studies had insufficient data.

3-Month Follow-Up

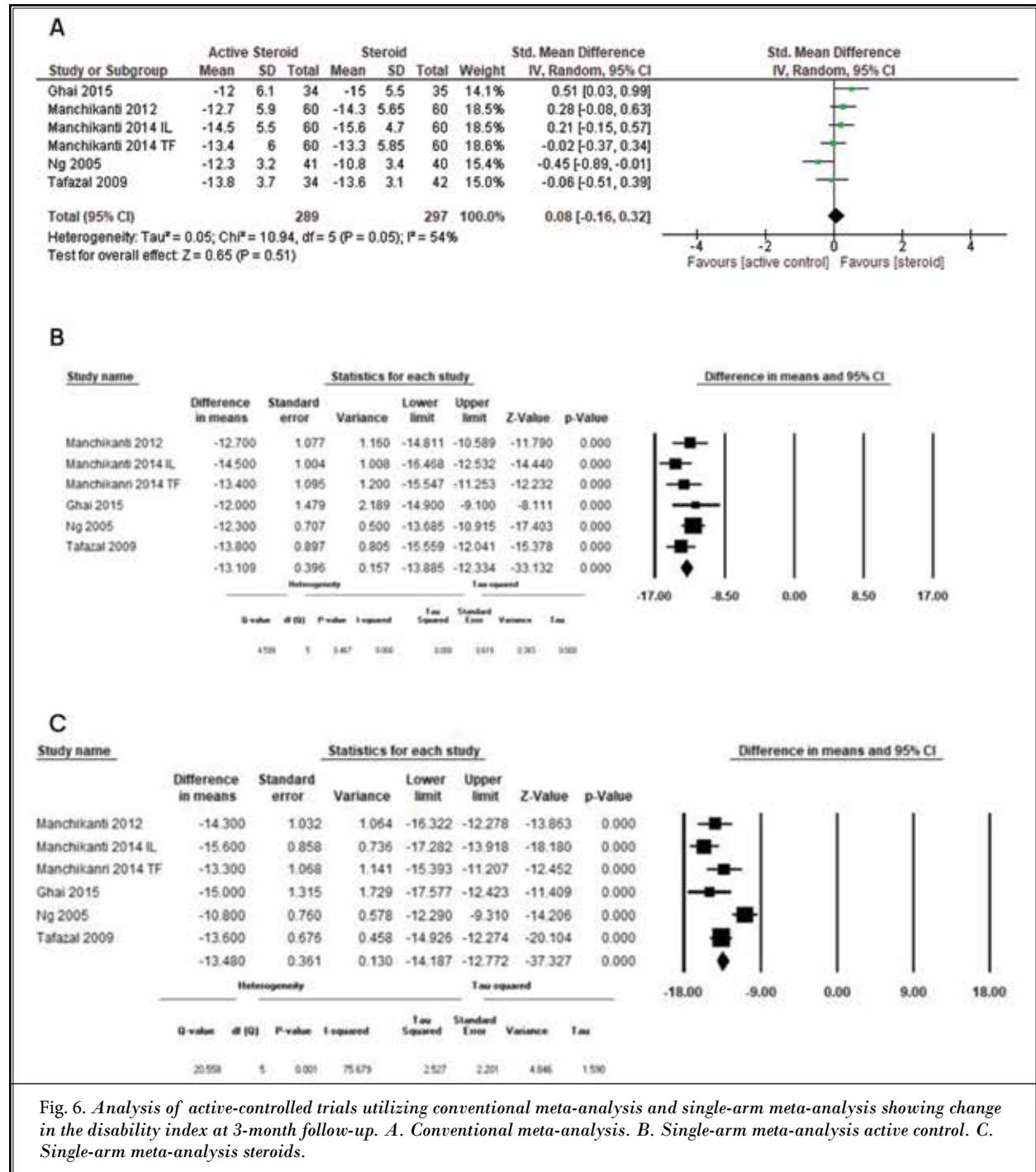
Figure 5 shows analysis of pain relief assessed by



VAS or NRS scoring and Fig. 6 shows functionality assessed by disability scoring using ODI or RMDQ at 3 months.

There were 7 trials (76,77,79-81,93,94) with 793 patients that compared the active control group

versus the steroid group in a dual-arm meta-analysis. Datta et al (79) used 3 different types of corticosteroids (dexamethasone-D, methylprednisolone-MP and triamcinolone-T) and compared these to an active control group. Results showed a statistically significant differ-



ence between these 2 groups [SMD 0.67 (0.16, 1.17), $P = 0.010$] (Fig. 5A).

Figure 5B shows results of a single-arm analysis utilizing the active control group. Seven trials (76,77,79-81,93,94) were used to assess the pain score at 3 months using VAS in patients who underwent injections with an active control. As shown in Fig. 5B, the pooled mean difference of pain score from baseline to 3 months follow-up was a decrease of 2.112 points (95% CI: -2.241 to -1.982, $P < 0.001$).

Figure 5C shows results of a single-arm analysis utilizing the steroid groups. Seven trials (76,77,79-81,93,94) were used to assess pain score at 3 months using VAS in patients who underwent injections of steroid plus anesthetic injections. As shown in Fig. 5C, the pooled mean difference of pain score from baseline to 3 months of follow-up decreased 2.582 points (95% CI: -2.690 to -2.474, $P < 0.001$).

There were 6 trials (76,77,80,81,93,94) with 586 patients that compared pain scores between the active control and the steroid groups. In a dual-arm meta-analysis, results showed no statistically significant difference in functionality between these 2 groups at 3 months. [SMD 0.08 (-0.16, 0.32), $P = 0.51$] (Fig. 6A).

Figure 6B shows results of a single-arm analysis utilizing the active control group. Six trials (76,77,80,81,93,94) were used to assess functionality at 3 months using ODI in patients who underwent the active control (local anesthetic) injections. As shown in Fig. 6B, the pooled mean difference of functionality score from baseline to 3 months of follow-up was a decrease of 13.109 points (95% CI: -13.885 to -12.334, $P < 0.001$).

Figure 6C shows results of a single-arm analysis utilizing the steroid group. Six trials (76,77,80,81,93,94) were used to assess functionality at 3 months using ODI in patients who underwent injections of steroid plus anesthetic. As shown in Fig. 6C, the pooled mean difference of pain score from baseline to 3 months of follow-up was a decrease of 13.480 points (95% CI: -14.187 to -12.772, $P < 0.001$).

6-Month Follow-Up

Figure 7 shows analysis of pain relief assessed by VAS or NRS scoring and Fig. 8 shows functionality assessed by disability scoring using ODI or RMDQ at 6 months.

There were 4 trials (76,77,80,81) with 429 patients that compared the active control group versus the steroid group in a dual-arm meta-analysis. Results showed no statistically significant difference between these 2 groups at 6 months. [SMD 0.25 (-0.18, 0.67), $P = 0.25$] (Fig. 7A).

Figure 7B shows results of a single-arm analysis utilizing the active control group. Four trials (76,77,80,81) were used to assess the pain scores at 6 months using VAS in patients who underwent active control injections. As shown in Fig. 7B, the pooled mean difference of pain scores from baseline to 6 months of follow-up was a decrease of 4.174 points (95% CI: -4.423 to -3.925, $P < 0.001$).

Figure 7C shows results of a single-arm analysis utilizing the steroid group. Four studies (76,77,80,81) were used to assess pain scores at 6 months using VAS in patients who underwent injections of steroid plus anesthetic. As shown in Fig. 7C, the pooled mean difference of pain scores from baseline to 3 months of follow-up was a decrease of 4.368 points (95% CI: -4.639 to -4.098, $P < 0.001$).

There were 4 trials (76,77,80,81) with 429 patients that compared the active control group versus the steroid group in a dual-arm meta-analysis. Results showed no statistically significant difference in functionality between these 2 groups at 6 months [SMD 0.21 (-0.12, 0.53), $P = 0.21$] (Fig. 8A).

Figure 8B shows results of a single-arm analysis utilizing the active control group. Four trials (76,77,80,81) were used to assess functionality at 6 months using ODI in patients who underwent active control injections. As shown in Fig. 8B, the pooled mean difference of functionality scores from baseline to 6 months of follow-up was a decrease of 14.064 points (95% CI: -15.183 to -12.945, $P < 0.001$).

Figure 8C shows results of a single-arm analysis utilizing the steroid group. Four trials (76,77,80,81) were used to assess functionality scores at 6 months using ODI in patients who underwent injections of steroid plus anesthetic. As shown in Fig. 8C, the pooled mean difference of functionality scores from baseline to 6 months of follow-up was a decrease of 15.236 points (95% CI: -16.262 to -14.209, $P < 0.001$).

12-Month Follow-Up

Figure 9 shows analysis of pain relief assessed by VAS or NRS scoring, and Figure 10 shows functionality assessed by disability scoring using ODI or RMDQ at 12 months.

There were 4 trials (76,77,80,81) with 429 patients that compared the active control group versus the steroid group in a dual-arm meta-analysis. Results showed no statistically significant difference in pain between these 2 groups at 12 months [SMD 0.35 (-0.15, 0.84), $P = 0.17$] (Fig. 9A).

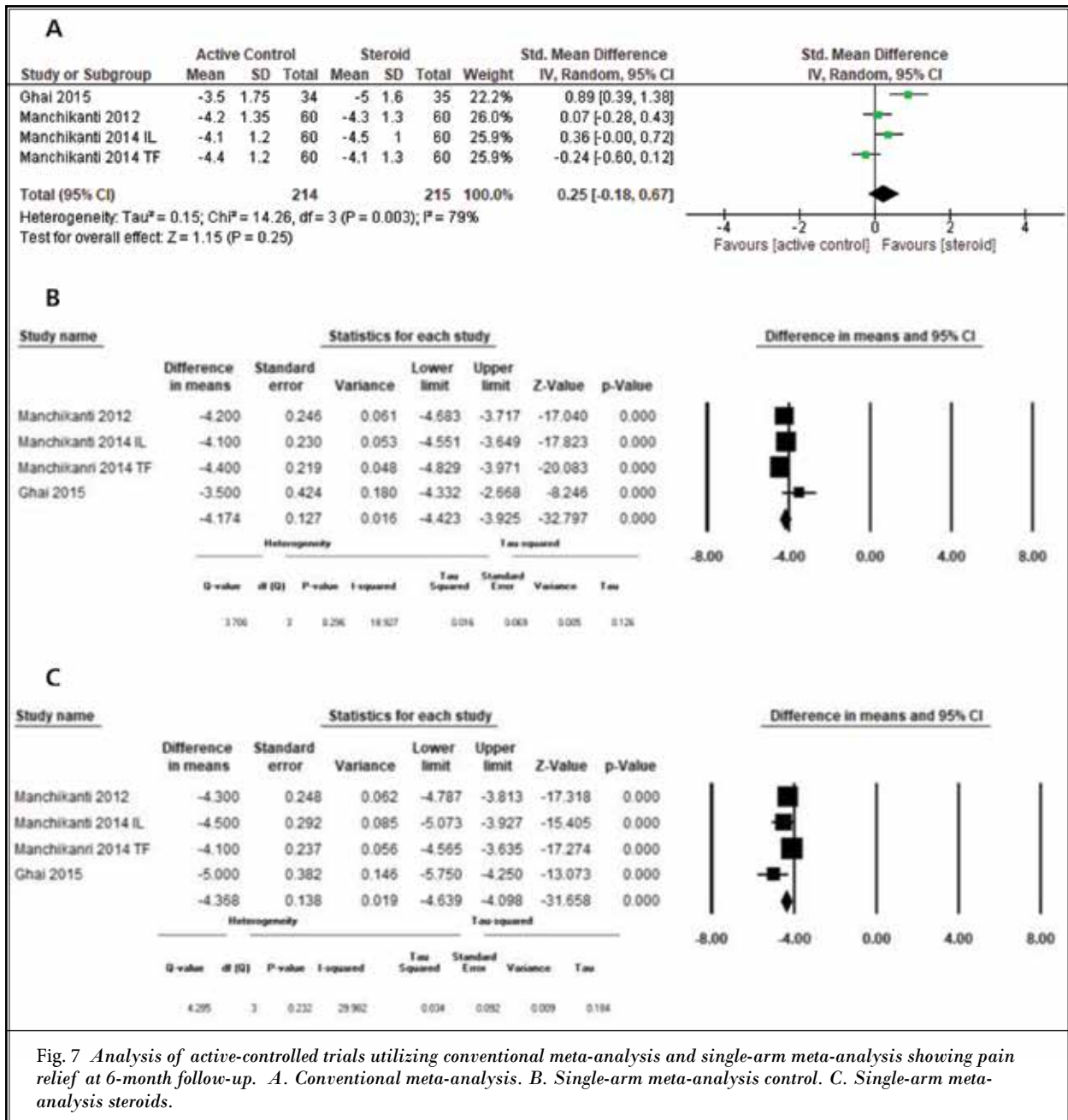


Figure 9B shows results of a single-arm analysis utilizing the active control group. Four trials (76,77,80,81) were used to assess pain scores at 12 months using VAS in patients who underwent active control injections. As shown in Fig. 9B, the pooled mean difference of pain score from baseline to 12 months of follow-up was a decrease of 4.150 points (95% CI: -4.398 to -3.903, $P < 0.001$).

Figure 9C shows results of a single-arm analysis

utilizing the steroid group. Four trials (76,77,80,81) were used to assess pain scores at 12 months using VAS in patients who underwent injections of steroid plus anesthetic. As shown in Fig. 9C, the pooled mean difference of pain score from baseline to 12 months of follow-up was a decrease of 4.493 points (95% CI: -4.732 to -4.253, $P < 0.001$).

