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Systematic Review and Meta-Analysis

Lack of Superiority of Epidural Injections with Lidocaine with Steroids Compared to Without Steroids in Spinal Pain: A Systematic Review and Meta-Analysis

Nebojsa Nick Knezevic, MD, PhD[1], Laxmaiah Manchikanti, MD[2], Ivan Urits, MD[3], Vwaire Orhurhu, MD, MPH[4], Brahma Prasad Vangala, MBBS[5] Rachana Vanaparthy, MBBS[6], Mahendra R. Sanapati, MD[7], Shalini Shah, MD[8], Amol Soin, MD[9], Amit Mahajan, MBBS[10], Sairam Atluri, MD[11], Alan D. Kaye, MD, PhD[12], and Joshua A. Hirsch, MD[13]

From: [1]Advocate Illinois Masonic Medical Center and College of Medicine, University of Illinois, Chicago, IL [2]Pain Management Centers of America, Paducah, KY; [3]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; [4]Massachusetts General Hospital and Harvard Medical School, Boston, MA; [5]Apollo Hospitals, Secunderabad, India; [6]Oregon Health and Science University, Portland, OR; [7]Pain Management Centers of America, Evansville, IN; [8]University of California Irvine, Orange, CA; [9]Ohio Pain Clinic, Centerville, OH, Wright State University, Dayton, OH; [10]Yale School of Medicine, New Haven, CT; [11]Tri-State Spine Care Institute, Cincinnati, OH; [12]LSU School of Medicine, Shreveport, LA; [13]Massachusetts General Hospital and Harvard Medical School, Boston, MA; and Neiman Health Care Policy Institute, Reston, VA

Address Correspondence:
Laxmaiah Manchikanti, MD
67 Lakeview Drive
Paducah, Kentucky 42001
E-mail: drlm@thepainmd.com

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Background: Multiple randomized controlled trials (RCTs) and systematic reviews have been conducted to summarize the evidence for administration of local anesthetic (lidocaine) alone or with steroids, with discordant opinions, more in favor of equal effect with local anesthetic alone or with steroids.

Objective: To evaluate the comparative effectiveness of lidocaine alone and lidocaine with steroids in managing spinal pain to assess superiority or equivalency.

Study Design: A systematic review of RCTs assessing the effectiveness of lidocaine alone compared with addition of steroids to lidocaine in managing spinal pain secondary to multiple causes (disc herniation, radiculitis, discogenic pain, spinal stenosis, and post-surgery syndrome).

Methods: This systematic review was performed utilizing Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) for literature search, Cochrane review criteria, and Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) to assess the methodologic quality assessment and qualitative analysis utilizing best evidence synthesis principles, and quantitative analysis utilizing conventional and single-arm meta-analysis.

PubMed, Cochrane Library, US National Guideline Clearinghouse, Google Scholar, and prior systematic reviews and reference lists were utilized in the literature search from 1966 through December 2019. The evidence was summarized utilizing principles of best evidence synthesis on a scale of 1 to 5.

Outcome Measures: A hard endpoint for the primary outcome was defined as the proportion of patients with 50% pain relief and improvement in function. Secondary outcome measures, or soft endpoints, were pain relief and/or improvement in function. Effectiveness was determined as short-term if it was less than 6 months. Improvement that lasted longer than 6 months, was defined as long-term.

Results: Based on search criteria, 15 manuscripts were identified and considered for inclusion for qualitative analysis, quantitative analysis with conventional meta-analysis, and single-arm meta-analysis. The results showed Level II, moderate evidence, for short-term and long-term improvement in pain and function with the application of epidural injections with local anesthetic with or without steroid in managing spinal pain of multiple origins.

Limitations: Despite 15 RCTs, evidence may still be considered as less than optimal and further studies are recommended.

Conclusion: Overall, the present meta-analysis shows moderate (Level II) evidence for epidural injections with lidocaine with or without steroids in managing spinal pain secondary to disc

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herniation, spinal stenosis, discogenic pain, and post-surgery syndrome based on relevant, high-quality RCTs. Results were similar for lidocaine, with or without steroids.

Key Words: Chronic spinal pain, epidural injections, local anesthetic, lidocaine, steroids, active control trials, placebo effect

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1.0 Introduction

Chronic spinal pain is widespread and disabling, consuming a significant proportion of health care expenditures, which has been estimated to be $134.5 billion per year in 2016 in the United States (1,2). While numerous modalities of treatments are provided in managing spinal pain, both conservative and interventional, including surgery, epidural injections continue to be one of the commonly employed interventional procedures in managing spinal pain (3-6). Despite multiple systematic reviews with randomized controlled trials (RCTs) (7-25), and favorable, cost-effectiveness analysis studies (26-31), the declining utilization of epidural injections in managing chronic spinal pain (3-6) has been seen with discordant opinions of effectiveness (7,20-23,25).

COVID-19 has affected the United States leading to a national emergency concerning both health care and economic impact, propelling the country into a generational recession (32-36). COVID-19 is a serious worldwide illness leading to numerous deaths in various countries, including the United States. Infections and deaths have been increasing rapidly; from 200 deaths on March 18 to over 100,000 in the United States at the end of May 2020. The United States, nationally and each state, individually, has taken numerous precautions to mitigate the risk of COVID-19 and reduce the death rate. Consequently, many medical practices and hospitals have come to a standstill with the stoppage of elective surgeries. Thus, recovery after the COVID-19 pandemic to impact many types of health care, and specifically multiple elective surgeries. Consequently, multiple guidelines have been developed and published in conjunction with the reopening America and the restarting elective surgeries (37-40). Shah et al (41) published risk mitigation/stratification strategies along with guidance for interventional pain physicians. One of the issues pertains to the effect of steroids on the risk from COVID-19 infection with the need to avoid steroids or using them at the lowest dosage (41). However, other guidelines have advocated the use of lower dose or the use of non-particulate steroids (39,40). In addition, Jha et al (42) have shown in their survey, designed primarily to study burnout, the devastating effect of COVID-19 on interventional pain management practices, with approximately 95% reductions in procedure volume. In addition, "steroid distancing" has been advocated with intraarticular injections by orthopedic surgeons (43,44).

The use of epidural injections with local anesthetic dates back to 1901 (45-50), the addition of steroids is a more recent phenomena and dates back only to 1952 (45,50-63). The data related to the effectiveness of local anesthetic with or without steroids also extends to various types of other spinal injections, including facet joint interventions (8,45,50,52-63). Multiple randomized trials and systematic reviews assessing the role of epidural injections with local anesthetics with or without steroids have resulted in discordant conclusions in managing spinal pain (9-23,30,31,50). However, these discordant conclusions are based on various challenges faced in the conduct of systematic reviews and meta-analysis either with placebo injected into active structures, placebos injected into the epidural space, or injection of local anesthetics without steroids (9-23,30,31,45,50,52-63). Thus, there is a lack of understanding of placebo control, differences between active versus placebo control studies, as well as misinterpretation of evidence, and finally conflicts/confluence of interest (7,8,11,13,14,20,23,25,32).

The previous systematic reviews by Pinto et al (25), Chou et al (23), and Cochrane Collaboration review by Oliveria et al (20) converted all active-control trials utilizing local anesthetic with or without steroids into placebo control trials, invalidating conclusions of manuscript authors and the reviews themselves (20,23,25). In contrast, other systematic reviews performed with appropriate analysis utilizing 2-arm meta-analysis (7,9,10,13,14,50), have shown lack of significant superiority.

Epidural steroid injections have been widely utilized in managing chronic spinal pain, started just

a decade after the discovery of the potency of their anti-inflammatory effect in the 1940's by Philip Hench (55,64). Beyond spinal conditions and intraarticular injections, steroids have also been extensively used for multiple other chronic painful conditions (45,56). In clinical practice, most steroid injections are combined with local anesthetics in clinical settings (45,56). The logic is that steroids should prolong the anti-inflammatory effect (57-59), whereas local anesthetic acts immediately and also reduces the discomfort of the injection itself. Thus far, there is no evidence that steroid injections are disease-modifying agents (62) nor that they have a direct effect on pain generation or transmission, with the exception of inflammatory conditions such as rheumatoid arthritis.

Corticosteroids are commonly used in epidural injections, intraarticular injections, and other nerve blocks. Corticosteroids, structurally and pharmacologically, are similar to the endogenous hormone, cortisol, with various functions like anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive effects. Anti-inflammatory effect is crucial and it is essential to determine if in fact the patient has inflammation, whereas immunosuppressive effects are important as they may increase the risk of COVID-19 infection (64,65). To date, no studies demonstrating an anti-inflammatory role of steroids or the differentiation of inflammatory radiculopathies from noninflammatory radiculopathies (62). Thus far, the primary argument in favor of epidural steroids has been that they were more effective in patients with increased cerebrospinal fluid protein levels, which indicated inflammatory radiculopathy (62). However, these criteria, have never been applied prospectively, and have been considered similar to other putative criteria of inflammatory radiculopathy (62). Contrary to the theory of an anti-inflammatory effect of steroids, methylprednisolone also has been described to possess reversible, local anesthetic effect, which may be the reason why methylprednisolone may be more effective than other particulate or nonparticulate steroids (64). Further, it also has been shown that lower dose will reduce the duration of adrenal suppression, while intensity of the suppression is the same with full dose of 40 mg of triamcinolone or with 20 mg of triamcinolone (65,66). In contrast, the proposed mechanism of long-lasting effects of local anesthetics based on the alteration of nociceptive input, the reflex mechanism of afferent fibers, the self-sustaining activity of the neurons and the pattern of central neuronal activities, has been demonstrated in multiple studies (67-79). Adding to this debate, studies also have shown that the addition of corticosteroids to a local anesthetic failed to provide any additional benefit in nerve infiltration for lumbar disc herniation (72). To further complicate the assessment of the effectiveness of steroids, the addition of either sodium chloride solution or dextrose exhibited pain relief and also increased the duration of effect of epidural steroid injection (50,63).

Contrary to the role of steroids, there is significant evidence of the effectiveness of local anesthetic alone in an overwhelming proportion of patients with chronic spinal pain. The demonstration of such evidence was shown with bupivacaine (50) and also with lidocaine in other studies (7-15), will facilitate the appropriate provision of care for spinal and non-spinal interventions in managing chronic pain especially in this era of more clinicians embracing "steroid distancing." Thus, to increase the understanding of the effect of local anesthetic (lidocaine) alone or with steroids in the epidural space, we have undertaken this systematic review and meta-analysis to assess the effectiveness of local anesthetic (lidocaine) alone compared to addition of particulate steroids.

2.0 Methods

Methodology for this systematic review and meta-analysis included utilizing guidance from the Institute of Medicine (IOM) (80), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (81), methodologic quality assessment (82,83), and grading of evidence (84).

2.1 Eligibility Criteria

Eligibility criteria included all relevant RCTs with reporting of appropriate outcomes, with at least 6 months data. The studies must have been performed in patients suffering with chronic spinal pain.

In this systematic review and meta-analysis, all approaches to the epidural space were utilized including caudal, lumbar, cervical, and thoracic interlaminar epidurals, and lumbar transforaminal epidural injections. Patient must have received either lidocaine alone or a combination of lidocaine with steroids.

2.2 Data Sources

All manuscripts published in English language or with English translation, providing appropriate management with outcome evaluations were considered for inclusion. Searches were performed from the PubMed and Cochrane Library from 1966 to December 2019.

2.3 Search Strategy

The search terminology was as follows:

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

2.4 Data Collection and Analysis

2.4.1 Data Collection Process

Search criteria for selection of the manuscripts, inclusion of the appropriate studies in the assessment, risk of bias assessment, methodologic quality evidence synthesis process was developed independently in an open standardized manner. Any disagreements were discussed by two authors and an additional third author. All issues were resolved and agreed upon by the full writing group. Conflicts of interest with respect to authorship or if reviewer was one of the authors, the author/reviewer did not participate in the review of the manuscript or methodologic quality assessment.

2.4.2 Outcome of the Studies

The primary outcome parameter, described as the hard parameter, was significant pain relief and functional status improvement defined as at least 50%, whereas, the secondary outcome measures, or soft measures, were either pain relief or functional status improvement alone with change of 50% from baseline or change in the pain scores of at least 3 points. Any relief of 6 months or less was considered as short-term and 12 months or longer was considered as long-term improvement.

2.5 Data Synthesis and Analysis

2.5.1 Risk of Bias of Individual Studies

The risk of bias assessment was conducted by Cochrane Review criteria (82) and quality of individual manuscripts was conducted by Interventional Pain Management techniques -- IPM – QRB for randomized trials (83).