There were 4 studies (76,77,80,81) with 429 patients that compared the active control group versus

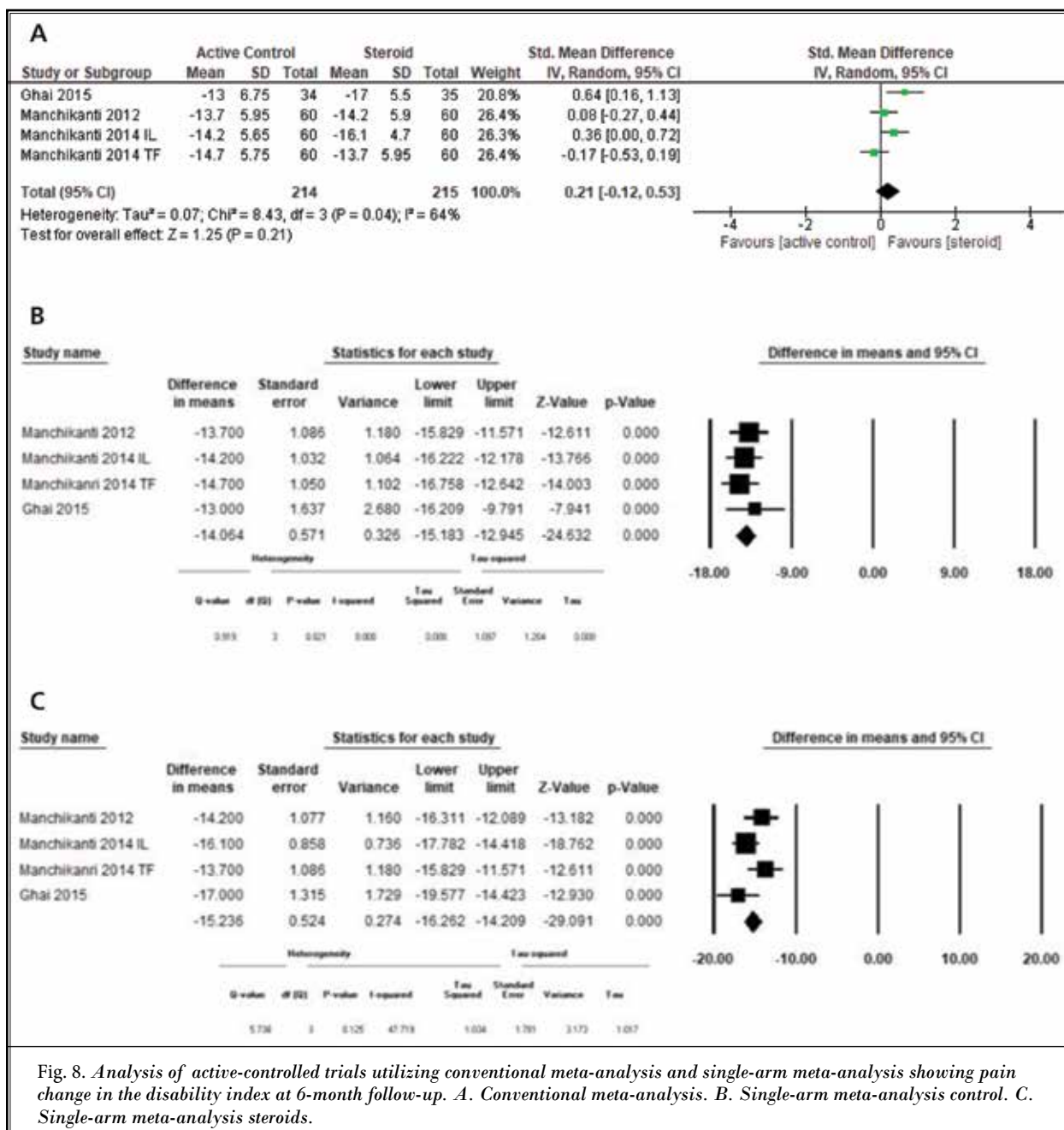


Fig. 8. Analysis of active-controlled trials utilizing conventional meta-analysis and single-arm meta-analysis showing pain change in the disability index at 6-month follow-up. A. Conventional meta-analysis. B. Single-arm meta-analysis control. C. Single-arm meta-analysis steroids.

the steroid group in a dual-arm meta-analysis. Results showed no statistically significant difference in functionality between these 2 groups at 12 months. [SMD 0.19 (-0.16, 0.54), P = 0.29] (Fig. 10A).

Figure 10B shows results of a single-arm analysis utilizing the active control group. Four trials (76,77,80,81) were used to assess pain score at 12 months using ODI in patients who underwent the active control (local anesthetic) injections. As shown in Fig. 10B, the pooled

mean difference of functionality score from baseline to 12 months of follow-up was a decrease of 14.336 points (95% CI: -15.482 to -13.191, P < 0.001).

Figure 10C shows results of a single-arm analysis utilizing the steroid group. Four trials (76,77,80,81) were used to assess functionality scores at 12 months using ODI in patients who underwent injections of steroid plus anesthetic. As shown in Fig. 10B, the pooled mean difference of functionality score from baseline to

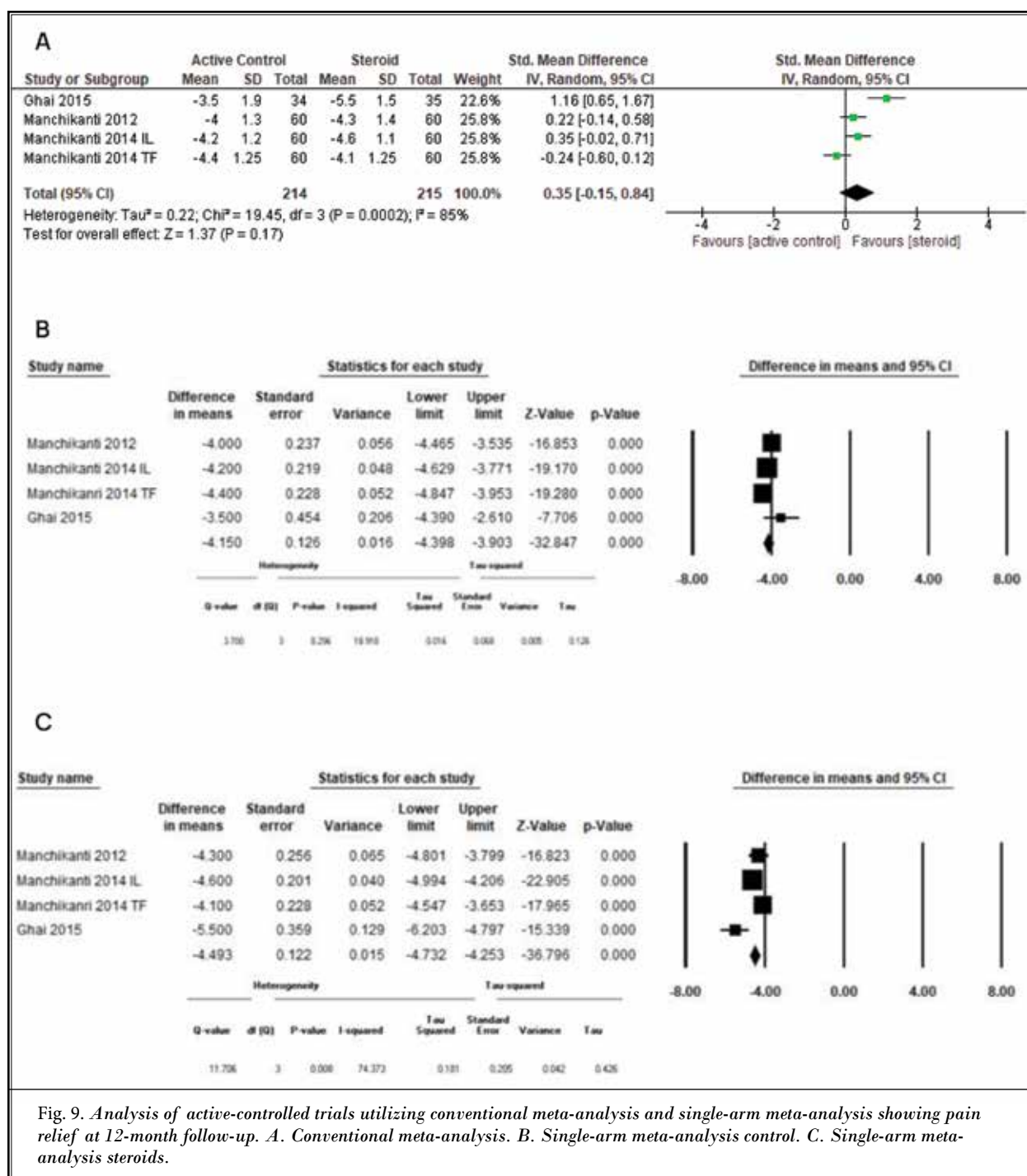


Fig. 9. Analysis of active-controlled trials utilizing conventional meta-analysis and single-arm meta-analysis showing pain relief at 12-month follow-up. A. Conventional meta-analysis. B. Single-arm meta-analysis control. C. Single-arm meta-analysis steroids.

12 months of follow-up was a decrease of 15.422 points (95% CI: -16.481 to -14.362, P < 0.001).

Summary of Evidence Synthesis

For qualitative and quantitative analysis, all 25 trials were utilized (75-99). Based on the analysis of 16 place-

bo-controlled studies (75,78,82-88,90-92,95,96,98,99), 6 trials (78,82,88,91,98,99) with 463 patients at one and 3-month follow-up met the inclusion criteria. Results showed a statistically significant difference in pain levels between these 2 groups at one-month, and a borderline significant difference between the placebo

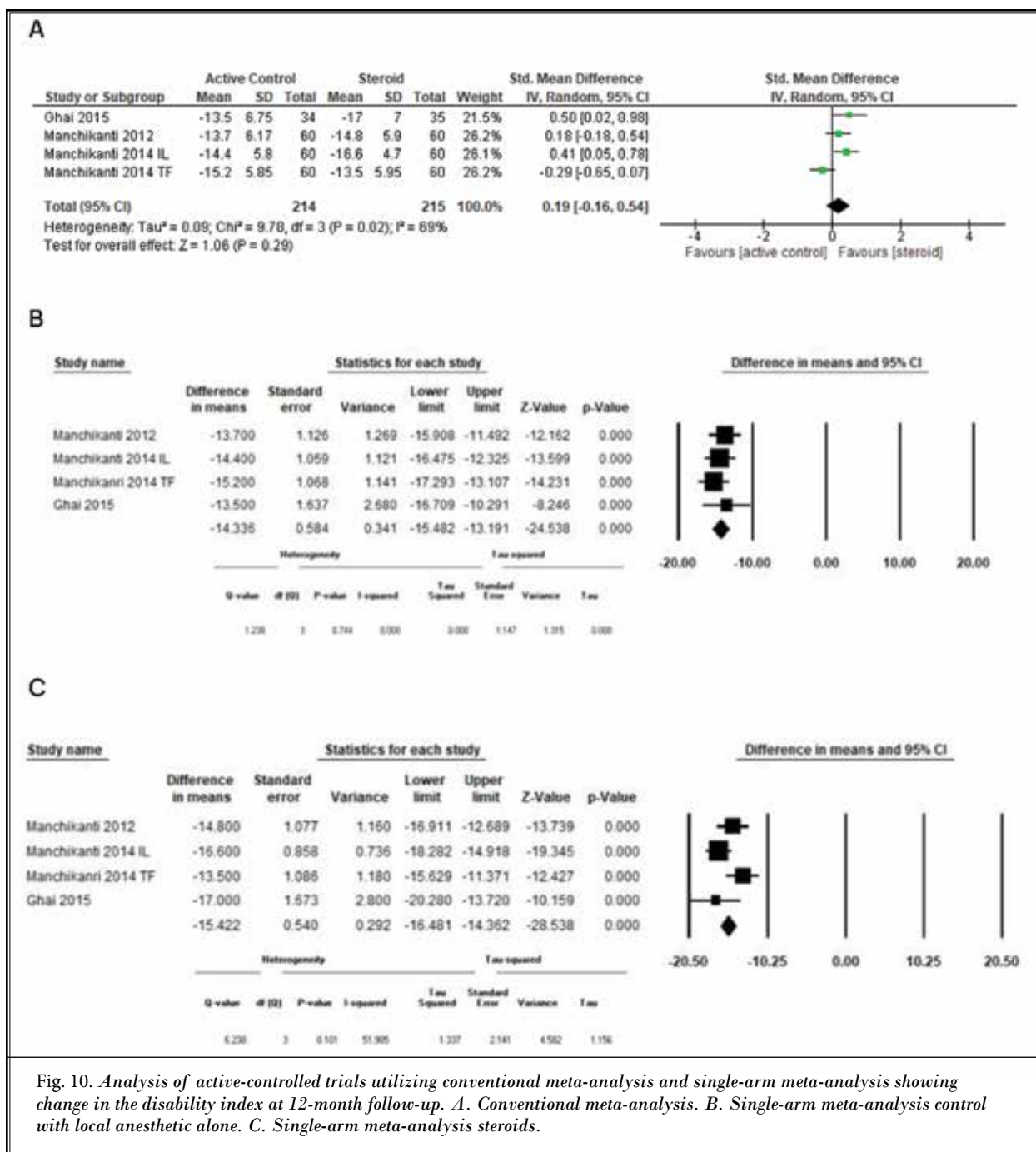


Fig. 10. Analysis of active-controlled trials utilizing conventional meta-analysis and single-arm meta-analysis showing change in the disability index at 12-month follow-up. A. Conventional meta-analysis. B. Single-arm meta-analysis control with local anesthetic alone. C. Single-arm meta-analysis steroids.

and the treatment group at 3 months. However, no significant difference in function was identified between these 2 groups at one-month or 3 months.

Active-controlled trials comprising 793 patients were evaluated, with 7 of 9 trials performed under fluoroscopic guidance (76,77,80,81,93,94,97). At the 3-month follow-up, a significant difference between

the local anesthetic group and the steroid group was found. The results were in favor of the steroid group. Single-arm meta-analysis showed the effectiveness of local anesthetic alone or a combination of local anesthetic and steroids. Functional status assessment showed no significant difference between local anesthetic alone versus steroids, but single-arm analysis

showed significant improvement from baseline to the 3-month follow-up. At the 6-month follow-up utilizing conventional meta-analysis of 4 trials (76,77,80,81) with 429 patients there was no significant difference using local anesthetic alone versus local anesthetic plus steroids, whereas the single-arm analysis showed significant improvement with either local anesthetic alone or local anesthetic plus steroids. Functional status assessment with conventional analysis showed no significant difference using local anesthetic alone versus local anesthetic plus steroids. However, there was significant improvement from baseline to 6-month follow-up in both local anesthetic and local anesthetic plus steroid groups. The results of a 12-month follow-up showed no significant difference between the local anesthetic group versus the local anesthetic plus steroids group. Single-arm analysis showed significant improvement from baseline to 12-month follow-up in both local anesthetic and local anesthetic plus steroid groups. Functional status assessment showed lack of significant difference between groups with dual-arm analysis, but a significant improvement with single-arm analysis from baseline to 12-month follow-up.

The evidence is Level I, or strong evidence, for epidural injections producing pain relief at one-month based on placebo-controlled trials. However, there was no significant difference in functional status. There was Level II, or moderate evidence, of pain relief at the 3-month follow-up with borderline significant difference using dual-arm analysis, and significant improvement compared to baseline with single-arm analysis. At 6 months and 12 months, there was no data available for placebo-controlled trials. Based on active controlled trials, there was Level I to II evidence of epidural injections with local anesthetic alone or local anesthetic plus steroids. The combined evidence based on placebo controlled and active controlled trials is Level I, or strong evidence, for pain relief and functional improvement at one and 3 months, and Level II, or moderate evidence, at 6 and 12 months.

Potential Systematic Bias

Potential systematic bias was evaluated using the selection criteria, interpretation, and estimation of effect.

Bias in Inclusion and Exclusion Criteria

Cochrane review was associated with significant bias in both inclusion and exclusion criteria, because it did not take into consideration common standards

of practice such as fluoroscopic image guidance as the standard of care and selection criteria for chronic spinal pain. In addition, Oliveira et al (27,28) excluded 8 trials (100,101,103,104,109-111,115), whereas the same trials were included by Chou et al in the AHRQ review (32). Many of the included studies had a lack of significant data beyond 3 months. In a comparative systematic review and meta-analysis of the trials from Cochrane review, Manchikanti et al (29) utilized a total of 21 image-guided RCTs with at least 6 months of follow-up. However, only 6 of the 25 trials from the Cochrane review met the same inclusion criteria.

Bias in Selecting Studies

Oliveira et al (27,28) have shown significant bias in their study selection by excluding many relevant studies, even though some of them were performed under fluoroscopic guidance and met all other types of criteria.

Bias in Allocating the Type of Studies

Oliveira et al (27,28) have also shown substantial bias in allocating studies into placebo controlled and active-controlled trials as has been extensively discussed in this and other manuscripts.

Bias in Interpreting the Results of the Selective Studies

The authors have shown significant bias based on personal preferences and misallocation of active-controlled trials to placebo controlled, misinterpretation of the true meaning of placebo, misinterpretation of methodologic strength, which produced misinterpretation of the results.

Wrong Estimation of Effect

The combination of the above factors has led to a wrong estimation of effect. This misinterpretation is clearly demonstrated in this manuscript showing Level I, or strong evidence, with one of the 2 RCTs (78,99) and 9 active-controlled trials based on single conventional meta-analysis showing no significant difference between placebo versus steroids or local anesthetic alone versus local anesthetic with steroids. However, significant difference were demonstrated with single-arm analysis; both local anesthetic alone and local anesthetic with steroids showed effectiveness.

DISCUSSION

Our comparative systematic review and meta-

analysis utilizing the same studies used in the Cochrane review by Oliveira et al yielded different results. Based on qualitative and quantitative evidence, separating placebo controlled trials from active control trials and those utilizing fluoroscopy performed in an appropriate setting as pragmatic trials, the evidence for epidural injections with local anesthetic and steroids at one-month follow-up is Level I, or strong evidence, for pain relief, but with no difference for functional status. At the 3-month follow-up, the evidence was Level I, or strong evidence, based on a significant difference in favor of steroids in the placebo-controlled trials and active controlled trials with conventional meta-analysis. There was a significant difference from baseline to follow-up period utilizing local anesthetic alone or local anesthetic with steroids, both showing improvement in pain as well as functional status with single-arm meta-analysis.

There was no data available at 6-month follow-up for the placebo-controlled trials. However, based on active controlled trials the evidence was Level II, or moderate evidence, for improvement in pain and functionality compared to baseline parameters utilizing a single-arm analysis.

These results contradict the results of the Cochrane review by Oliveira et al (27,28). In the Cochrane review they inappropriately converted active-controlled trials into placebo-controlled trials. Our results are in agreement with other systematic reviews (29,31,34,41,43,50-53,57-61).

The skepticism of the effectiveness of epidural injections and their clinical applications dates back to the initial systematic reviews. The debate continues long after the introduction of epidural injections for chronic low back pain. Kepes and Duncalf (54) in a 1985 review article questioned the scientific validity of epidural steroid injections. One year later Benzon (55) reviewed the same literature but produced a report with a more optimistic view in favor of epidural injections. Two systematic reviews published simultaneously 10 years later (46,47) also provided conflicting conclusions.

Of the 25 trials utilized in the Cochrane review by Oliveira et al, 16 were placebo-controlled trials and 9 were active controlled trials. Of the included studies, only 9 were performed with fluoroscopic guidance, including one caudal epidural trial (76), 2 lumbar interlaminar epidural trials (77,81), and 6 transforaminal epidural trials (78,80,93,94,97,99). Consequently, the pragmatic nature of the review was low and of limited clinical applicability. The timeline of publications for

the Cochrane review Oliveira et al was curious in that only 8 trials (76,77,79-82,95,97) were published from 2011 to 2020, 2 trials utilized a blind technique without imaging (79,82) and one utilized ultrasound guidance (95). Among the trials included in the Cochrane review, 2 were published prior to 1980 (83,84) and 5 were published from 1981 to 1990 (85-87,96,98). One could argue that much of the literature is outdated. There were also significant conflicts among their selections compared to Pinto et al (34), and Chou et al (32). The trials meeting the inclusion criteria for qualitative analysis were highly variable. At one-month follow-up, there were 6 studies (78,82,88,91,98,99) from the 16 trials with 463 patients that compared the placebo group to the caudal epidural group. These studies met the criteria for inclusion in a conventional dual-arm meta-analysis. However, only 3 studies (78,82,91) of the 16 trials with 336 patients had data for inclusion in the evaluation of functional assessment. At the 3-month follow-up, only 6 of the 16 trials placebo-controlled with 683 patients met the inclusion criteria for pain relief, and 5 of 16 placebo-controlled trials with 644 patients met the inclusion criteria for functional status assessment. Qualitative analysis, of these 16 trials was performed, with 5 (86,87,90,92,98) of these trials showing effectiveness of epidural steroid injections compared to placebo. Thus, the evidence was limited when based on placebo-controlled trials. However, with active control trials a different picture emerged. There were 9 active controlled trials, 7 of which utilized fluoroscopic guidance. At the 3-month follow-up 7 of these 9 trials with 793 patients met inclusion criteria comparing local anesthetic with the steroid group or to another steroid using dual-arm analysis. There was a significant difference between these 2 groups with steroids providing favorable results. However, with single-arm analysis the outcome was changed. Seven trials met the inclusion criteria comparing local anesthetic alone or local anesthetic with steroids. Both pain scores and functional status evaluation demonstrated improved results. At 6 months only 4 trials with 429 patients met inclusion criteria. Using conventional meta-analysis, there were no significant differences in pain or ODI scores between the groups. However, significant improvements in pain and ODI scores were obtained using single-arm analysis with baseline parameters compared to 3 months.

Lee et al (57) showed that the addition of steroids to local anesthetic or saline provided greater effectiveness compared to an injection of local anesthetic or saline without steroids. However, a recent systematic

review by Manchikanti et al (29) with the inclusion of 21 trials (76-78,80,81,94,100-115) used in the Cochrane review by Oliveira et al showed Level I, or strong evidence, for local anesthetic with steroids and Level I to II, or moderate to strong evidence, for local anesthetic alone based on multiple relevant high quality RCTs. Knezevic et al (53) in a systematic review and meta-analysis, including dual-arm and single-arm analysis, with inclusion of 15 manuscripts, showed Level II, or moderate evidence for similar improvements in both short-and long-term relief of pain and improvement in function with the epidural administration of lidocaine alone or with steroids. Mesregah et al (60) also evaluated cervical interlaminar epidural injections with or without local anesthetic with the conclusion that the addition of steroids to lidocaine was not associated with better pain and functional score outcomes compared to local anesthetic alone. Zhao et al (51) confirmed that the effectiveness of local anesthetic alone or with steroids was similar. Manchikanti et al (52) also showed epidural bupivacaine with or without steroids administered for low back and lower extremity pain is an active agent rather than a placebo with Level I, or strong evidence.

Manchikanti et al (43) also evaluated the role of sodium chloride solution as a true placebo, or an active control agent, utilizing conventional and single-arm analysis. They concluded that epidural saline and epidural saline with steroids showed effects beyond a true placebo, with strong evidence that neither epidural saline nor epidural saline with steroids are true placebos. Both are effective.

The present assessment revealed some startling facts that only one of the 6 studies of the caudal epidural and 2 of the 13 studies of interlaminar epidural included in this analysis were performed under fluoroscopic guidance, which is the standard of care based on LCDs and medical policies. Of these 3 studies, 2 of them were performed by the same group of authors (76,77) and another study (81) was performed utilizing the same methodology as the other 2 studies (76,77). In addition, these are active-controlled trials and there were no placebo-controlled trials performed under fluoroscopic guidance. Until after 2000, there were no fluoroscopic guided studies. From 2001 to 2010, only the fluoroscopic studies were related to transforaminal. Even from 2011 to 2020, there continue to be 2 of the 8 studies were performed without imaging. Further, only 3 studies performed under fluoroscopic guidance with one caudal and 2 interlaminar were active-controlled

trials as described above. The evidence also showed significant discrepancy in assessment patterns utilizing different instruments with widely used Cochrane review and a specific instrument developed for interventional techniques, IPM-QRB. There was agreement between Cochrane review scoring and IPM-QRB scoring in 11 of 25 trials and IPM-QRB scoring was shown at a lower grading than Cochrane review criteria in 14 trials. Interestingly enough, there was lack of clinical relevance and pragmatism in 16 of the 25 trials. Grade assessment also correlated with pragmatism to a significant extent studied with clinical relevance and pragmatism showing medium to high GRADE for clinically relevant studies and majority of the studies which were not relevant showed low to medium GRADE. Further, this assessment also showed that there was potential systematic bias with inclusion and exclusion criteria, in selection of the studies, allocation of the type of studies, in the results of the selective studies, and, finally, wrong estimation of effect.

The issues described herein highlight difficulties in performing systematic reviews. Further, they also reveal issues related to the primary studies.

Multiple guidelines and systematic reviews published in recent years have shown often incomplete information (27,28,120-124). These issues range from misinformation on contacting the authors (120), inclusion of all interventional pain management societies (121,122), and multiple issues related to evidence synthesis. In fact, Cohen, one of the authors of the manuscript by Oliveira et al (27,28) has written extensively in favor of epidural steroid injections while Oliveira et al shows lack of evidence (125,126). The practice guidelines published by the American College of Occupational and Environmental Medicine (ACOEM) (123) basically lack effectiveness of almost all interventional techniques. These guidelines elicited a strong response from the Spine Interventional Society (SIS), formerly known as International Spine Intervention Society (ISIS) (127). They described in their letter that the society has more than 3,000 physicians dedicated to the development and promotion of the highest standards for the practice of interventional pain procedures and the published literature from their society members represents the seminal references upon which interventions are developed. Further, they also emphasized that the organization has a strong record of working to eliminate fraudulent, unproven, and inappropriate procedures. However, there was no evidence or references provided to these assertions. They justifiably described various

issues related to the development of the guidelines. They received a professional reply from the panel (128) explaining the methodology and conclusions. SIS members continued to criticize the guidelines quoting the seminal manuscripts, which included Ghahreman et al (99), ISIS practice guidelines (129), along with multiple articles published by their membership. To the letter by Sayeed et al (130), Carragee et al (131) responded on behalf of the panel, which shed light on multiple issues, including the previous ISIS practice guidelines (129), lack of peer review, and nonavailability. They specifically criticized Ghahreman et al's publication results showing positive results only in 54% of the patients receiving transforaminal steroids. Further, it is also important to note that in this study, while transforaminal injection of local anesthetic was effective only in 7%, transforaminal injection of saline was effective in 19% and intramuscular saline was effective in 13%, providing a paradoxical response with no placebo effect noted with local anesthetic. This is a concerning factor. Similar to the above criticism, Oliveira et al (27,28) utilized a study by Cohen et al (97) assessing the transforaminal etanercept in subacute sciatica at one month follow up with 2 injections in a small number of patients. Their limitations included, as per the authors, short-term follow-up, small sample size, and a possibly subtherapeutic dose of etanercept. Above all, etanercept is not available in the United States. It is contraindicated to use any type of spinal injections. Thus, the guidelines developed on such evidence elicit numerous questions about a multitude of organizations, including the pain management organizations with their existent bias, practice variations, and, finally, academic superiority.