After the appropriate risk of bias assessment, studies meeting inclusion criteria of less than 5 were considered as low quality. Studies meeting inclusion criteria of 5 to 8 were considered as moderate quality, whereas studies meeting the inclusion criteria of 9 to 13 were considered as high quality.

For methodological quality, the IPM-QRB criteria for randomized trials were utilized showing studies with scores of less than 16 being considered as low quality, studies scoring from 16 to 31 considered as moderate quality, and studies scoring from 32 to 48 were considered as high quality.

2.5.2 Analysis and Grading of Evidence

Analysis of evidence was performed utilizing qualitative and quantitative analysis. Qualitative analysis was performed utilizing best evidence synthesis, modified and collated from multiple available criteria, including Cochrane Review criteria and United States Preventive Services Task Force (USPSTF) criteria as illustrated in Table 1 (84).

2.6 Qualitative and Quantitative Analysis

Qualitative analysis utilizing best assessment for strength of evidence was performed based on RCTs and meta-analysis available from this review.

Quantitative analysis or meta-analysis was performed utilizing conventional methodology, as well as single arm analysis.

2.6.1 Qualitative Analysis

Qualitative analysis of the evidence was performed based on the best evidence synthesis modified and collated from multiple available criteria, including Cochrane review criteria and USPSTF criteria as illustrated in Table 1 (84). The analysis was conducted using 5 levels of evidence ranging from strong to opinion- or consensus-based. The results of best evidence as per grading was utilized.

2.6.2 Meta-Analysis or Quantitative Analysis

For dual arm or conventional meta-analysis soft-

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

Level I	Strong	Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness
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 high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate or low quality relevant observational studies
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, and effectiveness of other measures.

Adapted from: Manchikanti L, et al. A modified approach to grading of evidence. Pain Physician 2014; 17:E319-E325 (84).

ware Review Manager (Rev Man 5.4) was used (The Cochrane Collaboration, May 2020). For pain and functionality improvement data, the studies were reported as the standardized mean differences (SMD) with 95% confidence intervals (CI). Data were plotted with using forest plots to evaluate treatment effects. Heterogeneity was interpreted through I2 statistics.

For single arm meta-analysis software Comprehensive 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 (MD) with 95% CI.

Data were plotted with using forest plots to evaluate treatment effects. Heterogeneity was interpreted through I2 statistics.

3.0 Results

3.1 Study Selection

Figure 1 shows a flow diagram of the study selection as recommended by PRISMA (81).

Following the appropriate search criteria, after assessing multiple manuscripts for inclusion, 15 manuscripts were identified for inclusion (85-99). These included a total of 15 studies, of which 4 were caudal (85-88), 2 were lumbar transforaminal (98,99), 5 were lumbar interlaminar (89-92,99), 4 were cervical interlaminar (93-96), and one was thoracic interlaminar (97).

3.2 Methodological Quality Assessment

A methodological quality assessment of the RCTs meeting inclusion criteria was carried out utilizing Cochrane review (82) criteria and IPM – QRB (83) criteria as shown in Tables 2 and 3 (85-98).

3.3 Study Characteristics

A description of the various studies included is shown in Table 4.

The methodological quality assessment was of high quality for 14 of 15 studies based on the Cochrane review criteria (Table 2) and IPM-QRB criteria (Table 3).

Manchikanti et al conducted 4 caudal trials (85-88), 3 lumbar interlaminar epidural trials (89, 91,92), 5 cervical/thoracic interlaminar epidural trials (93-97), and one lumbar transforaminal epidural trial (98). They used an identical protocol in each study: an active control design with a 2-year follow-up in 12 of 13 studies. These studies evaluated the effectiveness of epidural injections in 2 groups: one group received a local anesthetic only and the other group received a local anesthetic with a steroid. In these studies, the treatment diagnoses included; disc herniation, discogenic pain without facet joint or sacroiliac joint pain, central spinal stenosis, and post-surgery syndrome.

Ghai et al (90) conducted a study to compare the effectiveness of epidural injections of local anesthetic alone to epidural injections of local anesthetic with steroid using a parasagittal interlaminar approach for managing chronic low back pain and lumbosacral radicular pain. They concluded that using a parasagittal interlaminar approach and the addition of steroid to local anesthetic for epidural injections may provide superior effectiveness in terms of extent and duration of pain relief for managing chronic low back pain with unilateral lumbosacral radicular pain, even though, local anesthetic alone also was effective.

Friedly et al (99,100) conducted a large study with a poorly conducted complicated design, which was not practical, with high volume glucocorticoid steroid injection, but low volume lidocaine alone injections. They provided interlaminar epidural injections with lidocaine of 1-3 mL, 0.5% to 1%, whereas either interlaminar or transforaminal epidural injections with 1-3 mL of 0.25% to 1% of lidocaine. In addition to this, glucocorticoid was added in rather high doses in the group for glucocorticoid as much as 60-120 mg of triamcinolone, 6-12 mg of betametha-

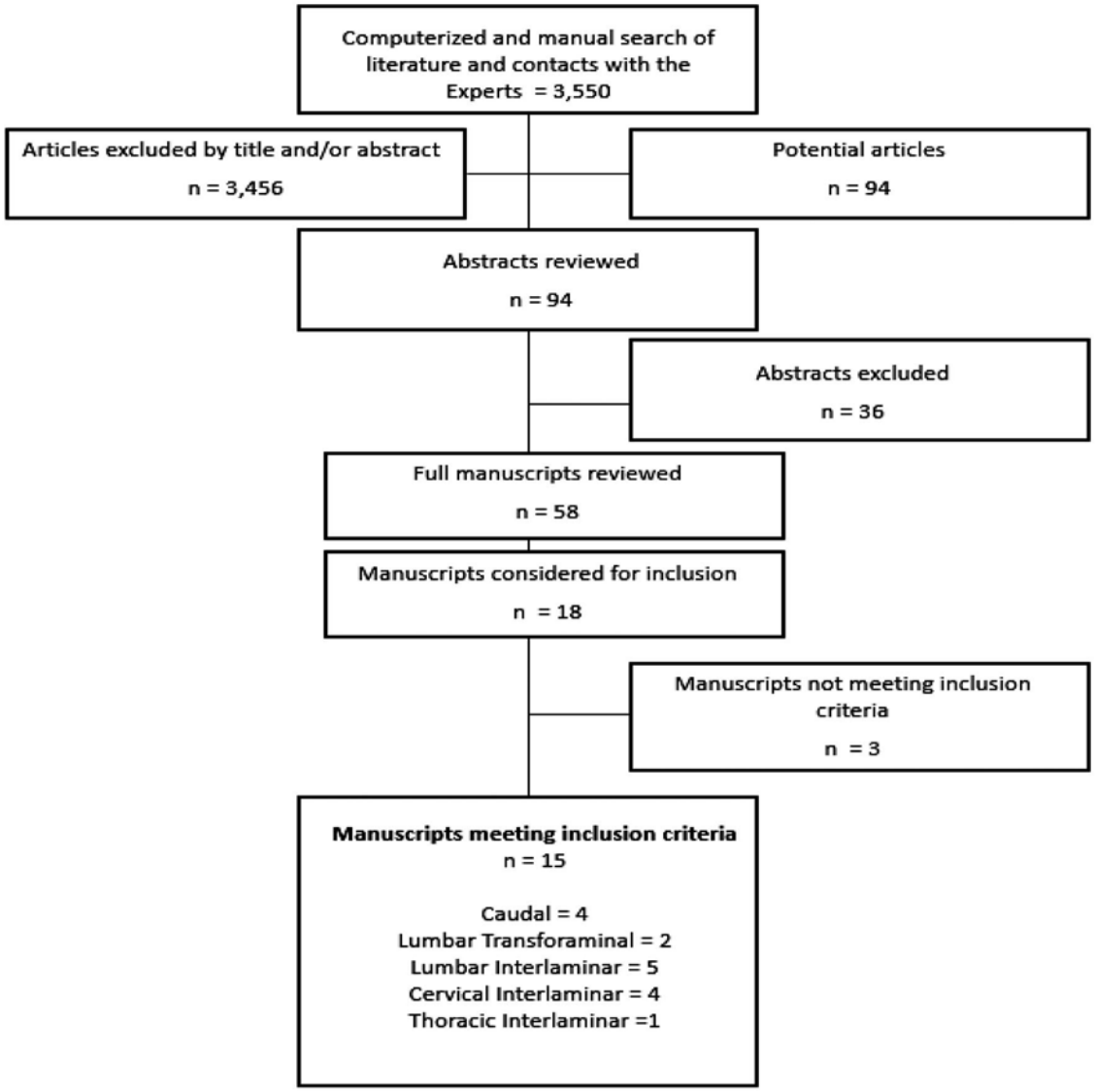

Fig. 1. *Flow diagram illustrating published literature evaluating epidural injections utilizing either lidocaine alone or lidocaine with steroids in managing spinal pain.*

sone, and 60-120 mg of methylprednisolone. There was no equivalency in these doses. Administrations were highly variable based on practice patterns. There were a total of 200 patients in each group. However, interlaminar approach with lidocaine alone was 139 compared to 143 in the groups with steroids and 61 had transforaminal lidocaine alone, whereas 57 had transforaminal lidocaine with glucocorticoids with extremely high doses. The study period lasted 6 weeks. The authors failed to assess the most common parameter, i.e., 50% improvement, with pain and physical function and the proportion of the patients. After 6 weeks, the analysis has taken inappropriate patterns without separation of interlaminar and transforaminal and with large crossover of the patients. Thus, it became an observational study. Further, repeat injections were very infrequent. During the first 6 weeks, only 76 patients (38%) in lidocaine

Table 2. *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Manchikanti et al (85)	Manchikanti et al (86)	Manchikanti et al (87)	Manchikanti et al (88)	Manchikanti et al (89)	Ghai et al (90)	Manchikanti et al (91)	Manchikanti et al (92)	Manchikanti et al (93)
Randomization adequate	Y	Y	Y	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	Y	Y	Y	Y	Y	Y	Y
Patient blinded	Y	Y	Y	Y	Y	Y	Y	Y	Y
Care provider blinded	N	Y	N	Y	Y	N	Y	Y	Y
Outcome assessor blinded	N	N	N	N	N	N	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	N	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	N	Y	N	N	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias likely	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	11/13	12/13	11/13	12/13	11/13	10/13	11/13	11/13	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 (82).

alone group, and 80 patients (40%) in corticosteroid plus lidocaine group received a second injection. None of them received 3 injections. It is not a practical approach. In addition, during 6 to 12 weeks, 91 patients (47.2%) in lidocaine alone received one injection and 26 patients (13.5%) received 2 injections, while none received 3 or more. During the same period, in corticosteroid and lidocaine group, 67 patients (34.7%) received one injection and 28 or 14.5% received 2 injections. Finally, from 12 weeks to 12 months, over 66% did not receive any additional injections. Only 12 or 6.6% in lidocaine alone group, and 16.4% or 31 in corticosteroid plus lidocaine group received one additional injection 12.6% and 13.8% with lidocaine alone or lidocaine with steroids received 3 or more injections. Overall, very few patients received more

Table 2 (cont.). Methodological quality assessment of randomized trials utilizing Cochrane review criteria.

	Manchikanti et al (94)	Manchikanti et al (95)	Manchikanti et al (96)	Manchikanti et al (97)	Manchikanti et al (98)	Friedly et al (99)
Randomization adequate	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	Y	Y	Y	N
Patient blinded	Y	Y	Y	Y	Y	N
Care provider blinded	Y	Y	Y	Y	Y	N
Outcome assessor blinded	N	N	N	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	N
Groups similar at baseline regarding most important prognostic indicators	N	N	N	Y	N	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	N
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y
Are other sources of potential bias likely	Y	Y	Y	Y	Y	N
Score	11/13	11/13	11/13	12/13	11/13	6/13

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 (82).

than 3 injections. This is not a common practice. Generally, responsive patients receive one injection once in 3 months, that is at least 4 injections if they are not responding in therapeutic phase, and 2 to judge in the diagnostic phase. Further, analysis was not very clear. There was no analysis performed with proportion of patients obtaining 50% or greater relief. Further, there was no analysis separately provided for lumbar interlaminar epidural injections compared to transforaminal epidural injections. They also reported significant side effects because of the high dose steroids in the steroid group. Based on the strictest criteria, this manuscript did not meet inclusion criteria. However, to avoid criticism, this manuscript was utilized in the analysis, which essentially showed similar effectiveness with lidocaine alone or lidocaine with steroids and significant effectiveness from baseline to follow-up periods utilizing mean improvement with leg pain intensity and disability index. Overall, despite a multitude of issues related to the study, this can be considered as a positive study which shows lidocaine alone is also effective, similar to with steroids, and also provides basis that it is not a placebo.