CONCLUSION

A comparative systematic review and meta-analysis of the Cochrane review (29) utilizing the same studies as the Oliveira et al reviews (27,28), but with appropriate criteria separating placebo-controlled trials from active-controlled trials, yielded different results. Our review, based on the evidence derived from placebo-controlled trials and active controlled trials, showed that the evidence is Level I, or strong evidence at one and 3 months and Level II, or moderate evidence, at 6 and 12 months. Our review once again emphasizes the importance of the allocation of studies to placebo-control and active-control groups, using standards of care where only those studies performed under fluoroscopic guidance are included.

Author Contributions

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

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REFERENCES

- Clarke M, Chalmers I. Reflections on the history of systematic reviews. *BMJ Evid Based Med* 2018; 23:121-122.
- Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014; 383:166-175.
- Systemic Bias. Wikipedia. Accessed 06/11/2021. https://en.wikipedia.org/wiki/Systemic_bias
- Jansen S. *Bias within systematic and non-systematic literature reviews: The case of the balanced scorecard*. University of Twente, Student Theses, 2017. Accessed 06/11/2021. <http://essay.utwente.nl/73771/>
- Hartog CS, Perner A. Narrative reviews from a fraudulent author: reasons to retract. *Intensive Care Med* 2019; 45:719-721.
- Urquhart B, MacLehose H, Foxlee R. A database to record the impact of fraud and misconduct in studies included in systematic reviews. Abstracts of the Global Evidence Summit, Cape Town, South Africa. *Cochrane Database of Systematic Reviews* 2017; (9 Suppl 1).
- Marret E, Elia N, Dahl JB, et al. Susceptibility to fraud in systematic reviews: lessons from the Reuben case. *Anesthesiology* 2009; 111:1279-1189.
- Amiri AR, Kanesalingam K, Cro S, Casey AT. Does source of funding and conflict of interest influence the outcome and quality of spinal research? *Spine J* 2014; 14:308-314.
- Hammami MM, Hammami S, Al-Swayeh R, Al-Gaai E, Farah FA, De Padua SJ. Drug* placebo interaction effect may bias clinical trials interpretation: Hybrid balanced placebo and randomized placebo-controlled design. *BMC Med Res Methodol* 2016; 16:166.
- Jefferson T, Demasi M, Doshi P. Statins for primary prevention: what is the regulator's role? *BMJ Evid Based Med* 2020; 11321.
- Demasi M, Götzsche PC. Presentation of benefits and harms of antidepressants on websites: A cross-sectional study. *Int J Risk Saf Med* 2020; 31:53-65.
- Demasi M. *Cochrane – A sinking ship*. BMJ EMB Spotlight. September 16, 2018. Accessed 6/11/2021. <https://blogs.bmj.com/bmjebmspotlight/2018/09/16/cochrane-a-sinking-ship/>
- Hussain N, Brull R, Noble J, et al. Statistically significant but clinically unimportant: a systematic review and meta-analysis of the analgesic benefits of erector spinae plane block following breast cancer surgery. *Reg Anesth Pain Med* 2021; 46:3-12.
- Booth A, Papaioannou D, Sutton A. *Systematic Approaches to a Successful Literature Review*. Sage Publications Inc, London, 2012.
- Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess* 2010; 14:iii, ix-xi, 1-193.

16. Petticrew M, Roberts H. *Systematic Reviews in the Social Sciences: A Practical Guide*. Blackwell Publishing, Malden, MA, 2006.
17. Dal-Ré R, Janiaud P, Ioannidis JPA. Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? *BMC Med* 2018; 16:49.
18. Cochrane (organisation). WIKIPEDIA. Accessed 6/11/2021. [https://en.wikipedia.org/wiki/Cochrane_\(organisation\)](https://en.wikipedia.org/wiki/Cochrane_(organisation))
19. Cochrane. Launch of Cochrane US Network. Cochrane launches a new network of US institutions to promote evidence-based health care and public health. June 4, 2019. Accessed 6/11/2021. <https://www.cochrane.org/news/launch-cochrane-us-network>
20. Bijl D. Cochrane's sinking ship and conflicts of interest. *International Society of Drug Bulletins*, September 25, 2018. Accessed 6/11/2021. <https://www.isdbweb.org/publication/cochrane-sinking-ship-and-conflicts-of-interest>
21. Moynihan R. Ray Moynihan: Let's stop the burning and the bleeding at Cochrane – there's too much at stake. *The BMJ Opinion*, September 17, 2018. Accessed 6/11/2021. <https://blogs.bmj.com/bmj/2018/09/17/ray-moynihan-lets-stop-the-burning-and-the-bleeding-at-cochrane-theres-too-much-at-stake/>
22. Clark W, Bird P, Diamond T, Gonski P, GebSKI V. Cochrane vertebroplasty review misrepresented evidence for vertebroplasty with early intervention in severely affected patients. *BMJ Evid Based Med* 2020; 25:85-89.
23. Nelemans PJ, de Bie RA, de Vet HC, Sturmans F. WITHDRAWN: Injection therapy for subacute and chronic benign low-back pain. *Cochrane Database Syst Rev* 2007; 2:CD001824.
24. Nelemans PJ, de Bie RA, de Vet HC, Sturmans F. Injection therapy for subacute and chronic benign low back pain. *Cochrane Database Syst Rev* 2000; 2:CD001824.
25. Staal JB, de Bie R, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824.
26. Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low back pain: An updated Cochrane review. *Spine (Phila Pa 1976)* 2009; 34:49-59.
27. Oliveira CB, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections for lumbosacral radicular pain. *Cochrane Database Syst Rev* 2020; 4:CD013577.
28. Oliveira CB, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections for sciatica: An abridged Cochrane systematic review and meta-analysis. *Spine (Phila Pa 1976)* 2020; 45:E1405-E1415.
29. Manchikanti L, Knezevic E, Knezevic NN, et al. Epidural injections for lumbar radiculopathy or sciatica: A comparative systematic review and meta-analysis of Cochrane review. *Pain Physician* 2021; 24:E539-E554.
30. Oliveira CB, Maher CG, Koes BW, Cohen SP, Pinto RZ. Reply to the letter to the editor concerning "epidural corticosteroid injections for sciatica: A Cochrane review of epidural corticosteroid injections distorts the truth". *Spine (Phila Pa 1976)* 2021; 46:E750-E751.
31. Manchikanti L, Hirsch JA. Letter to the Editor RE: Oliveira et al. Epidural corticosteroid injections for sciatica: A Cochrane review of epidural corticosteroid injections distorts the truth. *Spine (Phila Pa 1976)* 2021; 46:E750.
32. Chou R, Hashimoto R, Friedly JL, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:373-381.
33. Pinto RZ, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections in the management of sciatica: A systematic review and meta-analysis. *Ann Intern Med* 2012; 157:865-877.
34. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural injections for lumbar radiculopathy and spinal stenosis: A comparative systematic review and meta-analysis. *Pain Physician* 2016; 19:E365-E410.
35. Sicard MA. Les injections medicamenteuse extradurales par voie saracoccygiene. *C R Seances Soc Biol Fil* 1901; 53:396-398.
36. Cathelin F: Une nouvelle voie d'injection rachidienne: méthode des injections épidurales par le procédé du canal sacre - applications à l'homme. *Compt Rend Soc de Biol* 1901; 53:452-453.
37. Pasquier NM, Leri D. Injection intra-et extradurales de cocaine a dose minime dans le traitement de la sciatique. *Bull Gen Ther* 1901; 142:196.
38. Robecchi A, Capra R. Hydrocortisone (compound F); first clinical experiments in the field of rheumatology. *Minerva Med* 1952; 98:1259-1263.
39. Lievre JA, Bloch-Mechel H, Pean G. L'hydrocortisone en injection locale. *Rev Rhum* 1953; 20:310-311.
40. Dogliotti AM. Segmental peridural anesthesia. *Am J Surg* 1933; 20:107-118.
41. Shanthanna H, Busse J, Wang L, et al. Addition of corticosteroids to local anaesthetics for chronic non-cancer pain injections: A systematic review and meta-analysis of randomised controlled trials. *Br J Anaesth* 2020; 125:779-801.
42. Manchikanti L, Knezevic NN, Navani A, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. *Pain Physician* 2021; 24:S27-S208.
43. Manchikanti L, Knezevic NN, Sanapati J, et al. Is epidural injection of sodium chloride solution a true placebo or an active control agent? A systematic review and meta-analysis. *Pain Physician* 2021; 24:41-59.
44. de Bruijn TM, de Groot IB, Miedema HS, Haumann J, Ostelo RWJG. Clinical relevance of epidural steroid injections on lumbosacral radicular syndrome-related complaints: Systematic review and meta-analysis. *Clin J Pain* 2021; 37:524-537.
45. Hopayian K, Mugford M. Conflicting conclusions from two systematic reviews of epidural steroid injections for sciatica: Which evidence should general practitioners heed? *Br J Gen Pract* 1999; 49:57-61. Erratum in: *Br J Gen Pract* 1999; 49:840.
46. Watts RW, Silagy CA. A meta-analysis on the efficacy of epidural corticosteroids in the treatment of sciatica. *Anaesth Intensive Care* 1995; 23:564-569.
47. Koes BW, Scholten RJPM, Mens JMA, Bouter LM. Efficacy of epidural steroid injections for low-back pain and sciatica: A systematic review of randomized clinical trials. *Pain* 1995; 63:279-288.
48. McQuay HJ, Moore RA, Eccleston C, Morley S, Williams AC. Systematic review of outpatient services for chronic pain control. *Health Technol Assess* 1997; 1:i-iv, 1-135.
49. Bicket MC, Gupta A, Brown CH 4th, Cohen SP. Epidural injections for spinal pain: a systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. *Anesthesiology* 2013; 119:907-931.
50. Manchikanti L, Nampiarampil DE, Manchikanti KN, et al. Comparison of the efficacy of saline, local anesthetics,

- and steroids in epidural and facet joint injections for the management of spinal pain: A systematic review of randomized controlled trials. *Surg Neurol Int* 2015; 6:S194-S235.
51. Zhao W, Wang Y, Wu J, et al. Long-term outcomes of epidurals with lidocaine with or without steroids for lumbar disc herniation and spinal stenosis: A meta-analysis. *Pain Physician* 2020; 23:365-374.
 52. Manchikanti L, Knezevic NN, Parr A, Kaye AD, Sanapati M, Hirsch JA. Does epidural bupivacaine with or without steroids provide long-term relief? A systematic review and meta-analysis. *Curr Pain Headache Rep* 2020; 24:26.
 53. Knezevic N, Manchikanti L, Urits I, et al. Lack of superiority of epidural injections with lidocaine with steroids compared to without steroids in spinal pain: A systematic review and meta-analysis. *Pain Physician* 2020; 23:S239-S270.
 54. Kepes ER, Duncalf D. Treatment of backache with spinal injections of local anesthetics, spinal and systemic steroids. *Pain* 1985; 22:33-47.
 55. Benzon HT. Epidural steroid injections for low back pain and lumbosacral radiculopathy. *Pain* 1986; 24:277-295.
 56. Bogduk N, Christophidis N, Cherry D, et al. Epidural use of steroids in the management of back pain. Report of working party on epidural use of steroids in the management of back pain. National Health and Medical Research Council Commonwealth of Australia, Canberra 1994, pp 1-76.
 57. Lee JH, Kim DH, Kim DH, et al. Comparison of clinical efficacy of epidural injection with or without steroid in lumbosacral disc herniation: A systematic review and meta-analysis. *Pain Physician* 2018; 21:449-468.
 58. Lee JH, Shin KS, Park SJ, et al. Comparison of clinical efficacy between transforaminal and interlaminar epidural injections in lumbosacral disc herniation: A systematic review and meta-analysis. *Pain Physician* 2018; 21:433-448.
 59. Lee JH, Shin KH, Bahk SJ, et al. Comparison of clinical efficacy of transforaminal and caudal epidural steroid injection in lumbar and lumbosacral disc herniation: A systematic review and meta-analysis. *Spine J* 2018; 18:2343-2353.
 60. Mesregah MK, Feng W, Huang WH, et al. Clinical effectiveness of interlaminar epidural injections of local anesthetic with or without steroids for managing chronic neck pain: A systematic review and meta-analysis. *Pain Physician* 2020; 23:335-348.
 61. Helm II S, Harmon PC, Noe C, et al. Transforaminal epidural steroid injections: A Systematic Review and meta-analysis of efficacy and safety. *Pain Physician* 2021; 24:S209-S232.
 62. Coomes EN. A comparison between epidural anaesthesia and bed rest in sciatica. *Br Med J* 1961; 1:20-24.
 63. Tachihara H, Sekiguchi M, Kikuchi S, Konno S. Do corticosteroids produce additional benefit in nerve root infiltration for lumbar disc herniation. *Spine (Phila Pa 1976)* 2008; 33:743-747.
 64. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiol Scand* 2006; 50:265-282.
 65. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology* 2000; 93:858-875.
 66. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Accessed 2/17/2021. <http://prisma-statement.org/>
 67. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Ann Intern Med* 2009; 151:W65-W94.
 68. Manchikanti L, Atluri S, Boswell MV, et al. Methodology for evidence synthesis and development of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. *Pain Physician* 2021; 24:S1-S26.
 69. Eden J, Levit L, Berg A, Morton S (eds); Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Institute of Medicine. Finding What Works in Health Care. Standards for Systematic Reviews. The National Academies Press, Washington, DC, 2011. Accessed 2/19/2021. www.nap.edu/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews
 70. Furlan AD, Malmivaara A, Chou R, et al; 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.
 71. 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.
 72. 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.
 73. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64:401-406.
 74. Ryan R, Hill S. How to GRADE the quality of the evidence. Version 3.0. December 2016. Accessed 12/2/2021. <http://cccr.cochrane.org/author-resources>
 75. Carette S, Leclaire R, Marcoux S, et al. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997; 336:1634-1640.
 76. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. Effect of fluoroscopically guided caudal epidural steroid or local anesthetic injections in the treatment of lumbar disc herniation and radiculitis: A randomized, controlled, double blind trial with a two-year follow-up. *Pain Physician* 2012; 15:273-286.
 77. Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJE. A randomized, double blind, active-control trial of the effectiveness of lumbar interlaminar epidural injections in disc herniation. *Pain Physician* 2014; 17:E61-E74.
 78. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: A randomized controlled trial. *Spine (Phila Pa 1976)* 2001; 26:1059-1067.
 79. Datta R, Upadhyay KK. A Randomized clinical trial of three different steroid agents for treatment of low backache through the caudal route. *Med J Armed Forces India* 2011; 67:25-33.
 80. Manchikanti L, Cash KA, Pampati V, Falco FJE. Transforaminal epidural injections in chronic lumbar disc herniation: A randomized, double-blind, active-control trial. *Pain Physician* 2014; 17:E489-E501.
 81. Ghai B, Kumar K, Bansal D, Dhatt SS, Kanukula R, Batra YK. Effectiveness of parasagittal interlaminar epidural local anesthetic with or without steroid in chronic lumbosacral pain: A randomized, double-blind clinical trial. *Pain Physician* 2015; 18:237-248.
 82. Nandi J, Chowdhery A. A randomized