Finally, their conclusion was that epidural injections of corticosteroid plus lidocaine offered no benefit from 6 weeks to 12 months beyond that of injection of lidocaine alone. Further, they also opined that repeated injections of either type offered no additional long-term benefit if injection in the first 6 weeks did not improve pain. While this was affirmed by Manchikanti et al in multiple manuscripts (85-89,91-98), lack of effectiveness was contradictory. If they consider a 2-point change in leg pain intensity as significant difference and their results showed that leg pain intensity was reduced by a minimum of 2.2 ± 2.9 to 2.9 ± 3.1, the study presented a successful outcome rather than lack of outcome with similar effects of lidocaine alone and lidocaine with steroids.

Table 3. *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Manchikanti et al (85)	Manchikanti et al (86)	Manchikanti et al (87)	Manchikanti et al (88)	Manchikanti et al (89)	Ghai et al (90)	Manchikanti et al (91)	Manchikanti et al (92)
I.	TRIAL DESIGN AND GUIDANCE REPORTING								
1.	CONSORT or SPIRIT	3	3	3	3	3	3	3	3
II.	DESIGN FACTORS								
2.	Type and Design of Trial	2	2	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	2	2	2	2	2
4.	Imaging	3	3	3	3	3	3	3	3
5.	Sample Size	3	3	3	3	3	2	3	3
6.	Statistical Methodology	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS								
7.	Inclusiveness of Population	2	2	2	2	2	2	2	2
8.	Duration of Pain	2	2	2	2	2	1	2	2
9.	Previous Treatments	2	2	2	2	2	1	2	2
10.	Duration of Follow-up with Appropriate Interventions	3	3	3	3	3	3	3	3
IV.	OUTCOMES								
11.	Outcomes Assessment Criteria for Significant Improvement	4	4	4	4	4	4	4	4
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2	2	2
13.	Description of Drop Out Rate	2	2	2	2	2	0	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	1	1	1	1	2	0	1
15.	Role of Co-Interventions	1	1	1	1	1	1	1	1
V.	RANDOMIZATION								
16.	Method of Randomization	2	2	2	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT								
17.	Concealed Treatment Allocation	2	2	2	2	2	2	2	2
VII.	BLINDING								
18.	Patient Blinding	1	1	1	1	1	1	1	1
19.	Care Provider Blinding	1	1	1	1	1	0	1	1
20.	Outcome Assessor Blinding	0	0	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST								
21.	Funding and Sponsorship	2	2	2	2	2	2	2	2
22.	Conflicts of Interest	3	3	3	3	3	3	3	3
TOTAL		44	44	44	44	44	39	43	44

Source: Manchikanti L, 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 (83).

Table 3 (cont.). *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Manchikanti et al (93)	Manchikanti et al (94)	Manchikanti et al (95)	Manchikanti et al (96)	Manchikanti et al (97)	Manchikanti et al (98)	Friedly et al (99)
I.	TRIAL DESIGN AND GUIDANCE REPORTING							
1.	CONSORT or SPIRIT	3	3	3	3	3	3	3
II.	DESIGN FACTORS							
2.	Type and Design of Trial	2	2	2	2	2	2	0
3.	Setting/Physician	2	2	2	2	2	2	2
4.	Imaging	3	3	3	3	3	3	2
5.	Sample Size	3	2	3	2	3	3	3
6.	Statistical Methodology	1	1	1	1	1	1	1
III.	PATIENT FACTORS							
7.	Inclusiveness of Population	2	2	2	2	1	2	1
8.	Duration of Pain	2	2	2	2	2	2	1
9.	Previous Treatments	2	2	2	2	2	2	1
10.	Duration of Follow-up with Appropriate Interventions	3	2	3	2	3	3	0
IV.	OUTCOMES							
11.	Outcomes Assessment Criteria for Significant Improvement	4	4	4	4	4	4	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2	1
13.	Description of Drop Out Rate	2	2	2	2	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	1	1	1	1	1	1
15.	Role of Co-Interventions	1	1	1	1	1	1	1
V.	RANDOMIZATION							
16.	Method of Randomization	2	2	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT							
17.	Concealed Treatment Allocation	2	2	2	2	2	2	0
VII.	BLINDING							
18.	Patient Blinding	1	1	1	1	1	1	0
19.	Care Provider Blinding	1	1	1	1	1	1	0
20.	Outcome Assessor Blinding	0	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST							
21.	Funding and Sponsorship	2	2	2	2	2	2	2
22.	Conflicts of Interest	3	3	3	3	3	3	0
TOTAL		43	42	44	42	43	44	25

Source: Manchikanti L, 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 (83).

Table 4. Characteristics of fluoroscopic epidural injections with lidocaine alone or with steroids.

Study Study Characteristics Methodological Quality Scoring	Drugs Utilized and Volumes	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
				6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
CAUDAL										
Manchikanti et al, 2012 (85) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Lidocaine 10 mL versus lidocaine 9 mL + 1 mL particulate steroid	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.	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%	Overall: LA 60% vs. LA with steroid 65% Responsive: LA 77% vs. LA with steroid 76%	Lidocaine & lidocaine with steroid effective	Both treatments effective	Both treatments effective	• Positive double-blind randomiz thetic only and with steroids group. • Over a period of 2 years, on average, a total of 5-6 injections were provided.
Manchikanti et al, 2012 (86) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 12/13 IPM-QRB = 44/48	Lidocaine 10 mL versus lidocaine 9 mL + 1 mL particulate steroid	Total = 100 Lidocaine = 50 Lidocaine + steroid = 50 Lidocaine 0.5% vs.. lidocaine mixed with steroid. Average number of injections = 5 to 6 for 2 years	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.	Overall: LA 54% vs. LA with steroid 50% Responsive: LA 73% vs. LA with steroid 68%	Overall: LA 44% vs. LA with steroid 46% Responsive: LA 54% vs. LA with steroid 62%	Overall: LA 38% vs. LA with steroid 44% Responsive: LA 51% vs. LA with steroid 57%	Both treatments effective	Both treatments effective	Both treatments effective	• Double-blind design in a practical setting. • Similar results with local anesthetic or with local anesthetic and steroids. • Nonresponsive patients: local anesthetic = 13, steroids = 13. • A total of 5-6 injections on average were provided over a period of 2 years; compared to all patients with significant improvement of 38% in local anesthetic group, 44% in steroid group.

Table 4 (cont.). Characteristics of fluoroscopic epidural injections with lidocaine alone or with steroids.

Study Study Characteristics Methodological Quality Scoring	Drugs Utilized and Volumes	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
				6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Manchikanti et al, 2012 (87) RA, AC, F Axial or discogenic Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Lidocaine 10 mL versus lidocaine 9 mL + 1 mL particulate steroid	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs.. lidocaine mixed with steroid 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.	Overall: LA 62% vs. LA with steroid 72% Responsive: LA 89% vs. LA with steroid 93%	Overall: LA 56% vs. LA with steroid 68% Responsive: LA 84% vs. LA with steroid 85%	Overall: LA 54% vs. LA with steroid 60% Responsive: LA 84% vs. LA with steroid 73%	P	Both treatments effective	Both treatments effective	• Positive randomized double-blind trial with similar results with local anesthetic or with local anesthetic and steroids. • There was an inordinately high proportion of patients failing to respond initially in both groups, 23 in local anesthetic group, and 19 in steroid group. • On average, a total of 5-6 injections were provided over a period of 2 years.
Manchikanti et al, 2012 (88) RA, AC, F Post surgery syndrome Quality Scores: Cochrane = 12/13 IPM-QRB = 44/48	Lidocaine 10 mL versus lidocaine 9 mL + 1 mL particulate steroid	Total = 140 Lidocaine = 70 Lidocaine + steroid = 70 Lidocaine vs.. lidocaine mixed with non-particulate betamethasone Average number of injections = 5 to 6 for 2 years	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.	Overall: LA 56% vs. LA with steroid 61% Responsive: LA 74% vs. LA with steroid 78%	Overall: LA 53% vs. LA with steroid 59% Responsive: LA 70% vs. LA with steroid 75%	Overall: LA 47% vs. LA with steroid 58% Responsive: LA 62% vs. LA with steroid 69%	P	Both treatments effective	Both treatments effective	• Positive results with local anesthetics with or without steroids. • Similar results with local anesthetic or with local anesthetic and steroids. • Nonresponsive patients: local anesthetic = 17, steroids = 15. • On average, 5-6 injections were provided over a period of 2 years; compared to all patients with significant improvement of 47% in local anesthetic group, 58% in steroid group.

Table 4 (cont.). Characteristics of fluoroscopic epidural injections with lidocaine alone or with steroids.

Study Study Characteristics Methodological Quality Scoring	Drugs Utilized and Volumes	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
				6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
LUMBAR INTERLAMINAR										
Manchikanti et al, 2014 (89) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Lidocaine 6 mL versus lidocaine 5 mL + 1 mL particulate steroid	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.	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%	Overall: Lidocaine 60% vs. lidocaine with steroid 70% Responsive: Lidocaine 72% vs.. lidocaine with steroid 71%	Both treatments effective	Both treatments effective	Both treatments effective	• Positive randomized trial with long-term follow-up. • Similar results with local anesthetic or with local anesthetic and steroids, significant improvement. • Steroids were superior at 6 months with pain relief and 12 months with functional status • Significantly higher proportion of patients non-responsive to first 2 injections in local anesthetic group 10 vs. 1. • On average, a total of 5-6 injections provided over 2 years.
Ghai et al, 2015 (90) RA, DB, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 39/48	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	Total = 69 Lidocaine = 34 Lidocaine + methylprednisolone = 35 Average procedures: 2	Numeric rating scale and functional disability using Modified Oswestry Disability Questionnaire Follow-up: 1 year	Lidocaine: 56% Lidocaine with methylprednisolone: 86%	Lidocaine: 59% Lidocaine with methylprednisolone: 89%	NA	Both arms effective. Steroids superior	Both arms effective. Steroids superior	NA	Active control trial with long-term follow-up comparing lidocaine with lidocaine and methylprednisolone showed similar results after 3 months, even though quality of relief superior in local anesthetic with steroid group.
Manchikanti et al, 2015 (91) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 11/13 IPM-QRB = 43/48	Lidocaine 6 mL versus lidocaine 5 mL + 1 mL particulate steroid	Total = 120 Local anesthetics = 60 Local anesthetics and steroids = 60 Lidocaine alone or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures. Significant improvement: 50% in pain and function.	Overall: LA 72% vs. LA with steroid 75% Responsive: LA 78% vs. LA with steroid 83%	Overall: LA 77% vs. LA with steroid 67% Responsive: LA 84% vs. LA with steroid 71%	Overall: LA 72% vs. LA with steroid 73% Responsive: LA 84% vs. LA with steroid 85%	Both treatments effective	Both treatments effective	Both treatments effective	• Positive results in a large active control trial. • Both local anesthetic alone or with steroids were effective with no significant difference between the groups. • On average, a total of 5-6 injections were administered over a period of 2 years.

Table 4 (cont.). Characteristics of fluoroscopic epidural injections with lidocaine alone or with steroids.

Study Study Characteristics Methodological Quality Scoring	Drugs Utilized and Volumes	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
				6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Manchikanti et al, 2013 (92) RA, AC, F Axial or discogenic Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Lidocaine 6 mL versus lidocaine 5 mL + 1 mL particulate steroid	Total = 120 Local anesthetics = 60 Local anesthetics and steroids = 60 Lidocaine alone or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 72% vs. LA with steroid 75% Responsive: LA 78% vs. LA with steroid 83%	Overall: LA 77% vs. LA with steroid 67% Responsive: LA 84% vs. LA with steroid 71%	Overall: LA 72% vs. LA with steroid 67% Responsive: LA 78% vs. LA with steroid 70%	P	Both treatments effective	Both treatments effective	• Positive results in a large active control trial. • Both local anesthetic alone or with steroids were effective with no significant difference between the groups. • On average, a total of 5-6 injections were administered over a period of 2 years.
Friedly et al, 2017 (99) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 6/13 IPM-QRB = 25/48	Lidocaine 1-3 mL of 0.25% to 1% or lidocaine 1-3 mL of 0.25% with 60-120 mg of triamcinolone, 6-12 mg of betamethasone, 8-10 mg of dexamethasone, or 60-120 mg of methylprednisolone	Total = 280 Lidocaine alone = 139 Lidocaine with glucocorticoids = 143	Roland-Morris Disability questionnaire, intensity of leg pain	Proportion of patients improving above 50% was not provided At 3 weeks, glucocorticoid with lidocaine showed significantly better improvement with Roland-Morris Disability questionnaire scores and leg pain intensity Both groups showed equal improvement	Proportion of patients improving above 50% was not provided At 3 weeks, glucocorticoid with lidocaine showed significantly better improvement with Roland-Morris Disability questionnaire scores and leg pain intensity Both groups showed equal improvement with lidocaine alone or lidocaine with steroids concluded as both equal and ineffective	NA	Equal relief with lidocaine alone or lidocaine with steroids	Equal relief with lidocaine alone or lidocaine with steroids	N	• Very poorly designed and conducted study with only 6 weeks of follow-up without assessment of proportion of patients with 50% pain relief and crossover after 6 weeks. Essentially this is a 6-week follow-up study published in a high impact journal, New England Journal of Medicine, with follow-up published in a different journal.