- controlled clinical trial to determine the effectiveness of caudal epidural steroid injection in lumbosacral sciatica. *J Clin Diagn Res* 2017; 11:RC04-RC08.
83. Dilke TF, Burry HC, Grahame R. Extradural corticosteroid injection in management of lumbar nerve root compression. *Br Med J* 1973; 2:635-637.
 84. Snoek W, Weber H, Jorgensen B. Double blind evaluation of extradural methyl prednisolone for herniated lumbar discs. *Acta Orthop Scand* 1977; 48:635-641.
 85. Klenerman L, Greenwood R, Davenport HT, et al. Lumbar epidural injections in the treatment of sciatica. *Br J Rheumatol* 1984; 23:35-38.
 86. Mathews JA, Mills SB, Jenkins VM, et al. Back pain and sciatica: controlled trials of manipulation, traction, sclerosant and epidural injections. *Br J Rheumatol* 1987; 26:416-423.
 87. Ridley MG, Kingsley GH, Gibson T, et al. Outpatient lumbar epidural corticosteroid injection in the management of sciatica. *Br J Rheumatol* 1988; 27:295-299.
 88. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. *Spine (Phila Pa 1976)* 1991; 16:572-575.
 89. Rogers P, Nash T, Schiller D, et al. Epidural steroids for sciatica. *Pain Clinic* 1992; 5:67-72.
 90. Kraemer J, Ludwig J, Bickert U, et al. Lumbar epidural perineural injection: a new technique. *Eur Spine J* 1997; 6:357-361.
 91. Valat JP, Giraudeau B, Rozenberg S, et al. Epidural corticosteroid injections for sciatica: a randomised, double blind, controlled clinical trial. *Ann Rheum Dis* 2003; 62:639-643.
 92. Arden NK, Price C, Reading I, et al. A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: The WEST study. *Rheumatology (Oxford)* 2005; 44:1399-1406.
 93. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain. *Spine (Phila Pa 1976)* 2005; 30:857-862.
 94. Tafazal S, Ng L, Chaudhary N, Sell P. Corticosteroids in peri-radicular infiltration for radicular pain: A randomised double blind controlled trial: One year results and subgroup analysis. *Eur Spine J* 2009; 18:1220-1225.
 95. Iversen T, Solberg TK, Romner B, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: Multicentre, blinded, randomised controlled trial. *BMJ* 2011; 343:d5278.
 96. Cuckler JM, Bernini PA, Wiesel SW, et al. The use of epidural steroids in the treatment of lumbar radicular pain. A prospective, randomized, double-blind study. *J Bone Joint Surg Am* 1985; 67:63-66.
 97. Cohen SP, White RL, Kurihara C, et al. Epidural steroids, etanercept, or saline in subacute sciatica: a multicenter, randomized trial. *Ann Intern Med* 2012; 156:551-559.
 98. Helliwell M, Robertson JC, Ellis RM. Outpatient treatment of low back pain and sciatica by a single extradural corticosteroid injection. *Br J Clin Pract* 1985; 39:228-231.
 99. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010; 11:1149-1168.
 100. Riew D, Park JB, Cho YS, et al. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006; 88:1722-1725.
 101. Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain: A prospective, randomized, controlled, double-blind study. *J Bone Joint Surg Am* 2000; 82:1589-1593.
 102. Murakibhavi VG, Khemka AG. Caudal epidural steroid injection: A randomized controlled trial. *Evid Based Spine Care J* 2011; 2:19-26.
 103. Ökmen K, Ökmen BM. The efficacy of interlaminar epidural steroid administration in multilevel intervertebral disc disease with chronic low back pain: A randomized, blinded, prospective study. *Spine J* 2017; 17:168-174.
 104. Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007; 104:1217-1222.
 105. Dashfield A, Taylor M, Cleaver J, Farrow D. Comparison of caudal steroid epidural with targeted steroid placement during spinal endoscopy for chronic sciatica: A prospective, randomized, double-blind trial. *Br J Anaesth* 2005; 94:514-519.
 106. Kamble PC, Sharma A, Singh V, Natraj B, Devani D, Khapane V. Outcome of single level disc prolapse treated with transforaminal steroid versus epidural steroid versus caudal steroids. *Eur Spine J* 2016; 25:217-221.
 107. Pandey RA. Efficacy of epidural steroid injection in management of lumbar prolapsed intervertebral disc: A comparison of caudal, transforaminal and interlaminar routes. *J Clin Diagn Res* 2016; 10:RC05-11.
 108. Singh S, Kumar S, Chahal G, Verma R. Selective nerve root blocks vs. caudal epidural injection for single level prolapsed lumbar intervertebral disc - A prospective randomized study. *J Clin Orthop Trauma* 2017; 8:142-147.
 109. Rados I, Sakic K, Fingler M, Kapural L. Efficacy of interlaminar vs transforaminal epidural steroid injection for the treatment of chronic unilateral radicular pain: Prospective, randomized study. *Pain Med* 2011; 12:1316-1321.
 110. Ghai B, Bansal D, Kay JP, Vadaje KS, Wig J. Transforaminal versus parasagittal interlaminar epidural steroid injection in low back pain with radicular pain: A randomized, double-blind, active-control trial. *Pain Physician* 2014; 17:277-290.
 111. Candido KD, Rana MV, Sauer R, et al. Concordant pressure paresthesia during interlaminar lumbar epidural steroid injections correlates with pain relief in patients with unilateral radicular pain. *Pain Physician* 2013; 16:497-511.
 112. Amr YM. Effect of addition of epidural ketamine to steroid in lumbar radiculitis: One-year follow-up. *Pain Physician* 2011; 14:475-481.
 113. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. *Spine (Phila Pa 1976)* 2002; 27:11-16.
 114. Jeong HS, Lee JW, Kim SH, Myung JS, Kim JH, Kang HS. Effectiveness of transforaminal epidural steroid injection by using a preganglionic approach: A prospective randomized controlled study. *Radiology* 2007; 245:584-590.
 115. Kennedy D, Plataras C, Casey E, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: A prospective, randomized, double-blind trial. *Pain Med* 2014; 15:548-555.
 116. Price C, Arden N, Coglán L, Rogers

- P. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technol Assess* 2005; 9:1-58.
117. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. A randomized, controlled, double-blind trial of fluoroscopic caudal epidural injections in the treatment of lumbar disc herniation and radiculitis. *Spine (Phila Pa 1976)* 2011; 36:1897-1905.
118. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of the effectiveness of lumbar interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:343-355.
119. Swerdlow M, Sayle-Creer WS. A study of extradural medication in the relief of the lumbosciatic syndrome. *Anaesthesia* 1970; 25:341-345.
120. Manchikanti L, Soin A, Boswell MV, Kaye AD, Sanapati M, Hirsch JA. Effectiveness of percutaneous adhesiolysis in post lumbar surgery syndrome: A systematic analysis of findings of systematic reviews. *Pain Physician* 2019; 22:307-322.
121. Cohen SP, Bhaskar A, Bhatia A, et al. Consensus practice guidelines on interventions for lumbar facet joint pain from a multispecialty, international working group. *Reg Anesth Pain Med* 2020; 45:424-467.
122. Hurley RW, Adams MCB, Barad M, et al. Consensus practice guidelines on interventions for cervical spine (facet) joint pain from a multispecialty international working group. *Reg Anesth Pain Med* 2022; 47:3-59.
123. Hegmann KT, Travis R, Andersson GBJ, et al. Invasive treatments for low back disorders. *J Occup Environ Med* 2021; 63:e215-e241.
124. Doshi TL, Cohen SP. Cracks in the case against epidural steroids: Examining the evidence for vertebral fracture risk. *Pain Med* 2018; 19:417-418.
125. de Bruijn TM, de Groot IB, Miedema HS, Haumann J, Ostelo RWJG. Authors' response to Letter to the Editor of Van Boxem et al Titled "Systematic Review on Epidural Steroid Injections: Quo Vadis?". *Clin J Pain* 2022; 38:308-309.
126. Cohen SP, Greuber E, Vought K, Lissin D. Safety of epidural steroid injections for lumbosacral radicular pain: Unmet medical need. *Clin J Pain* 2021; 37:707-717.
127. Sayeed Y, Chang RG, Chhatre A, et al; Health Policy Division of the Spine Intervention Society. Response to: Invasive treatments for low back disorders and the ACOEM practice guidelines. *J Occup Environ Med* 2022; 64:e81-e83.
128. Travis R, Andersson GBJ, Belcourt RM, et al. Reply to Sayeed et al. *J Occup Environ Med* 2022; 64:e84-e86.
129. Bogduk N, (ed). Practice Guidelines for Spinal Diagnostic and Treatment Procedures, 2nd edn. International Spine Intervention Society, San Francisco, 2013.
130. Sayeed Y, Chang RG, Chhatre A, et al. Response to: Reply to Sayeed et al. *J Occup Environ Med* 2022; 64:e389-e390.
131. Carragee EJ, Andersson GBJ, Belcourt RM, et al. Reply to Sayeed et al's Reply to Reply. *J Occup Environ Med* 2022; 64:e391-e392.

Appendix Table 1. *Imaging guidance for epidural steroid manuscripts included in Cochrane review.*

	BLIND	ULTRASOUND	FLUOROSCOPY
CAUDAL			
Manchikanti et al, 2012 (76)			X
Datta & Upadhyay, 2011 (79)	X		
Mathews et al, 1987 (86)	X		
Bush & Hillier, 1991 (88)	X		
Iversen et al, 2011 (95)		X	
Nandi & Chowdhery, 2017 (82)	X		
INTERLAMINAR			
Manchikanti et al, 2014 (77)			X
Ghai et al, 2015 (81)			X
Dilke et al, 1973 (83)	X		
Snoek et al, 1977 (84)	X		
Klenerman et al, 1984 (85)	X		
Ridley et al, 1988 (87)	X		
Rogers et al, 1992 (89)	X		
Kraemer et al, 1997 (90)	X		
Valat et al, 2003 (91)	X		
Arden et al, 2005 (92)	X		
Cuckler et al, 1985 (96)	X		
Carette et al, 1997 (75)	X		
Helliwell et al, 1985 (98)	X		
TRANSFORAMINAL			
Ghahreman et al, 2010 (99)			X
Karppinen et al, 2001 (78)			X
Manchikanti et al, 2014 (80)			X
Tafazal et al, 2009 (94)			X
Ng et al, 2005 (93)			X
Cohen et al, 2012 (97)			X

Appendix Table 2. *Timeline of publication of randomized controlled trials included in Cochrane review manuscript of epidural steroids.*

Before 1980 = 2	IMAGING
Dilke et al (83), 1973	Blind
Snoek et al (84), 1977	Blind
1981-1990 = 5	
Klenerman et al (85), 1984	Blind
Cuckler et al (96), 1985	Blind
Helliwell et al (98), 1985	Blind
Mathews et al (86), 1987	Blind
Ridley et al (87), 1988	Blind
1991-2000 = 4	
Bush & Hillier (88), 1991	Blind
Rogers et al (89), 1992	Blind
Kraemer et al (90), 1997	Blind
Carette et al (75), 1997	Blind
2001-2010 = 6	
Karppinen et al (78), 2001	Fluoroscopy
Valat et al (91), 2003	Blind
Arden et al (92), 2005	Blind
Ng et al (93), 2005	Fluoroscopy
Tafazal et al (94), 2009	Fluoroscopy
Ghahreman et al (99), 2010	Fluoroscopy
2011 -2020 = 8	
Datta & Upadhyay (79), 2011	Blind
Iversen et al (95), 2011	Ultrasound
Manchikanti et al (76), 2012	Fluoroscopy
Cohen et al (97), 2012	Fluoroscopy
Manchikanti et al (80), 2014	Fluoroscopy
Manchikanti et al (77), 2014	Fluoroscopy
Ghai et al (81), 2015	Fluoroscopy
Nandi & Chowdhery (82), 2017	Blind

Appendix Table 3. Listing of the trials included in 4 systematic reviews.

Trial	Manchikanti et al (29)	Oliveira (27,28)	Pinto et al (33)	Chou et al (32)
Manchikanti et al, 2012 (76)	X	X		X
Manchikanti et al, 2011 (117)			X	
Ackerman & Ahmad, 2007 (104)	X			X
Dashfield et al, 2005 (105)	X			
Murakibhavi & Khemka, 2011 (102)	X			
Kamble et al, 2016 (106)	X			
Pandey, 2016 (107)	X			
Singh et al, 2017 (108)	X			
Manchikanti et al, 2014 (77)	X	X		X
Manchikanti et al, 2010 (118)			X	
Ghai et al, 2015 (81)	X	X		X
Ökmen & Ökmen 2017 (103)	X			
Rados et al, 2011 (109)	X			X
Ghai et al, 2014 (110)	X			X
Candido et al, 2013 (111)	X			X
Amr, 2011 (112)	X			
Karppinen et al, 2001 (78)	X	X	X	X
Manchikanti et al, 2014 (80)	X	X		X
Riew et al, 2000 & 2006 (100,101)	X		X	X
Tafazal et al, 2009 (94)	X	X	X	X
Vad et al, 2002 (113)	X		X	
Jeong et al, 2007 (114)	X			
Kennedy et al, 2014 (115)	X			X
Datta & Upadhyay, 2011 (79)		X		X
Dilke et al, 1973 (83)		X	X	X
Snoek et al, 1977 (84)		X	X	X
Klenerman et al, 1984 (85)		X	X	X
Mathews et al, 1987 (86)		X	X	X
Ridley et al, 1988 (87)		X	X	X
Bush & Hillier, 1991 (88)		X	X	X
Rogers et al, 1992 (89)		X	X	X
Kraemer et al, 1997 (90)		X	X	X
Valat et al, 2003 (91)		X	X	X
Arden et al, 2005 (92)		X	X	X
Price et al, 2005 (116)			X	X
Ng et al, 2005 (93)		X	X	X
Iversen et al, 2011 (95)		X	X	X
Cuckler et al, 1985 (96)		X	X	X
Carette et al, 1997 (75)		X	X	X
Cohen et al, 2012 (97)		X	X	X
Helliwell et al, 1985 (98)		X	X	X
Ghahreman et al, 2010 (99)		X	X	X
Nandi & Chowdhery, 2017 (82)		X		
Swerdlow & Sayle-Creer, 1970 (119)			X	

Appendix Table 4. *Methodological quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing Cochrane review criteria.*

	Manchikanti et al (76)	Manchikanti et al (77)	Ghai et al (81)	Karppinen et al (78)	Manchikanti et al (80)	Tafazal et al (94)	Datta & Upadhyay (79)	Dilke et al (83)
Randomization adequate	Y	Y	Y	Y	Y	Y	U	N
Concealed treatment allocation	Y	Y	Y	Y	Y	Y	U	N
Patient blinded	Y	Y	Y	Y	Y	Y	U	Y
Care provider blinded	Y	Y	N	Y	Y	Y	U	N
Outcome assessor blinded	N	N	N	Y	N	N	U	Y
Drop-out rate described	Y	Y	N	Y	Y	Y	N	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	N	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	U	Y
Groups similar at baseline regarding most important prognostic indicators	Y	N	Y	Y	N	Y	Y	N
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	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 not likely	Y	Y	Y	Y	Y	Y	Y	Y
Score	12/13	11/13	10/13	13/13	11/13	11/13	6/13	9/13

Y = Yes; N = No; U = Unclear

Appendix Table 4 (continued). *Methodological quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing Cochrane review criteria.*

	Snoek et al (84)	Klenerman et al (85)	Mathews et al (86)	Ridley et al (87)	Bush & Hillier (88)	Rogers et al (89)	Kraemer et al (90)	Valat et al (91)
Randomization adequate	Y	Y	Y	Y	Y	Y	U	Y
Concealed treatment allocation	U	Y	Y	Y	Y	Y	U	Y
Patient blinded	Y	Y	U	Y	Y	Y	Y	Y
Care provider blinded	N	N	N	N	N	N	N	N
Outcome assessor blinded	U	Y	N	U	Y	Y	U	Y
Drop-out rate described	Y	Y	Y	N	Y	Y	N	Y
All randomized participants analyzed in the group	Y	Y	Y	N	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	N	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	N	Y	Y	Y
Co-interventions avoided or similar	U	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	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 not likely	Y	Y	Y	Y	Y	Y	N	Y
Score	9/13	12/13	10/13	9/13	11/13	12/13	6/13	12/13

Y = Yes; N = No; U = Unclear

Appendix Table 4 (continued). *Methodological quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing Cochrane review criteria.*

	Arden et al (92)	Ng et al (93)	Iversen et al (95)	Cuckler et al (96)	Carette et al (75)	Cohen et al (97)	Helliwell et al (98)
Randomization adequate	Y	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	Y	Y	Y	Y	Y
Patient blinded	Y	Y	U	Y	Y	Y	Y
Care provider blinded	N	N	U	U	N	Y	N
Outcome assessor blinded	Y	Y	U	U	Y	Y	Y
Drop-out rate described	Y	Y	N	U	Y	Y	Y
All randomized participants analyzed in the group	N	Y	N	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	N	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	N	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	N	Y	Y	Y	Y
Compliance acceptable in all group	N	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	Y	Y	Y	Y	Y	Y	Y
Score	10/13	12/13	5/13	10/13	12/13	13/13	12/13

Y = Yes; N = No; U = Unclear

Appendix Table 4 (continued). *Methodological quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing Cochrane review criteria.*

	Ghahreman et al (99)	Nandi & Chowdhery (82)
Randomization adequate	Y	Y
Concealed treatment allocation	Y	Y
Patient blinded	Y	Y
Care provider blinded	Y	N
Outcome assessor blinded	Y	Y
Drop-out rate described	Y	Y
All randomized participants analyzed in the group	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y
Groups similar at baseline regarding most important prognostic indicators	N	Y
Co-interventions avoided or similar	Y	Y
Compliance acceptable in all group	Y	Y
Time of outcome assessment in all groups similar	Y	Y
Are other sources of potential bias not likely	Y	Y
Score	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 (70).

Appendix Table 5. *Methodologic quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing IPM – QRB.*

	Manchikanti et al (76)	Manchikanti et al (77)	Ghai et al (81)	Karppinen et al (78)	Manchikanti et al (80)	Tafazal et al (94)	Datta & Upadhyay (79)	Dilke et al (83)
I. TRIAL DESIGN AND GUIDANCE REPORTING								
1. CONSORT or SPIRIT	3	3	3	2	3	2	0	0
II. DESIGN FACTORS								
2. Type and Design of Trial	2	2	2	2	2	2	2	3
3. Setting/Physician	2	2	2	1	2	1	2	2
4. Imaging	3	3	3	3	3	3	0	0
5. Sample Size	3	3	2	3	3	1	2	3
6. Statistical Methodology	1	1	1	1	1	1	1	1
III. PATIENT FACTORS								
7. Inclusiveness of Population	2	2	2	2	2	1	1	2
8. Duration of Pain	2	2	1	0	2	1	1	0
9. Previous Treatments	2	2	1	0	2	2	1	0

Appendix Table 5 (continued). *Methodologic quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing IPM – QRB.*

	Snoek et al (84)	Klenerman et al (85)	Mathews et al (86)	Ridley et al (87)	Bush & Hillier (88)	Rogers et al (89)	Kraemer et al (90)	Valat et al (91)
4. Imaging	0	0	0	0	0	0	0	0
5. Sample Size	1	0	0	0	0	0	0	2
6. Statistical Methodology	1	1	0	0	1	0	0	1
III. PATIENT FACTORS								
7. Inclusiveness of Population	0	0	1	0	1	0	0	2
8. Duration of Pain	0	0	1	0	0	1	1	0
9. Previous Treatments	0	1	1	1	1	1	1	0
10. Duration of Follow-up with Appropriate Interventions	0	0	0	0	1	1	1	0
IV. OUTCOMES								
11. Outcomes Assessment Criteria for Significant Improvement	0	0	0	0	0	0	0	2
12. Analysis of all Randomized Participants in the Groups	1	1	1	0	1	0	0	2
13. Description of Drop Out Rate	1	1	1	1	1	1	1	2
14. Similarity of Groups at Baseline for Important Prognostic Indicators	1	1	1	1	0	0	0	2
15. Role of Co-Interventions	0	1	1	1	1	1	0	0
V. RANDOMIZATION								
16. Method of Randomization	1	1	1	1	1	1	1	2
VI. ALLOCATION CONCEALMENT								
17. Concealed Treatment Allocation	0	1	1	1	1	1	0	2
VII. BLINDING								
18. Patient Blinding	1	1	0	1	1	1	1	1
19. Care Provider Blinding	0	0	0	0	0	0	0	0
20. Outcome Assessor Blinding	0	1	0	0	1	1	0	1
VIII. CONFLICTS OF INTEREST								
21. Funding and Sponsorship	0	0	0	0	0	0	0	2
22. Conflicts of Interest	0	0	0	0	0	0	0	3
TOTAL	10/48	13/48	12/48	10/48	14/48	12/48	7/48	28/48

Appendix Table 5 (continued). *Methodologic quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing IPM – QRB.*

	Arden et al (92)	Ng et al (93)	Iversen et al (95)	Cuckler et al (96)	Carette et al (75)	Cohen et al (97)	Helliwell et al (98)	Ghahreman et al (99)	Nandi & Chowdhery (82)
I. TRIAL DESIGN AND GUIDANCE REPORTING									
1.	3	2	2	0	1	3	1	3	0
II. DESIGN FACTORS									
2.	3	2	3	2	2	3	2	2	2
3.	1	1	1	1	2	2	2	2	2
4.	0	3	0	0	0	3	0	3	0
5.	3	2	2	0	3	2	1	2	1
6.	1	1	1	1	1	1	1	1	1
III. PATIENT FACTORS									
7.	2	2	1	0	2	1	1	2	1
8.	1	2	1	0	0	1	1	1	0
9.	0	2	1	0	0	1	1	0	1
10.	0	1	1	0	0	1	0	0	1
IV. OUTCOMES									
11.	2	1	2	0	0	2	1	4	1
12.	1	2	1	1	2	2	1	2	1
13.	2	2	1	1	1	2	1	2	1
14.	2	2	0	1	1	1	1	1	1
15.	0	1	0	1	0	1	1	0	1
V. RANDOMIZATION									
16.	2	2	2	2	2	2	0	2	1
VI. ALLOCATION CONCEALMENT									
17.	2	2	2	2	2	2	1	2	1
VII. BLINDING									
18.	1	1	0	1	1	1	1	1	1
19.	0	1	0	0	0	1	0	1	0
20.	1	0	1	0	1	1	1	1	1

Appendix Table 5 (continued). *Methodologic quality assessment of randomized trials of epidural injections in lumbar radiculopathy or sciatica utilizing IPM – QRB.*

	Arden et al (92)	Ng et al (93)	Iversen et al (95)	Cuckler et al (96)	Carette et al (75)	Cohen et al (97)	Helliwell et al (98)	Ghahreman et al (99)	Nandi & Chowdhery (82)
VIII. CONFLICTS OF INTEREST									
21.	Funding and Sponsorship	3	2	2	3	2	0	2	0
22.	Conflicts of Interest	1	0	0	3	3	0	3	2
TOTAL		31/48	24/48	13/48	27/48	38/48	18/48	37/48	20/48

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 (71).

Appendix Table 6. *Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.*

Study	Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function					Comment(s)
				1 month	3 mos.	6 mos.	12 mos.		
Carette et al, 1997 (75) 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 to 3	VAS and ODI Follow-up: 3 weeks, 6 weeks, 3 months	At 6 weeks the only significant difference was the improvement in leg pain in the methylprednisolone group and after 3 months there were no significant differences between the groups. NSD	NA	NA	NA	NA	<ul style="list-style-type: none"> Methylprednisolone with epidural saline was superior in the short-term. Overall, there was no significant difference between sodium chloride solution alone or sodium chloride solution with steroids. Methylprednisolone with saline or saline alone were equally ineffective except in short-term 	
Karppinen et al, 2001 (78) 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: 12 months with only initial procedures	NA NA	A significant 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.	Lack of effectiveness of steroid with bupivacaine	<ul style="list-style-type: none"> An ineffective or inappropriate placebo design, without applicable results. Overall saline appears to have been superior at 3 months and 6 months, but no significant difference at one 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. 	