Table 4 (cont.). Characteristics of fluoroscopic epidural injections with lidocaine alone or with steroids.

Study Study Characteristics Methodological Quality Scoring	Drugs Utilized and Volumes	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
				6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
CERVICAL/THORACIC INTERLAMINAR										
Manchikanti et al, 2013 (93) RA, AC, DB, F Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 12/13 IPM-QRB = 43/48	Lidocaine 5 mL versus lidocaine 4 mL + 1 mL particulate steroid	Total = 120 Local anesthetic = 60 Local anesthetic with steroids = 60 Local anesthetic or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, NDI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 82% vs. LA with steroid 73% Responsive: LA 91% vs. LA with steroid 86%	Overall: LA 72% vs. LA with steroid 68% Responsive: LA 77% vs. LA with steroid 82%	Overall: LA 72% vs. LA with steroid 68% Responsive: LA 77% vs. LA with steroid 80%	P	Both treatments effective	Both treatments effective	• Positive results in a randomized large trial performed under fluoroscopy with long-term follow-up. • Similar results with local anesthetic or with local anesthetic and steroids. • Overall, a total of 5-6 injections were administered over a period of 2 years.
Manchikanti et al, 2012 (94) RA, AC, F Cervical spinal stenosis Quality Scores: Cochrane = 11/13 IPM-QRB = 42/48	Lidocaine 5 mL versus lidocaine 4 mL + 1 mL particulate steroid	Total = 60 Local anesthetic only = 30 Local anesthetic with steroids = 30 Local anesthetic or with Celestone Average number of injections = 3 to 4 for 1 year	NRS, NDI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures.	Overall: LA 87% vs. LA with steroid 80% Responsive: LA 79% vs. LA with steroid 92%	Overall: LA 73% vs. LA with steroid 70% Responsive: LA 90% vs. LA with steroid 89%	NA	P	Both treatments effective	NA	• Preliminary results of a large randomized trial performed under fluoroscopy with positive results. • Similar results with local anesthetic or with local anesthetic and steroids. • Overall, 3-4 injections were provided over a period of 1 year.
Manchikanti et al, 2014 (95) RA, DB, AC, F Cervical axial or discogenic Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Lidocaine 5 mL versus lidocaine 4 mL + 1 mL particulate steroid	Total = 120 Local anesthetic only = 60 Local anesthetic with steroids = 60 Local anesthetic or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, NDI, opioid intake, employment, changes in weight Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 67% vs. LA with steroid 73% Responsive: LA 73% vs. LA with steroid 79%	Overall: LA 72% vs. LA with steroid 68% Responsive: LA 78% vs. LA with steroid 83%	Overall: LA 73% vs. LA with steroid 70% Responsive: LA 78% vs. LA with steroid 75%	P	Both treatments effective	Both treatments effective	• Positive results of a large randomized controlled trial performed under fluoroscopy. • Similar results with local anesthetic or with local anesthetic and steroids. • A total of 5-6 injections on average were provided over a period of 2 years.

Table 4 (cont.). Characteristics of fluoroscopic epidural injections with lidocaine alone or with steroids.

Study Study Characteristics Methodological Quality Scoring	Drugs Utilized and Volumes	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
				6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term		
								≥ 12 mos.	24 mos.	
Manchikanti et al, 2018 (96) RA, AC, F Cervical post surgery syndrome Quality Scores: Cochrane = 11/13 IPM-QRB = 42/48	Lidocaine 5 mL versus lidocaine 4 mL + 1 mL particulate steroid	Total = 56 Local anesthetic only = 28 Local anesthetic with steroids = 28 Local anesthetic or with Celestone Average number of injections = 3 to 4 for one year	NRS, NDI, employment status, opioid intake. Significant improvement > 50% pain relief and > 50% functional status improvement. Responsive defined as patients responding with at least 3 weeks of improvement with the first 2 procedures.	Overall: LA 64% vs. LA with steroid 71% Responsive: LA 78% vs. LA with steroid 80%	Overall: LA 71% vs. LA with steroid 64% Responsive: LA 87% vs. LA with steroid 72%	NA	P	Both treatments effective	NA	• An active-control trial conducted with fluoroscopy with positive results. • Similar results with local anesthetic or with local anesthetic and steroids. • On average, 3-4 injections were provided.
Manchikanti et al, 2014 (97) RA, AC, DB, F Thoracic pain Quality Scores: Cochrane = 12/13 IPM-QRB = 43/48	Lidocaine 6 mL versus lidocaine 5 mL + 1 mL particulate steroid	Total = 110 Local anesthetic only = 55 Local anesthetic with steroids = 55 6 mL local anesthetic only or 6 mL local anesthetic with 6 mg of nonparticulate betamethasone Average number of injections = 5 - 6 for 2 years	NRS, ODI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 74% vs. LA with steroid 84% Responsive: LA 84% vs. LA with steroid 90%	Overall: LA 71% vs. LA with steroid 84% Responsive: LA 80% vs. LA with steroid 90%	Overall: LA 71% vs. LA with steroid 80% Responsive: LA 80% vs. LA with steroid 86%	P	Both treatments effective	Both treatments effective	• First large randomized trial with active control design and long-term follow-up. • Similar results with local anesthetic or with local anesthetic and steroids. • On average, 5-6 total procedures were performed over a period of 2 years.
LUMBAR TRANSFORAMINAL										
Manchikanti et al, 2014 (98) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Lidocaine 2 mL versus lidocaine 1.5 mL + 0.5 mL particulate steroid	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.	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%	Overall: LA 65% vs. LA with steroid 57% Responsive LA 80% vs. LA with steroid 73%	Effectiveness in both groups. Lidocaine alone or with steroids effective.	Effectiveness in both groups. Lidocaine alone or with steroids effective.	Effectiveness in both groups. Lidocaine alone or with steroids effective.	• 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.

Table 4 (cont.). Characteristics of fluoroscopic epidural injections with lidocaine alone or with steroids.

Study Study Characteristics Methodological Quality Scoring	Drugs Utilized and Volumes	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
				6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Friedly et al, 2017 (99) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 6/13 IPM-QRB = 25/48	Lidocaine 1-3 mL of 0.25% to 1% or lidocaine 1-3 mL of 0.25% with 60-120 mg of triamcinolone, 6-12 mg of betamethasone, 8-10 mg of dexamethasone, or 60-120 mg of methylprednisolone	Total = 118 Lidocaine alone = 61 Lidocaine with glucocorticoids = 57	Roland-Morris Disability questionnaire, intensity of leg pain	Proportion of patients improving above 50% was not provided At 3 weeks, glucocorticoid with lidocaine showed significantly better improvement with Roland-Morris Disability questionnaire scores and leg pain intensity Both groups showed equal improvement	Proportion of patients improving above 50% was not provided At 3 weeks, glucocorticoid with lidocaine showed significantly better improvement with Roland-Morris Disability questionnaire scores and leg pain intensity Both groups showed equal improvement with lidocaine alone or lidocaine with steroids concluded as both equal and ineffective	NA	Equal relief with lidocaine alone or lidocaine with steroids	Equal relief with lidocaine alone or lidocaine with steroids	N	• Very poorly designed and conducted study with only 6 weeks of follow-up without assessment of proportion of patients with 50% pain relief and crossover after 6 weeks. Essentially this is a 6-week follow-up study published in a high impact journal, New England Journal of Medicine, with follow-up published in a different journal.

RA = Randomized; AC = Active Control; F = Fluoroscopy; DB = Double-Blind; P = Positive; NA = Not Applicable; LA = local anesthetic; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; NDI = Neck Disability Index; IPM – QRB = Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment

3.4 Meta-Analysis

Meta-analysis was performed utilizing conventional dual-arm analysis and a single-arm analysis of all the studies meeting inclusion criteria.

3.4.1 Pain and Function at 6 Months

3.4.1.1 Dual-Arm Meta-Analysis

As demonstrated in Fig. 2, there were 15 studies (85-99) which provided results eligible for analysis of spinal pain and functional improvement using numeric rating scale (NRS) and Disability Index after 6 months. Conventional and dual arm meta-analysis showed no statistical significance between the 2 groups at 6 months follow-up [SMD -0.14 (-0.64, 0.36), P = 0.59]..

As shown in Fig. 2B, no statistical significance for functional status and improvement between the 2 groups at 6 months follow-up [SMD -0.10 (-0.57, 0.37), P = 0.68].

3.4.1.2 Single-Arm Meta-Analysis

Singe-arm meta-analysis was performed for lidocaine alone and lidocaine with steroids for pain relief utilizing data from 15 studies as shown in Fig. 3 (85-99).

Figure 3A shows changes from baseline at 6 months in patients with spinal pain treated with lidocaine with 4.16-point decrease. Figure 3B shows changes from baseline at 6 months in patients with spinal pain treated with lidocaine and steroids with 5.5-point decrease.

Figure 3C demonstrates changes from baseline at 6 months in patients with spinal pain treated with

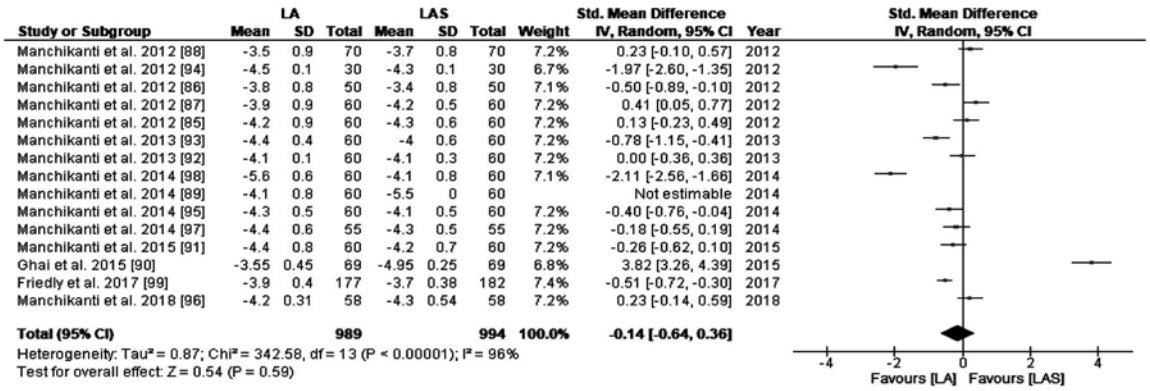

Fig. 2A. *Change in pain level using Numeric Rating Scale (NRS) at 6 months*

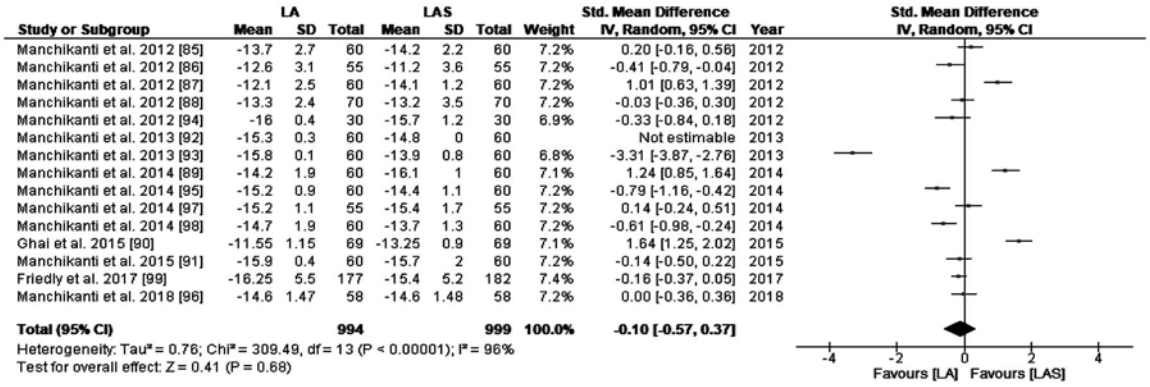

Fig. 2B. Change in functionality using Disability Index at 6 months.

Fig. 2. *Changes in spinal pain levels and functionality using Numeric Pain Rating scales (NRS) and disability scales (2A-2B) from baseline at 6-month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids utilizing conventional dual-arm analysis.*

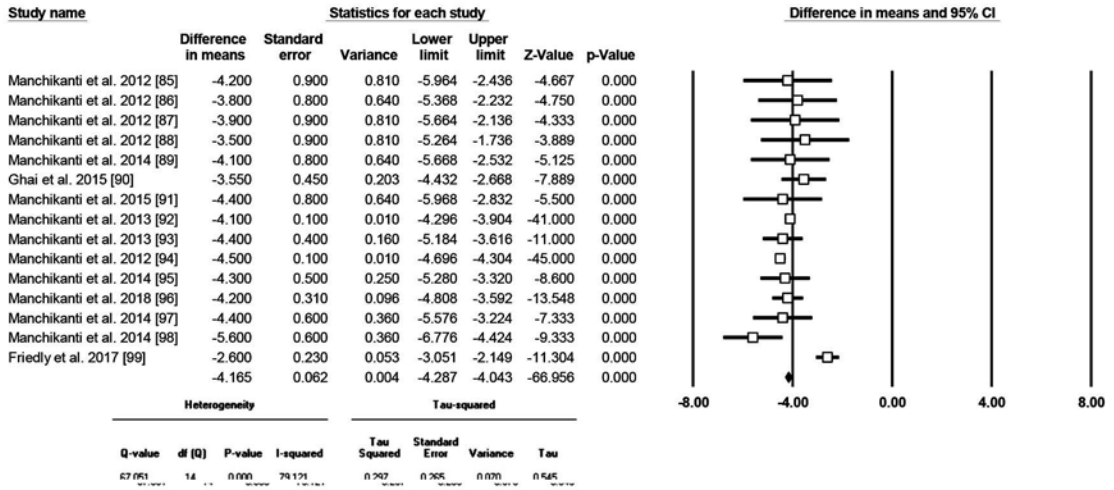

Fig. 3A. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 6 months in patients treated with lidocaine with single arm analysis.

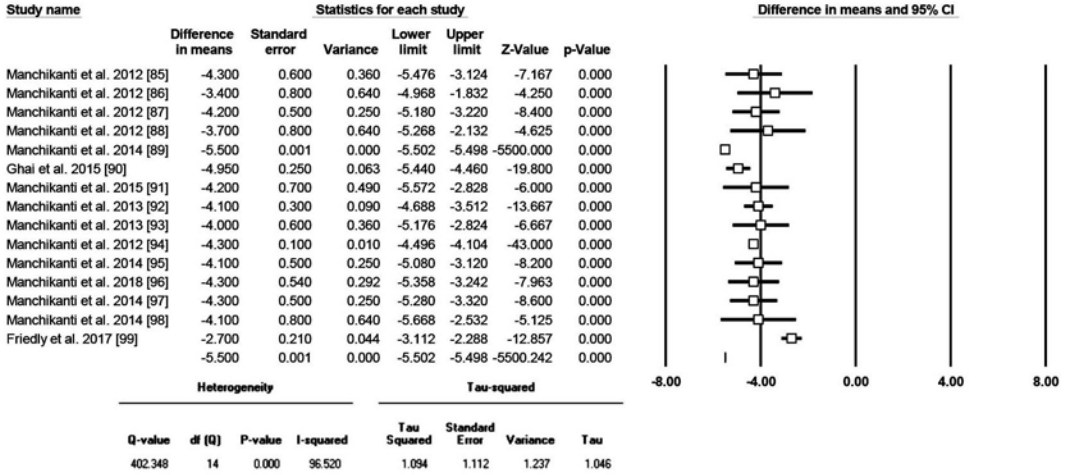

Fig. 3B. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 6 months in patients treated with lidocaine + steroids with single arm analysis.

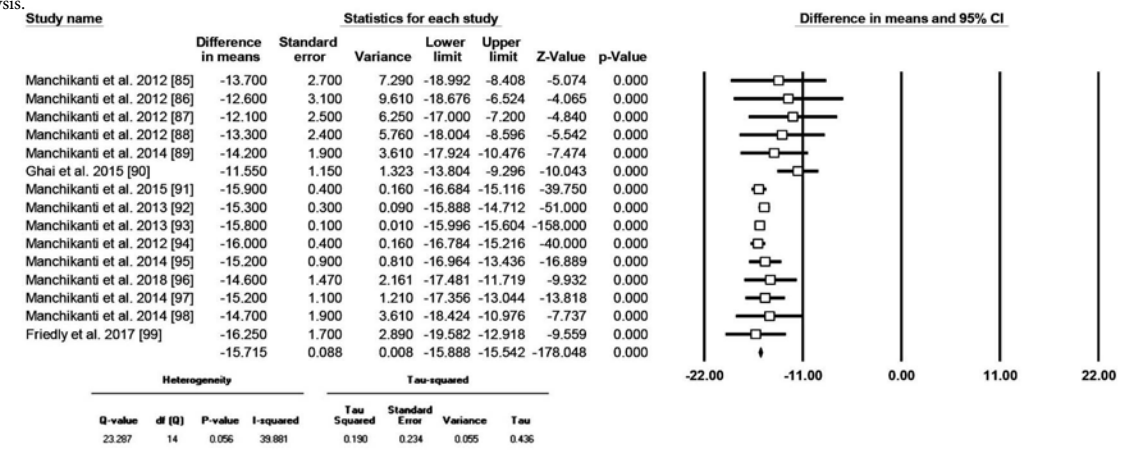

Fig. 3C. *Change in functional level using Disability Index from baseline at 6 months in patients treated with lidocaine.*

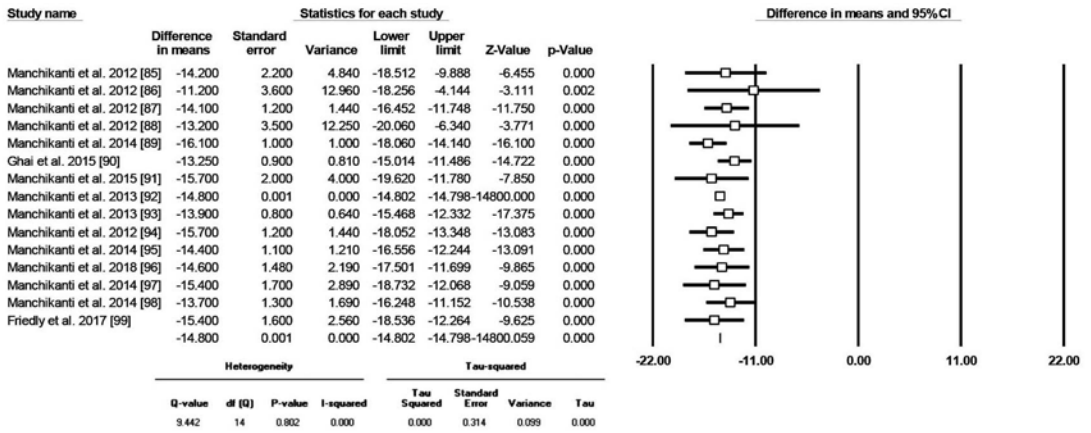

Fig. 3D. *Change in functional level using Disability Index from baseline at 6 months in patients treated with lidocaine + steroids.*

Fig. 3. Changes in spinal pain levels and functionality using numeric pain rating scales (NRS) and disability scales from baseline at 6 month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids utilizing single-arm analysis.

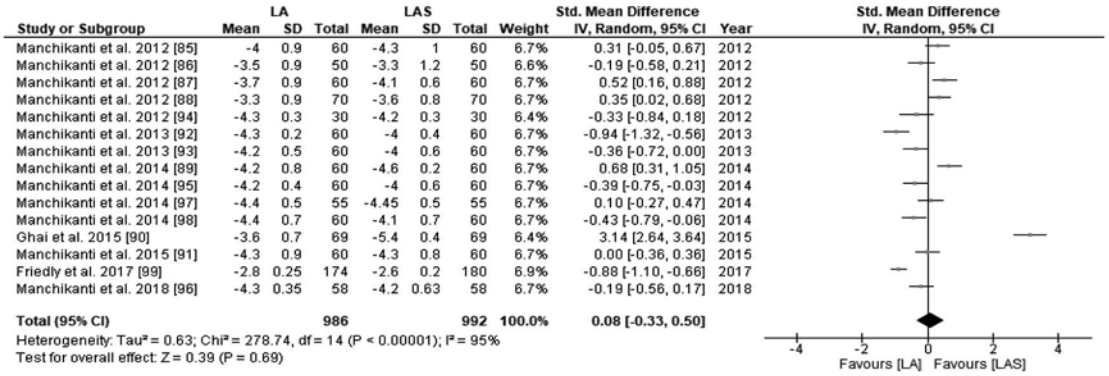

Fig. 4A. Change in pain level using Numeric Rating Scale (NRS) at 12 months.

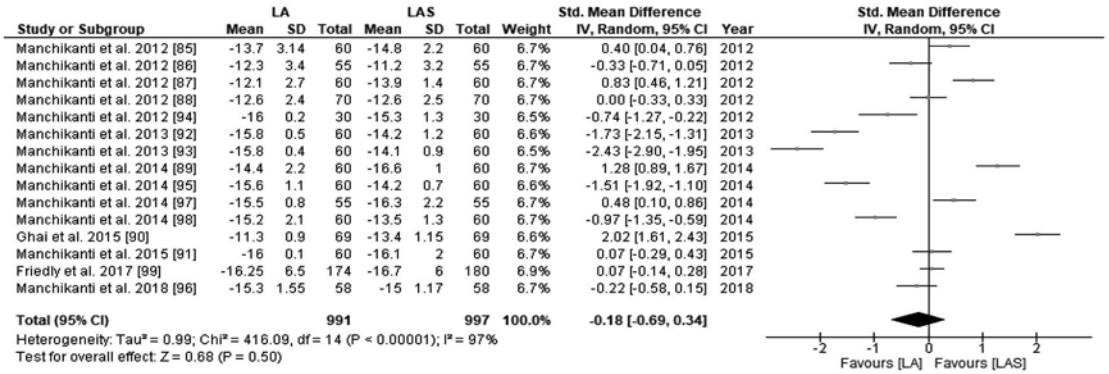

Fig. 4B. Change in functionality using Disability Index at 12 months.

Fig. 4. Changes in spinal pain levels using numeric pain rating scales (NRS) and disability scales from baseline at 12-month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids utilizing dual-arm analysis.

lidocaine with 15.71-point decrease. Figure 3D shows changes from baseline at 6 months in patients with spinal pain treated with lidocaine and steroids with a 14.8-point decrease.

3.4.2 Pain and Function at 12 Months

3.4.2.1 Dual-Arm Meta-analysis

There were 15 studies (85-99) which provided results eligible for analysis of spinal pain improvement using NRS and Disability Index after 12 months (Fig. 4). Analysis showed no statistically significant difference between the 2 groups at 12 months follow-up [SMD 0.08 (-0.33, 0.50), P = 0.69] in pain relief (Fig. 4A).

Analysis showed no statistically significant difference between the 2 groups at 12 months follow-up [SMD -0.18 (-0.69,0.34), P = 0.50] in functionality (Fig. 4B).

3.4.2.2 Single-Arm Meta-analysis

Singe-arm meta-analysis was performed for lidocaine alone and lidocaine with steroids for pain relief and Disability Index utilizing data from 15 studies as shown in Fig. 5 (85-99).

Figure 5A shows changes from baseline at 12 months in patients with spinal pain treated with lidocaine with a 3.96-point decrease. Figure 5B shows changes from baseline at 12 months in patients with spinal pain treated with lidocaine and steroids with a 3.99-point decrease.