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function				Comment(s)
			1 month	3 mos.	6 mos.	12 mos.	
Nandi & Chowdhery, 2017 (82) RA, PC, DB Sciatica Quality Scores: Cochrane = 12/13 IPM-QRB = 20/48	Placebo group: 46 patients receiving 20 mL of isotonic saline with caudal approach Treatment group: 47 patients: Caudal epidural with 20 mL mixture of isotonic saline with 80 mg of Depo-Medrol	Success or failure of the treatment based on participant perceived degree of overall improvement or deterioration. VAS, SLR, Schober Test, ODI, RMDQ Outcomes were assessed at baseline, 4 weeks, and 12 weeks	Success rate in steroid group was 68% and sodium chloride solution group was 17% with significant difference in favor of steroid group. P	Success rate in placebo group: 52% Steroid group: 48% Failure: Placebo 34% Steroid group 36% VAS	NA	NA	<ul style="list-style-type: none"> This is a negative randomized controlled trial of caudal epidural injections with high volume sodium chloride solution or sodium chloride solution with steroids with short-term follow-up. While the primary outcome was significantly better at 4 weeks with 17% in the placebo group and 68% in the steroid group considered as successful. 48% of patients in the placebo group and 60% of the patients in the steroid were considered as success. Overall, it appears that steroids may be somewhat better.
Dilke et al, 1973 (83) 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	NA	Interspinous sodium chloride injection of 1 mL: Steroids: Clear relief = 32% Some relief = 10% Placebo: Clear relief = 8% Some relief = 14% Positive	NA	NA	<ul style="list-style-type: none"> This is a positive placebo-controlled trial A true placebo control trial with interspinous injection of saline with significant difference at 3 months
Snoek et al, 1977 (84) RA, PC, B Disc herniation Quality Scores: Cochrane = 9/13 IPM-QRB = 10/48	Total: 51 Placebo: 24 Injection of 2 mL of normal saline into lumbar epidural space Treatment: 27 Injection of 2 mL (80 mg methylprednisolone) into epidural space Number of injections: 1	Pain relief, analgesic consumption, patients subjective improvement, avoidance of surgery	No change NA	Early results showed improvement with steroid; however, there was no statistically significant difference in any of the aspects.	NA	NA	<ul style="list-style-type: none"> This is shown as a negative study. This study was excluded in many reviews in the past. The authors evaluated a single epidural injection in acute and subacute radiculitis. The inclusion criteria were patients with lumbar root compression syndrome of 12 days' to 36 weeks' duration, thus including a large number of acute and subacute pain patients, in a fairly small sample. No local anesthetic was used.

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function					Comment(s)
			1 month	3 mos.	6 mos.	12 mos.		
<p>Mathews et al, 1987 (86) RA, DB, PC Sciatica Quality Scores: Cochrane = 10/13 IPM-QRB = 12/48</p>	<p>Total = 57 Placebo control group: 34 2 mL of lidocaine over the sacral hiatus or onto a tender spot Treatment group: 23 Caudal epidural injection of 20 mL of 0.125 bupivacaine and 2 mL 80 mg of methylprednisolone acetate at 2-week intervals Number of procedures: 1 to 3 at 2-week intervals</p>	<p>NRS & VAS, definite improvement, recovered and not recovered</p>	<p>The results showed 67% of epidural steroid group improved compared to 56% of placebo group, with the difference not reaching statistical significance.</p>	<p>The results showed 61% of epidural steroid group improved compared to 50% of placebo group, with the difference not reaching statistical significance.</p>	NA	NA	<ul style="list-style-type: none"> The study by Mathews et al is very small, performed in 1987. It is also a complicated design with multiple groups with sclerosant injection, manipulation, traction, and, finally, epidural injection groups. Inadequate outcomes were reported. There was no significant difference between injection over sacral hiatus and steroid epidural injection. A negative study 	
<p>Ridley et al, 1988 (87) RA, PC, B Sciatica Quality Scores: Cochrane = 9/13 IPM-QRB = 10/48</p>	<p>Total: 35 Placebo group: 16 Interspinous ligament injection of 2 mL of normal saline Treatment group: 19 Epidural injection of 10 mL of normal saline with 2 mL of methylprednisolone. Depo preparation 80 mg Injection was repeated weekly for 3 times if there was no improvement Patients were allowed to cross over if no improvement</p>	<p>Pain relief by VAS, SLR, walking</p>	<p>Steroid group showed significant improvements in both rest, walking, and pain</p>	<p>Steroid group showed significant improvements in both rest, walking, and pain</p>	<p>There was no significant improvement noted at 24 weeks.</p>	NA	<ul style="list-style-type: none"> This trial was excluded in multiple previous reviews. Overall, it is a small study with inclusion of acute disc herniation and non-blinded follow-up. There was no local anesthetic injected with steroids. Even then, steroids showed significant improvement at 12 weeks, which is appropriate improvement for 2 procedures given one week apart. 	

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function					Comment(s)
			1 month	3 mos.	6 mos.	12 mos.		
<p>Bush & Hillier, 1991 (88)</p> <p>DB, PC, B</p> <p>Sciatica</p> <p>Quality Scores: Cochrane = 11/13 IPM-QRB = 14/48</p>	<p>Total = 54</p> <p>Placebo group: 11</p> <p>Caudal injection of 20 mL of sodium chloride solution</p> <p>Treatment group: 12</p> <p>25 mL containing 80 mg of triamcinolone acetate in normal saline with 0.5% procaine hydrochloride</p> <p>Number of procedures: 2 at 2 weeks apart</p>	<p>VAS, SLR, lifestyle improvement</p> <p>At 4 weeks, there was no significant changes in the objective or subjective measures in the placebo group. However, actively treated group demonstrated significant improvement in all aspects with reduction in pain (P=0.02) while lifestyle significantly improved (P=0.02). Physical improvement measured by change in SLR was significant.</p>	<p>At 4 weeks, VAS decreased from a baseline average of 38.5 to 16 in treatment group and 49.2 to 45 in placebo group.</p> <p>SLR angle in placebo increased from 63.2 to 65.</p> <p>In active group, it increased from 43.8 to 73.3.</p> <p>Statistically significant difference between the 2 groups in SLR ability, with less mobility impairment in the placebo group.</p> <p>P</p>	<p>NA</p>	<p>NA</p>	<p>In placebo group, VAS decreased from 49.2 to 29.6 and SLR from 63.2 to 74.1.</p> <p>In treatment group, VAS decreased from 38.5 to 14.2. SLR increased from 43.8 to 80.3.</p> <p>P</p>	<ul style="list-style-type: none"> A positive study with only 2 injections showing significant improvement with steroids combined with local anesthetic. The study baseline parameters were significantly different with SLR with 43.8 in the control group compared to 63.2 in placebo group, which may indicate that more severe patients were included in treatment group. Very small study with inability to assess statistical significance. At 4 weeks, there was no significant changes in the objective or subjective measures in the placebo group. However, actively treated group demonstrated significant improvement in all aspects with reduction in pain (P=0.02) while lifestyle significantly improved (P=0.02). Physical improvement measured by change in SLR was significant. Even though data looks superior with steroids, analysis no longer showed a significant difference for pain relief for lifestyle, even though objective assessment of SLR still showed a more significant benefit in the actively treated group (P=0.01). 	

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function					Comment(s)
			1 month	3 mos.	6 mos.	12 mos.		
Kraemer et al, 1997 (90) RA, PC, B Lumbar radiculopathy Quality Scores: Cochrane = 6/13 IPM-QRB = 7/48	Total: 136 Placebo group: 46 Paravertebral local anesthetic injection Conventional epidural injection: 40 Interlaminar epidural perineural injection: 47	VAS, SLR Good: Leg pain less than 10%, back pain less than 20%, return to same work and sports as before Fair: Leg and back pain less than 50%, return to reduced work, return to reduced sports, SLR positive Poor/Surgery: Same pain, unable to work, unable to do sports, SLR+	NA	Epidural conventional corticosteroid injection and epidural/perineural corticosteroid injection showed significantly better results than paravertebral local anesthetic injection	NA	NA	<ul style="list-style-type: none"> The study shows positive results; however, this is a very poorly conducted blind study with a small sample size, confusing with very little information in reference to the doses injected and follow-up periods. The epidural perineural technique is not an accepted technique and may be associated with high risk. Study protocol involved 3 injections in 1 week 	
Valat et al, 2003 (91) RA, PC, B Sciatica Quality Scores: Cochrane = 12/13 IPM-QRB = 28/48	Total: 85 Control group: 42 Epidural injection of 2 mL of isotonic saline Treatment group: 43 Epidural injection of 2 mL of prednisone acetate (50 mg) 3 epidural injections at 2 day intervals	VAS, SLR, Schober test, French validated version of the Dallas Pain Questionnaire, RMDQ Success or failure of the treatment at day 20 Success = recovery or marked improvement Failure = slight improvement or worse	35 days after the treatment There was marked improvement from baseline for all pain and other secondary parameters; however, there was no significant difference between the groups. NSD	NA	NA	NA	<ul style="list-style-type: none"> A small study with an extremely short follow-up period. There was no local anesthetic with steroid injected. Very small volumes for both injections. 3 epidural injections at 2-day intervals is not a standard of care or a common practice. The authors concluded that epidural steroids provided no additional improvement, even though the efficacy of isotonic saline administered epidural for sciatica cannot be excluded. 	

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function				Comment(s)
			1 month	3 mos.	6 mos.	12 mos.	
Arden et al, 2005 (92) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 31/48	Total = 228 Steroid group = 120 Placebo group = 108 Injectate: Triamcinolone and bupivacaine or normal saline into interspinous ligament Number of injections: 1	ODQ, pain relief, VAS, SF-36, 75% improvement Follow-up: 12 months with only one procedure	At 3 weeks, the ESI group demonstrated a transient benefit over the placebo group (patients achieving a 75% improvement in ODQ, 12.5 versus 3.7% with a number needed to treat of 11.4.) NSD	75% improvement 12.5% bupivacaine with triamcinolone vs. Placebo 3.7% at 3 weeks NSD	NSD	NSD	<ul style="list-style-type: none"> Lack of efficacy after 6 weeks Meaningful follow-up only 3 months 50% improvement not considered Limited procedures with appropriate response for one injection.
Iversen et al, 2011 (95) RA, PC, Ultrasound Lumbar radiculopathy Quality Scores: Cochrane = 5/13 IPM-QRB = 24/48	Sham group: 40 Subcutaneous injection of 2 mL of 0.9% saline (n=40) Caudal epidural injection of 30 mL of 0.9% sodium chloride solution (n=39) Epidural steroid group: 37 patients Injection of 40 mg of triamcinolone acetamide in 20 mL of 0.9% saline Number of injections: 2	ODI, European quality of life measure, VAS Follow-up periods of 6, 12, and 52 weeks	NA	No significant difference between the epidural injection groups and the sham group. The observed differences were not clinically important NA	NA	No significant difference between the epidural injection groups and the sham group. The observed differences were not clinically important	<ul style="list-style-type: none"> This study was designed to be multicenter and providing answers to the conversation on epidural injections. The authors provided only 2 injections 2 weeks apart and expected these to last for one year without any significant support in the literature for such long duration of steroid action. However, there were multiple differences in the baseline data among the groups, which may have influenced the results. The study was performed under ultrasound without fluoroscopic guidance – not a standard of practice in the United States. There was no local anesthetic added with steroids. The authors say there is no significant difference without showing actual P values. The authors compared outcomes and showed only the differences between sham group and saline and saline with steroids groups; however, they have not shown the outcomes in the sham group except for paracetamol intake, etc. Overall, the data is presented very poorly with negative results for steroids with sodium chloride solution without local anesthetic. Essentially, it appeared that the sham group had better improvement than either epidural saline or epidural steroid group.

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function					Comment(s)
			1 month	3 mos.	6 mos.	12 mos.		
Helliwell et al, 1985 (98) RA, B, PC Low back pain and sciatica Quality Scores: Cochrane = 12/13 IPM-QRB = 18/48	Total = 39 Control (placebo) 5 mL of normal saline of interspinous injection = 19 Treatment (steroid) 80 mg of methylprednisolone in 10 mL of normal saline = 20 Number of injections = 1	VAS, sciatic tension signs, range of motion Classification of outcomes: definite improvement or no improvement	NA	Definite improvement: Steroid group = 70% Placebo group 26%	NA	NA	NA	A small non-fluoroscopic trial conducted in 1985. Appropriately randomized and placebo-control trial. No local anesthetic was administered with steroids. Steroids showed definite improvement at 3-month follow-up.
Ghahreman et al, 2010 (99) 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 injection of 2 mL of 0.5% bupivacaine in the local anesthetic group Transforaminal local anesthetic with steroid, 40 mg per mL or 70 mg of triamcinolone Intramuscular sodium chloride solution injection 0.2 to 0.5 mL Transforaminal sodium chloride injection 2 mL Intramuscular steroids 40 mg/mL, 1.7 mL or 70 mg of triamcinolone Number of injections: 1 to 3 for 12 months	At least 50% pain relief at least 1 month after treatment, SF-36, RMDQ Follow-up: 1-3 months	At one month follow-up: Transforaminal epidural with steroids = 54% Transforaminal local anesthetic = 7% Transforaminal injection of sodium chloride solution = 19% Intramuscular steroids = 21% Intramuscular sodium chloride = 13%	NA	NA	NA	NA	<ul style="list-style-type: none"> In this short-term assessment in a small number of patients, high-dose steroids (70 mg of triamcinolone) were superior to local anesthetic and saline. They described worst outcomes with transforaminal bupivacaine, even worse than intramuscular saline. Only successful patients were followed to 12 months, very small numbers to draw conclusions (15 of 150 patients).

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function					Comment(s)
			1 month	3 mos.	6 mos.	12 mos.		
<p>Klenerman et al, 1984 (85) RA, PC, B Sciatica Quality Scores: Cochrane = 12/13 IPM-QRB = 13/48</p>	<p>Total: 63 Placebo group: 16 20 mL of interlaminar epidural normal saline Local anesthetic group: 16 20 mL of 0.25% bupivacaine solution Treatment group: 19 80 mg of DepoMedrol in normal saline made up 20 mL Acupuncture group: 12 patients Needling with a standard Tuohy injection needle into the interspinous ligament, but no injection</p>	<p>Patients were placed into one of the groups: "Failed", "Improved", "Cured" Improved or Cured groups were pooled Pain relief by VAS, SLR, flexion, assessment up to 70 days</p>	<p>NA</p>	<p>69% improved in saline group 69% improved in bupivacaine group 79% improved in steroid group 83% improved in interspinous injection group</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<ul style="list-style-type: none"> The inclusion criteria were unilateral sciatica for a maximum of 6 months, thus including a majority of acute and subacute patients. Follow-up period is very short. Small sample size No significant difference between local anesthetic and steroids, or even placebo. Steroids were injected without local anesthetic.