Figure 5C shows change in Disability Index from baseline at 12 months in patients with spinal pain

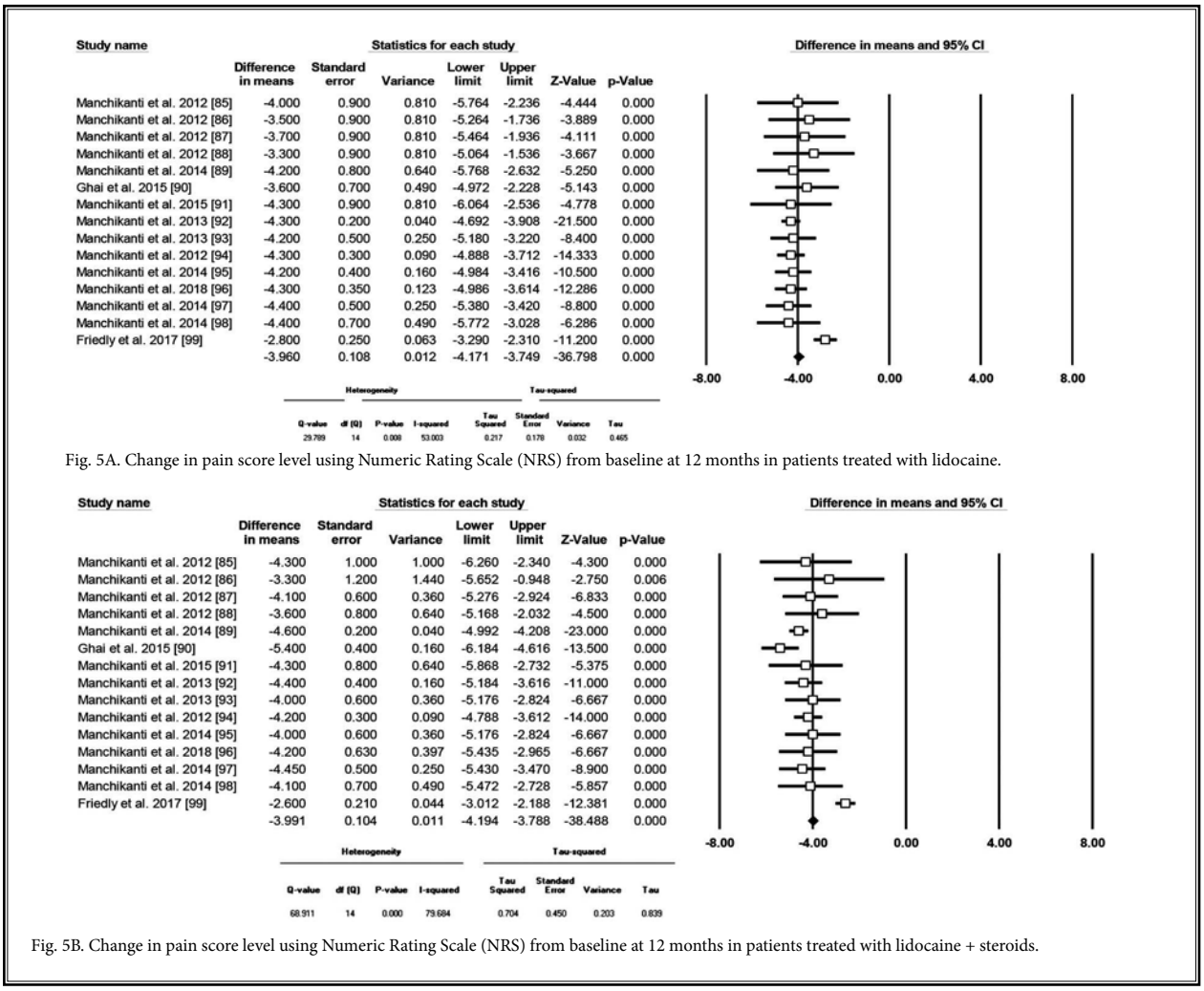

Fig. 5A. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 12 months in patients treated with lidocaine.

Fig. 5B. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 12 months in patients treated with lidocaine + steroids.

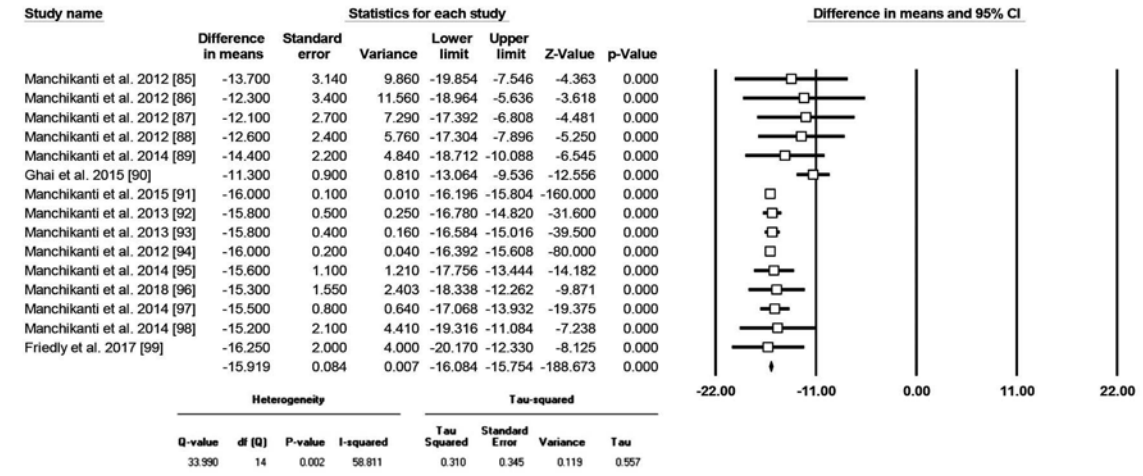

Fig. 5C. Change in functional level using Disability Index from baseline at 12 months in patients treated with lidocaine.

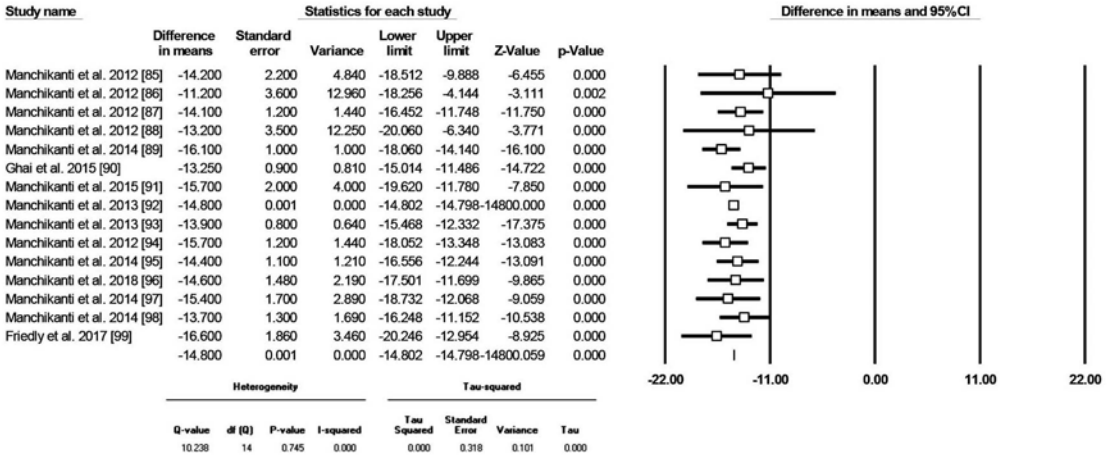

Fig. 5D. Change in functional level using Disability Index from baseline at 12 months in patients treated with lidocaine + steroids.

Fig. 5. Changes in spinal pain levels and functionality using numeric pain rating scales (NRS) and disability scales from baseline at 12 month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids utilizing single-arm analysis.

treated with lidocaine with a 15.91-point decrease. Figure 5D shows change in Disability Index from baseline at 12 months in patients with spinal pain treated with lidocaine and steroids with a 14.8-point decrease.

3.4.3 Pain and Function at 24 Months

3.4.3.1 Dual-Arm Meta-Analysis

There were 11 studies (85-87,89,91-93,95-98) which provided results eligible for analysis of pain and functionality improvement using NRS and Disability Index after 24 months (Fig. 6). Analysis showed no statistically significant difference between the 2 groups at 24 months follow-up [SMD 0.03 (-0.13, 0.18), P = 0.75] with pain (Fig. 6A). The analysis also showed no statistically significant difference between the 2 groups at 24 months follow-up [SMD -0.22 (-0.81,0.37), P = 0.47] with regard to functionality (Fig. 6B).

3.4.3.2- Single-arm Meta-analysis

Single-arm meta-analysis was performed for lidocaine alone and lidocaine with steroids for pain relief and functionality utilizing data from 11 studies as shown in Fig. 7 (85-87,89,91-93,95-98).

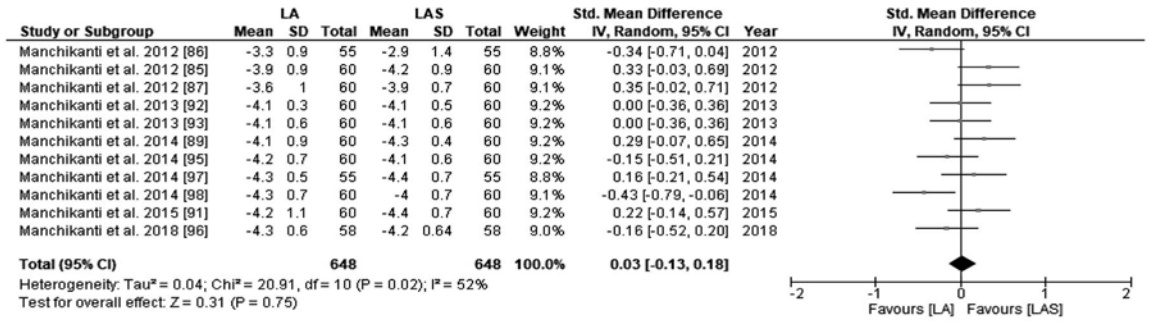

Fig. 6A. Change in pain level using Numeric Rating Scale (NRS) at 24 months.

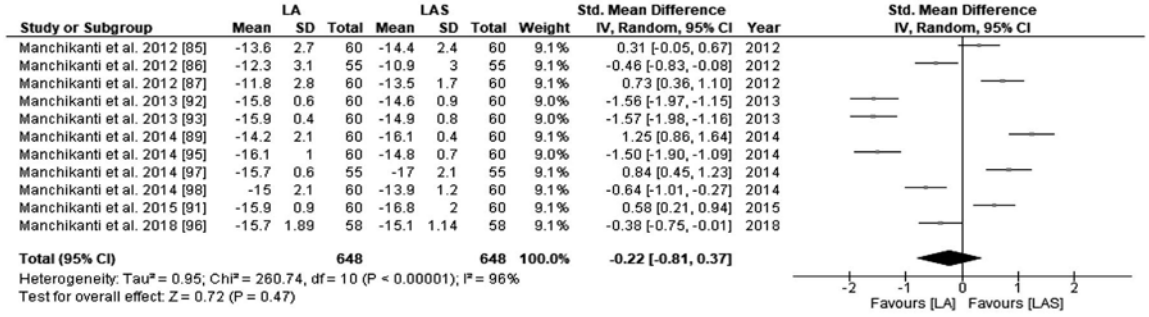

Fig. 6B. Change in functionality using Disability Index at 24 months.

Fig. 6. *Changes in spinal pain levels and functionality using Numeric Pain Rating scales (NRS) and disability scales from baseline at 24-month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids with dual-arm analysis.*

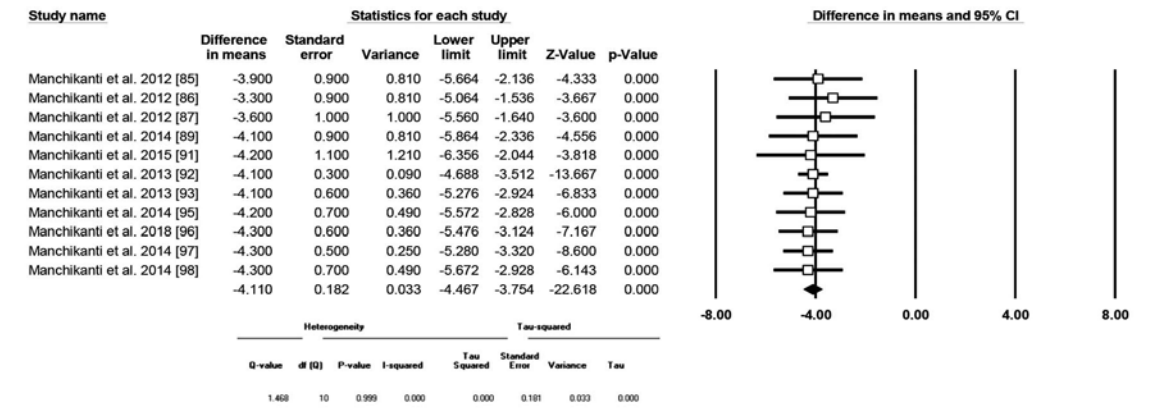

Fig. 7A. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 24 months in patients treated with lidocaine

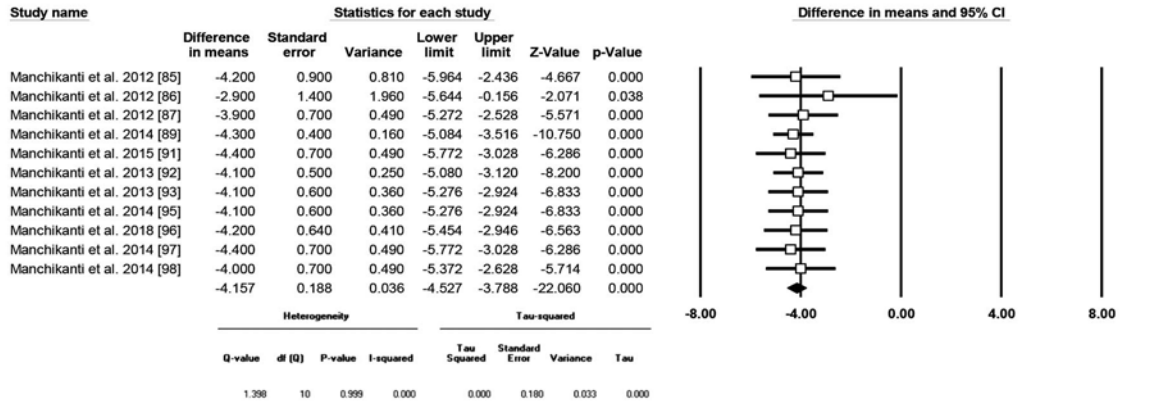

Fig. 7B. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 24 months in patients treated with lidocaine + steroids.

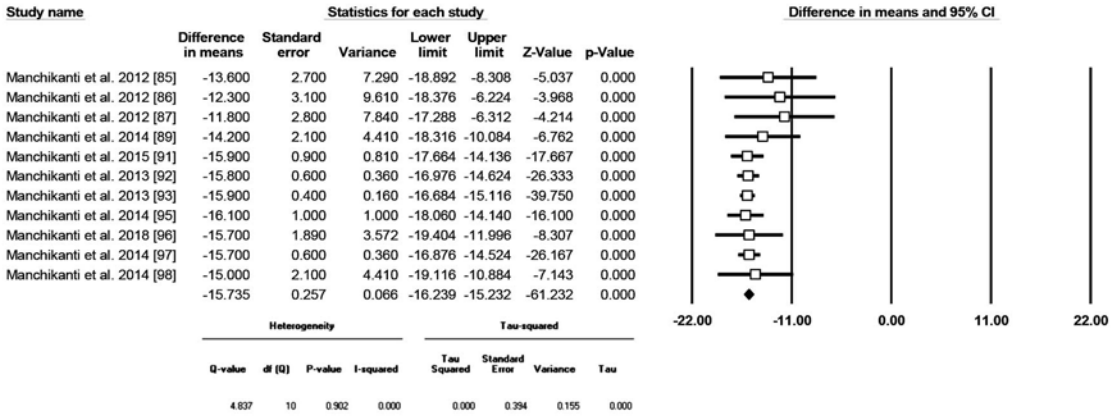

Fig. 7C. Change in functional level using Disability Index from baseline at 24 months in patients treated with lidocaine.

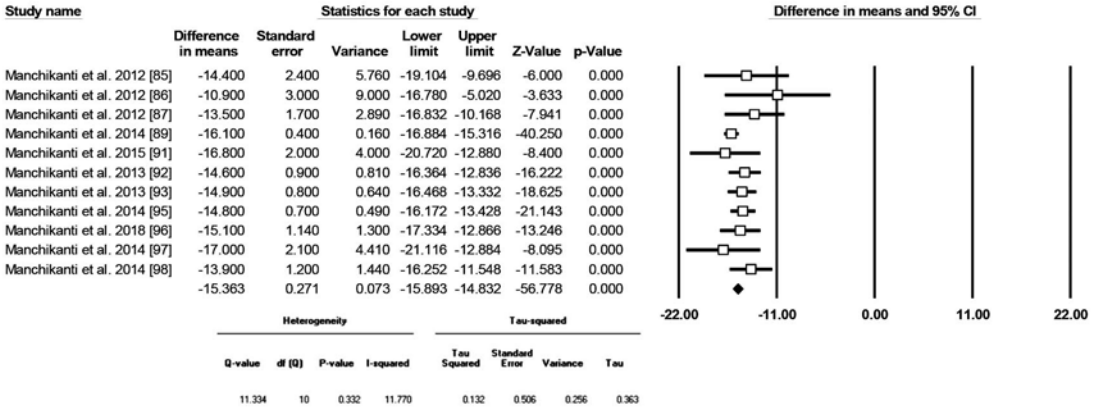

Fig. 7D. Change in functional level using Disability Index from baseline at 24 months in patients treated with lidocaine + steroids.

Fig. 7. Changes in spinal pain levels and functionality using numeric pain rating scales (NRS) and disability scales from baseline at 24-month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids with single-arm analysis.

Figure 7A shows changes from baseline at 24 months in patients with pain treated with lidocaine with a 4.11-point decrease. Figure 7B shows changes from baseline at 24 months in patients with pain treated with lidocaine and steroids with a 4.15-point decrease.

Figure 7C shows changes from baseline at 24 months in patients with functional status improvement treated with lidocaine with a 15.73-point decrease, whereas, Fig. 7D shows changes from baseline at 24 months in patients with functionality treated with lidocaine and steroids with a 15.36-point decrease.

3.5 Analysis of Significant Improvement

Greater than 50% pain relief and improvement in functional status was considered as a hard outcome and 50% or greater improvement (significant improvement) in pain relief or functional status alone was considered as a soft outcome.

Of the 15 studies, 14 of them met inclusion criteria with data available for significant improvement with pain relief and function at 12 months, whereas at 24 months, only 12 of 15 studies met the inclusion criteria.

Table 5 shows significant improvement (≥ 50%) in pain relief and functional status at 12 months and Table 6 shows the results at 24 months.

There was no statistically significant difference in the proportion of patients demonstrating improvement with local anesthetic alone or local anesthetic with steroids. In addition, this was also assessed for all patients participating in the treatment and those patients that were responsive and continued with the treatments after the first 2 treatments with significant improvement as defined in the manuscripts, when available, with pain and function The data was available only for the studies by Manchikanti et al (85-89,91-98), whereas it was not available for the studies by Ghai et al (90) and Friedly et al (99).

Table 5. Significant improvement at 12 months – significant improvement (≥ 50%) of pain and function.

Study	All patients			Responsive Patients		
	Lidocaine Only	Lidocaine + Steroids	Difference (P value)	Lidocaine Only	Lidocaine + Steroids	Difference
Disc herniation						
Manchikanti et al (85)	67% (40/60)	72% (43/60)	0.5536	85% (40/47)	84% (42/50)	0.8924
Manchikanti et al (89)	67% (40/60)	85% (51/60)	0.0215	80% (40/50)	86% (51/59)	0.4050
Manchikanti et al (93)	72% (43/60)	68% (41/60)	0.6340	77% (41/53)	82% (41/50)	0.5324
Manchikanti et al (97)	71% (39/55)	84% (46/55)	0.1041	80% (39/49)	90% (46/51)	0.1625
Manchikanti et al (98)	75% (45/60)	57% (34/60)	0.0382	92% (45/49)	73% (33/45)	0.0150
Pooled#	70% (207/295)	73% (215/295)	0.4260	83% (205/248)	84% (213/255)	0.7628
Discogenic pain						
Manchikanti et al (87)	56% (34/60)	68% (41/60)	0.1775	84% (28/33)	85% (35/41)	0.9064
Manchikanti et al (92)	77% (46/60)	67% (40/60)	0.2244	84% (45/54)	71% (38/54)	0.1074
Manchikanti et al (95)	72% (43/60)	68% (41/60)	0.6340	78% (43/55)	73% (41/56)	0.5432
Pooled	68% (123/180)	67% (121/180)	0.8397	82% (116/142)	75% (114/151)	0.1464
Spinal stenosis						
Manchikanti et al (86)	44% (22/50)	46% (23/50)	0.5466	60% (22/37)	60% (22/37)	1.000
Manchikanti et al (91)	73% (44/60)	73% (44/60)	1.000	86% (44/51)	83% (44/53)	0.6743
Manchikanti et al (94)	73% (22/30)	70% (21/30)	0.7985	76% (22/29)	77% (20/26)	0.9311
Pooled	63% (88/140)	63% (88/140)	1.000	75% (88/117)	74% (86/116)	0.8613
Post-surgery syndrome						
Manchikanti et al (88)	53% (37/70)	59% (41/70)	0.4761	70% (37/53)	52% (42/56)	0.0555
Manchikanti et al (96)	74% (43/58)	69% (40/58)	0.5526	79% (42/53)	81% (38/47)	0.8041
Pooled	63% (80/128)	63% (81/128)	0.9340	75% (79/106)	78% (80/103)	0.6100

Table 6. *Significant improvement at 24 months – significant improvement (≥ 50%) of pain and function.*

Study	All patients			Responsive Patients		
	Lidocaine Only	Lidocaine + Steroids	Difference	Lidocaine Only	Lidocaine + Steroids	Difference
Disc herniation						
Manchikanti et al (85)	60% (36/60)	65% (39/60)	0.5732	77% (36/47)	76% (38/50)	0.9081
Manchikanti et al (89)	60% (36/60)	70% (42/60)	0.2528	72% (36/50)	71% (42/59)	0.9087
Manchikanti et al (93)	72% (43/60)	68% (41/60)	0.6340	77% (41/53)	80% (40/50)	0.7126
Manchikanti et al (97)	71% (39/55)	80% (44/55)	0.2747	80% (39/49)	86% (44/51)	0.4263
Manchikanti et al (98)	65% (39/60)	57% (34/60)	0.3710	80% (39/45)	73% (33/45)	0.4361
Pooled#	65% (193/295)	68% (200/295)	0.4405	77% (191/248)	77% (197/255)	1.0000
Discogenic pain						
Manchikanti et al (87)	54% (32/60)	60% (36/60)	0.5086	84% (28/33)	73% (30/41)	0.4856
Manchikanti et al (92)	72% (43/60)	67% (40/60)	0.5536	78% (42/54)	70% (38/54)	0.3455
Manchikanti et al (95)	73% (44/60)	70% (42/60)	0.7170	78% (43/55)	75% (42/56)	0.7107
Pooled	66% (119/180)	66% (118/180)	0.9204	80% (113/142)	73% (110/151)	0.1592
Spinal stenosis						
Manchikanti et al (86)	38% (19/50)	44% (22/50)	0.5439	51% (19/37)	57% (21/37)	0.6071
Manchikanti et al (91)	72% (43/60)	73% (44/60)	0.9028	84% (43/51)	85% (45/53)	0.8885
Pooled	56% (62/110)	60% (66/110)	0.5487	70% (62/88)	73% (66/90)	0.6584
Post-surgery syndrome						
Manchikanti et al (88)	47% (33/70)	58% (39/70)	0.1941	62% (33/53)	69% (39/56)	0.4440
Manchikanti et al (96)	69% (40/58)	71% (41/58)	0.8150	74% (39/53)	79% (37/47)	0.5590
Pooled	57% (73/128)	63% (80/128)	0.3281	68% (72/106)	74% (76/103)	0.3406

3.6 Publication Bias

To elucidate publication bias, Egger's test was performed showing the non-significant P value at 6, 12, and 24 months post procedure (P = 0.086, P = 0.534, P = 0.472, P = 0.680, P = 0.666, respectively) suggesting an absence of publication bias. In addition, we performed a funnel plot for NRS ≥50% pain reduction (Appendix Figs. 1A-1C) and for functional improvement ≥50% (Appendix Figs. 2A-2C) which also revealed an absence of publication bias.