Appendix Table 6 (continued). Characteristics of randomized trials of placebo and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function				Comment(s)
			1 month	3 mos.	6 mos.	12 mos.	
Cuckler et al, 1985 (96) RA, PC, B Acute sciatica Quality Scores: Cochrane = 10/13 IPM-QRB = 13/48	Total: 73 Of 73, acute hermiated nucleus pulposus: 36 patients and spinal stenosis 37 patients Placebo group: 14 patients Local anesthetic group: 2 mL of sodium chloride solution combined with 5 mL of 1% procaine Steroids with local anesthetic: 22 patients 2 mL of sterile water containing 80 mg of methylprednisolone acetate combined with 5 mL of 1% procaine A second injection was provided within 24 hours if there was no response to the first one.	Pain relief Success= subjective improvement of 75% or more Failure = less than 75% improvement Success was 5 of 9 in placebo group and 7 of 15 in treatment group with 75% improvement or more	NA	NA	NA	At 13 months, success in placebo with 75% improvement was 2 of 11 (18%) and in steroid group, 6 of 17 (35%)	<ul style="list-style-type: none"> This is a very small study with a small number of patients with acute disc herniation with bizarre parameters of 75% improvement as success. Even then, there was significant improvement both in steroid and local anesthetic group, which they termed inaccurately as placebo. Based on outcome parameters, it is very difficult to assess if this is a positive or negative study.

NRS = Numeric Rating Scale; RA = Randomized; PC = Placebo-control; DB = Double-blind; B = Blind; IPM-QRB = Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; ODI = Oswestry Disability Index; VAS = Visual Analog Scale; SLR = Straight Leg Raise; SF-36 = Short-Form-36; ODQ = Oxford Depression Questionnaire; NA = Not Applicable; P = Positive; NDS = No Significant Difference; RMDQ = Roland Morris Disability Questionnaire

Appendix Table 7. Characteristics of randomized, active-controlled with local anesthetic and steroids in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function				Comment(s)
			1 month	3 mos.	6 mos.	12 mos.	
Manchikanti et al, 2012 (76) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 12/13 IPM-QRB = 44/48	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs. lidocaine mixed with steroid Number of injections = 1 to 5	NRS, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	NA	Overall: LA 62% vs. LA with steroid 72% Responsive: LA 77% vs LA with steroid 80	Overall: LA 72% vs LA with steroid 73% Responsive: LA 87% vs LA with steroid 86%	Overall: LA 67% vs LA with steroid 72% Responsive: LA 85% vs LA with steroid 84%	<ul style="list-style-type: none"> Positive double-blind randomized trial with superiority of steroids with average pain relief for steroids. Overall improvement with local anesthetic alone or with steroids was similar. Nonresponsive patients were also similar with 13 and 10 in local anesthetic only and with steroids group. Over a period of 2 years, on average, a total of 5-6 injections were provided.
			NA	Lidocaine & lidocaine with steroid effective	Lidocaine & lidocaine with steroid effective	Lidocaine & lidocaine with steroid effective	
Manchikanti et al, 2014 (77) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Total = 120 Local anesthetic = 60 Local anesthetic and steroids = 60 Xylocaine or Xylocaine with non-particulate Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake, significant improvement 50% or greater of NRS scores and ODI scores Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	NA	Overall: Lidocaine 72% vs. lidocaine with steroid 82% Responsive: Lidocaine 86% vs. lidocaine with steroid 83%	Overall: Lidocaine 63% vs. lidocaine with steroid 85% Responsive: Lidocaine 76% vs. lidocaine with steroid 86%	Overall: Lidocaine 67% vs. lidocaine with steroid 85% Responsive: Lidocaine 80% vs. lidocaine with steroid 86%	<ul style="list-style-type: none"> Positive randomized trial with long-term follow-up. Overall, similar results with local anesthetic or with local anesthetic and steroids with significant improvement. Steroids were superior at 6 months with pain relief and 12 months with functional status A significantly higher proportion of patients non-responsive to the first 2 injections in the local anesthetic group 10 vs one. On average, a total of 5-6 injections were provided over a period of 2 years.
			NA	Both treatments are effective	Both treatments are effective	Both treatments are effective	

Appendix Table 7. Characteristics of randomized, active-controlled with local anesthetic and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function				Comment(s)
			1 month	3 mos.	6 mos.	12 mos.	
Datta & Upadhyay, 2011 (79) RA, AC, B Disc herniation or radiculopathy Quality Scores: Cochrane = 6/13 IPM-QRB = 18/48	Total: 163 Group A: Caudal injection of 10-15 mL of 0.125% bupivacaine = 55 Group B: Bupivacaine and 80 mg of methylprednisolone = 50 Group C: Bupivacaine and 80 mg of triamcinolone = 52 Group D: Bupivacaine and 15 mg of dexamethasone = 50 Number of injections: 1 to 3	VAS, RMDQ, Lasègue's Sign, SLR, Finger to Floor Distance, Assessment of paravertebral muscle spasm, motor or sensory deficits	Pain relief was present in all 4 groups by 3 weeks with no difference between the groups	COMPLETE OR SATISFACTORY RELIEF Group A: 60% Group B: 83% Group C: 80% Group D: 73%	NA	NA	<ul style="list-style-type: none"> Positive randomized controlled trial with superiority of bupivacaine with steroids. However, bupivacaine was also significantly effective. <p>The amount of injectate was rather high with a blind approach of 15 mL.</p> <ul style="list-style-type: none"> Short-term outcomes
Manchikanti et al, 2014 (80) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs lidocaine mixed with steroid with infraneural approach Average number of injections = 5 to 6 for 2 years	NRS pain scale, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	NA	Overall: LA 75% vs LA with steroid 67% Responsive: LA 90% vs LA with steroid 82%	Overall: LA 73% vs LA with steroid 67% Responsive LA 88% vs LA with steroid 87%	Overall: LA 75% vs LA with steroid 57% Responsive LA 92% vs LA with steroid 73%	<ul style="list-style-type: none"> Similar results with local anesthetic or with local anesthetic and steroids. Nonresponsive patients: local anesthetic = 11, steroids = 15. Local anesthetics were somewhat superior; though not statistically significant. On average, a total of 5-6 injections were administered over a period of 2 years.

Appendix Table 7. Characteristics of randomized, active-controlled with local anesthetic and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function				Comment(s)
			1 month	3 mos.	6 mos.	12 mos.	
Ghai et al, 2015 (81) RA, DB, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 39/48	Total = 69 Lidocaine = 34 Lidocaine + methylprednisolone = 35 Local anesthetic group: 8 mL of 0.5% lidocaine Lidocaine + methylprednisolone: 6 mL of 0.5% lidocaine mixed with 80 mg (2 mL) of methylprednisolone acetate Average procedures: 2	NRS and functional disability using Modified Oswestry Disability Questionnaire Follow-up: 1 year	NA	Lidocaine: 50% Lidocaine with methylprednisolone: 86%	Lidocaine: 56% Lidocaine with methylprednisolone: 86%	Lidocaine: 59% Lidocaine with methylprednisolone: 89%	This active-controlled trial with a long-term follow-up comparing lidocaine alone with lidocaine with methylprednisolone showed similar results after 3 months, even though quality of relief was superior in the local anesthetic with steroid group.
Rogers et al, 1992 (89) RA, AC, B Sciatica Quality Scores: Cochrane = 12/13 IPM-QRB = 12/48	Total: 30 Local anesthetic group: 15 Lidocaine 2%, 14 mL, with normal saline, 6 mL, with a total of 20 mL Lidocaine with steroid group: 15 Local anesthetic and steroid mixture with lidocaine 2%, 14 mL, methylprednisolone acetate, 80 mg in 2 mL, and normal saline, 4 mL, with a total of 20 mL	Pain score, work status, analgesic consumption, SLR	One month follow-up results: pain relief of no pain to mild pain was 3 of 15 in local anesthetic group and 7 of 15 in steroid with local anesthetic group. SLR improved significantly in the steroid with local anesthetic group. Steroids effective	NA	NA	NA	<ul style="list-style-type: none"> This is a small study with an extremely short-term follow-up of one month. Overall, the study showed positive results with injection of local anesthetic and steroids.

Appendix Table 7. Characteristics of randomized, active-controlled with local anesthetic and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function				Comment(s)
			1 month	3 mos.	6 mos.	12 mos.	
Ng et al, 2005 (93) RA, AC, F Disc herniation or radiculopathy and spinal stenosis (foraminal) Quality Scores: Cochrane = 12/13 IPM-QRB = 37/48	Total = 86 Disc herniation = 48 Stenosis = 32 Bupivacaine only: Disc herniation = 26 Foraminal stenosis = 15 Bupivacaine + steroid with methylprednisolone Disc herniation = 23 Stenosis = 17 Number of injections = 1	VAS, ODI, change in walking distance, claudication, satisfaction of the outcome Follow-up: 3 months	Both groups showed improvement	Bupivacaine = 47.5% Bupivacaine + steroid = 41.5%	NA	NA	<ul style="list-style-type: none"> Positive results in a small study with short-term follow-up. Both groups showed similar improvement when administered with bupivacaine alone or bupivacaine with steroids. Local anesthetic alone or local anesthetic with steroids were equally effective. The response in disc herniation and stenosis was similar.
Tafazal et al. 2009 (94) RA, AC, F Disc herniation or radiculopathy and spinal stenosis Quality Scores: Cochrane = 11/13 IPM-QRB = 32/48	Total: 150 Lumbar disc herniation: 76 Local anesthetic = 34 Local anesthetic with steroid = 42 Local anesthetic group: Injection of 2 mL of 0.25% bupivacaine Local anesthetic with steroid group: Injection of 2 mL of 0.25% bupivacaine and 40 mg of methylprednisolone. Bupivacaine only: Lumbar disc herniation: 34 Foraminal stenosis: 25 Bupivacaine with steroids Lumbar disc herniation: 42 Foraminal stenosis: 23 Number of injections = 1 to 3	VAS, ODI, LBOS Avoidance of surgery Outcomes: 12 weeks 1 year for surgery Excellent outcome	NA	ODI: LA 13.8 ± 3.7 versus LA with steroid 13.6 ± 3.1 VAS leg pain: LA 24.3 ± 5.5 versus LA with steroid 27.46 ± 4.7	NA	Disc herniation group showed greater reduction in the ODI with a mean change of 15 points from baseline of 46.6 in the bupivacaine only group and 43.4 in bupivacaine and steroid group. There was a mean change in the VAS of 26 mm in the disc prolapse group. The requirements for treatments were the same in local anesthetic alone group or local anesthetic with steroids. Overall surgery rates were 18%, the surgery rate was 22% in the bupivacaine only group and 14% in the bupivacaine and steroid group	<ul style="list-style-type: none"> Corticosteroid addition to local anesthetic failed to provide any additional benefit when compared to local anesthetic injection alone. There was no significant difference between both groups. Surgery was avoided in both groups.

Appendix Table 7. Characteristics of randomized, active-controlled with local anesthetic and steroids in lumbosacral epidural injections in lumbar radiculopathy or sciatica.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Results of Pain Relief and Function					Comment(s)
			1 month	3 mos.	6 mos.	12 mos.		
Cohen et al, 2012 (97) RA, AC, F Subacute sciatica Quality Scores: Cochrane = 13/13 IPM-QRB = 38/48	A multicenter, 3-group, randomized, trial conducted from 2008 to 2011. Total number of patients = 84 adults Bupivacaine + saline = 30 Bupivacaine + steroid = 28 Bupivacaine + etanercept = 26 Randomized active-controlled conducted; local anesthetic 0.5% bupivacaine 0.5 mL was injected at all levels, followed by the concealed study drug. Consequently, this is considered as an active-controlled trial.	NRS scores for leg pain, NRS scores for back pain, ODI scores for functionality Follow-up: One-month, 3 months Bupivacaine + 3-month follow-up Bupivacaine + sodium chloride solution, leg pain for sodium chloride solution Bupivacaine + saline 6.31 to 3.78 Bupivacaine + steroids 5.71 to 2.54 Bupivacaine + etanercept 6.62 to 3.56 ODI scores: Saline = 40.87 to 30 Steroids = 42.93 to 24.1 Etanercept = 41.1 to 40.26 (one month)	Positive for steroids group, compared to LA or etanercept	NA	NA	NA	NA	<ul style="list-style-type: none"> Bupivacaine with steroid was more effective than Bupivacaine with saline or etanercept, specifically with functional status. This is a small study with a confusing design, even though it is designed as placebo-controlled trial it included injection of bupivacaine and active drug long-acting local anesthetic which has been shown to be effective. This was followed by saline, steroids, or etanercept. The inclusion criteria was subacute sciatica. There was clinically noticeable difference between NRS scores for back pain with bupivacaine with saline at 4.75 compared to 5.30 for epidural steroids, and 6.08 for epidural etanercept at baseline. Authors used a supranatural approach with particulate steroid associated with high risks of arterial injection and resulting paralysis. The study was not selected by Chou et al (32) in their systematic review for inclusion, even though it was published in same journal as the systematic review.

RA = Randomized; AC = Active-Control; F = Fluoroscopy; DB = Double-Blind; IPM-QRB = Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; VAS = Visual Analog Scale; RMDQ = Roland-Morris Disability Questionnaire; SLR = Straight Leg Raise; LBOS = Low Back Outcome Score; LA = Local Anesthetic; NA = Not Applicable;