3.7 Synthesis of Results

3.7.1 Qualitative Analysis

Qualitative analysis with all of the high-quality RCTs shows lack of significant difference in outcomes or superiority of one modality over the other with defined hard and soft outcomes of significant improvement at 6, 12, and 24-month follow-up period, with epidural lidocaine alone or addition of steroids.

As shown in Tables 5 and 6, there was no significant difference at 12 months or 24 months measured by significant improvement with ≥ 50% pain relief and improvement in function, isolated to all patients or responsive patients. However, responsive patients showed a higher proportion of patients with a better response compared to all patients, both at 12 month and 24-month follow-up.

3.7.2 Quantitative Analysis

3.7.2.1 Dual Arm Meta-Analysis

Based on the dual-arm meta-analysis, there was no significant difference between lidocaine alone or with steroids at 6, 12, or 24 months in managing spinal pain of various origins including disc herniation, radiculitis, discogenic pain, central spinal stenosis, and post-surgery syndrome.

3.7.2.2 Single Arm Meta-Analysis

Based on the single-arm meta-analysis of pain relief and function, lidocaine or lidocaine with steroids provided significant improvement from baseline to follow-up periods of 6 months, 12 months, and 24 months in managing spinal pain of various origins including disc

herniation, radiculitis, discogenic pain, central spinal stenosis, and post-surgery syndrome.

3.7.3 Level of Evidence

Based on this systematic review with inclusion of multiple high-quality systematic reviews, there is strong evidence that lidocaine alone is equally efficacious compared to lidocaine with steroids. Further, there is also Level I or strong evidence that local anesthetic alone or local anesthetic with steroids are effective in managing spinal pain.

3.8 Funding

There was no external funding in the preparation of this manuscript, all funding was from internal sources.

4.0 Discussion

This systematic review with inclusion of 15 RCTs with one moderate quality and 14 high-quality RCTs utilizing qualitative and quantitative analysis showed significant effectiveness of local anesthetic (lidocaine) alone or local anesthetic with steroids with no significant difference in any of the outcomes in pain management of disc herniation with or without radiculitis, discogenic pain, central spinal stenosis, and post-surgery syndrome at 6, 12, and 24 months follow-up. Both treatments were shown to be significantly effective in relieving pain and improving the functional status at 6, 12, and 24 months in all categories. Each of these trials reported that epidural injections, whether with local anesthetic only or local anesthetic with steroid, were efficacious in 50% to 80% of those treated. These patients were divided into those who responded to the treatment and those who did not. A responsive patient was one who had at least a 50% improvement in both pain and function for 3 weeks with the initial 2 procedures. Those who responded and those who did not were not significantly different for any of the pathologies studied, no matter which injection was received. The significant improvement in pain and function was observed in 53% to 92% of the patients with local anesthetic alone at 12 months, and 51% to 84% at 24 months, with administration of lidocaine alone, and 52% to 92% at 12 months and 57% to 86% at 24 months with addition of steroids to lidocaine in responsive patients as shown in Tables 5 and 6.

Cost utility analysis was also favorable (26-29). However, the literature related to local anesthetic alone and steroids is sparse and controversial (7,8,9,20,23,25,50). Many of the authors have continued to consider local anesthetic as placebo to only equalize local anesthetics with steroids and judge that neither one is effective (20,23,25). There have been other systematic reviews comparing local anesthetics with or without steroids in spinal stenosis and disc herniation in the lumbar region (9-14,50). Consequently, this is the first manuscript to assess the effectiveness of lidocaine alone or with steroids and shows that lidocaine is effective independently of steroids and also shows that there is no superiority of either modality of treatment.

Cost-utility analysis was assessed for caudal and interlaminar epidural injections (26-29) with no significant difference between lidocaine alone or with steroids in various conditions with cost-utility dates ranging from one year quality of life improvement of $3,628 for caudal epidural injections, $3,301 for lumbar interlaminar epidural injections, $3,785.89 for cervical interlaminar epidural injections, and $3,245.20 for thoracic interlaminar epidural injections.

Conflicts and confluence of interest have been described in the literature in various aspects of evidence synthesis including authorship and analysis of the evidence (7,50,64,65,71,80). However, in synthesizing evidence from epidural injections with local anesthetic with or without steroids, the primary conflict lies in the fact that active control trials with local anesthetic are converted into placebo control trials (20,23,25). Further, the systematic reviews and meta-analyses are also performed to address a specific research question which must involve a reproducible and a thorough search of the literature with critical assessment of methodologic quality of the studies (80).

Conversion of local anesthetic into placebo has been utilized subtly (23,25) and more brazenly recently by the Cochrane Collaboration review (20) wherein the design of the study appears to have been changed from active to placebo control. In fact, a systematic review by Manchikanti et al (63) utilizing qualitative and quantitative analysis with utilizing single-arm analysis has shown that the effectiveness of epidural saline or epidural steroids with saline, the pain score reductions were greater than 20% at 3 months in Level II or moderate evidence. Thus, this systematic review demonstrated the lack of true placebo effect with saline and the limited effectiveness of steroids. Further, quantitative analysis showed a lack of significant difference between epidural saline and epidural steroids with lack of effectiveness with epidural saline and epidural steroids with conventional dual-arm analysis.

This study also showed lack of effectiveness in improving function with single-arm analysis with epidural saline and epidural steroids. Furthermore, this study essentially showed that epidural administration of sodium chloride solution was shown to be effective in 40% of the patients, compared to saline and epidural steroids and in 52% of the patients at 3-month follow-up. Thus, extremely low doses of sodium chloride solution administered without fluoroscopy were shown to be effective indicating lack of true placebo effect when injected into the epidural space. In addition, this study also showed that steroids were not placebo and exerted an effect on their own.

This systematic review is the first of its nature with a single-arm meta-analysis, utilizing all available RCTs showing the effectiveness of epidurally injected lidocaine in reducing pain and improving function, showing that it is not a placebo. This also explains multiple discordant conclusions reached in the past, which are based on various challenges, specifically the lack of understanding of placebo control and active-controlled trials, thus leading to the misinterpretation of evidence. Consequently, this analysis also reinforces the major tenet of evidence-based medicine that clinical decisions should be influenced by all relevant high-quality evidence.

Limitations of this analysis include that majority of the studies were performed by one group of authors from one center in private practice (Manchikanti et al). Other limitations include addition of one study which was not conducted in a practical or reliable manner to transfer the data to clinical practice settings (99,100). Due to the nature of the studies, which are active control, and which were wrongly assigned as placebo control in other analysis, conventional dual arm analysis has not shown any significant difference because both were equally effective.

The limitations of this study may be considered as strengths, mainly because appropriately conducted studies were from 2 different countries and practical in nature, which can be applied in clinical practice.

5.0 Conclusion

This systematic review was performed with appropriate methodology for assessment of the evidence, utilized 15 RCTs utilizing either lidocaine alone or lidocaine with steroids. The evidence was assessed with single-arm and dual-arm meta-analysis along with best evidence synthesis for grading the levels of the evidence. Overall, the present meta-analysis shows moderate or Level II evidence for epidural injections with lidocaine with or without steroids in managing spinal pain secondary to disc herniation, spinal stenosis, discogenic pain, and post-surgery syndrome.

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Author Contributions

The study was designed by LM, NNK, ADK, and JAH.

Statistical analysis was performed by NNK.

All authors contributed to preparation to the manuscript, reviewed, and approved the content with final version.

Dr. Knezevic is Vice Chair for Research and Education; Department of Anesthesiology; Advocate Illinois Masonic Medical Center, Chicago, IL and Clinical Associate Professor, Department of Anesthesiology and Surgery, College of Medicine, University of Illinois, Chicago, IL.

Email: nick.knezevic@gmail.com

Dr. Manchikanti is Co-Director, Pain Management Centers of America, Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY, and Professor of Anesthesiology-Research, Department of Anesthesiology, School of Medicine, LSU Health Sciences Center, New Orleans, LA, 67 Lakeview Dr., Paducah, Kentucky 42001. Phone: 270-554-8373 ext. 4101. Fax: 270-554-8987. Email: drlm@thepainmd.com

Dr. Urits is with Beth Israel Deaconess Medical Center, Department of Anesthesiology, Critical Care and Pain Medicine, Harvard Medical School, Boston, MA iurits@bidmc.harvard.edu

Dr. Orhurhu is with Massachusetts General Hospital, Department of Anesthesiology, Critical Care and Pain Medicine, Harvard Medical School, Boston, MA vwo569@mail.harvard.edu

Dr. Vangala is a Consultant Neurosurgeon at Apollo Hospitals, Secunderabad, India
brahma.tejv@gmail.com

Dr. Vanaparthy is a Research Assistant, Oregon Health and Science University, Portland, OR.
vanaparthyrachana@gmail.com

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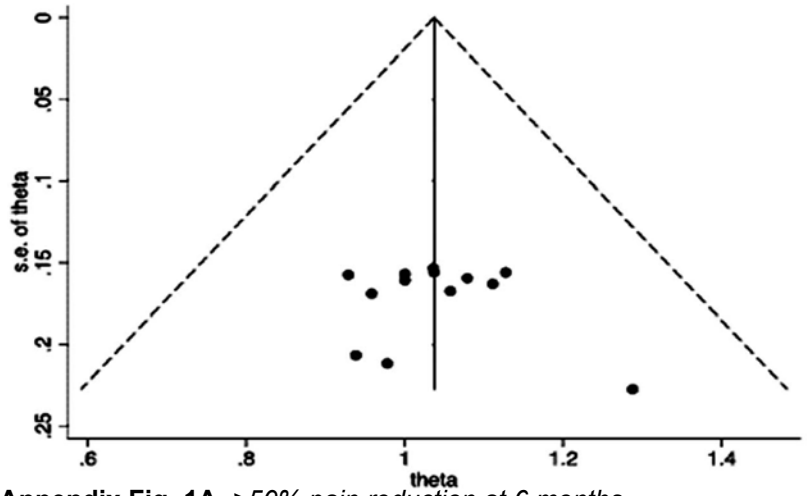
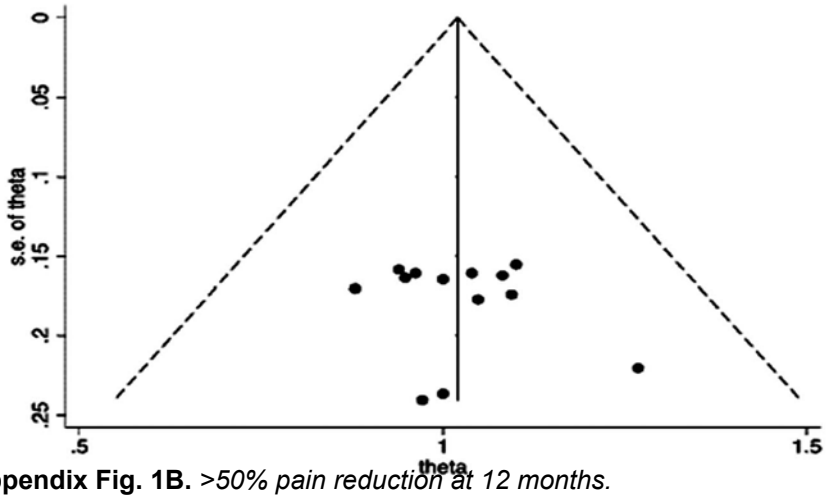
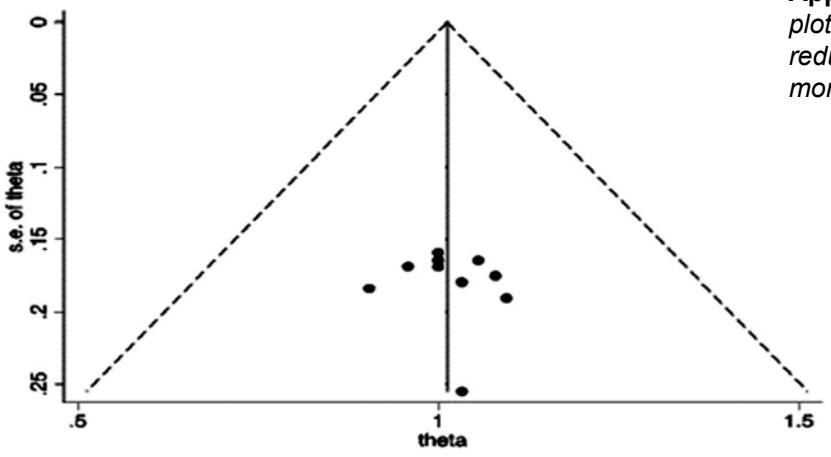


Appendix Fig. 1A. *>50% pain reduction at 6 months.*

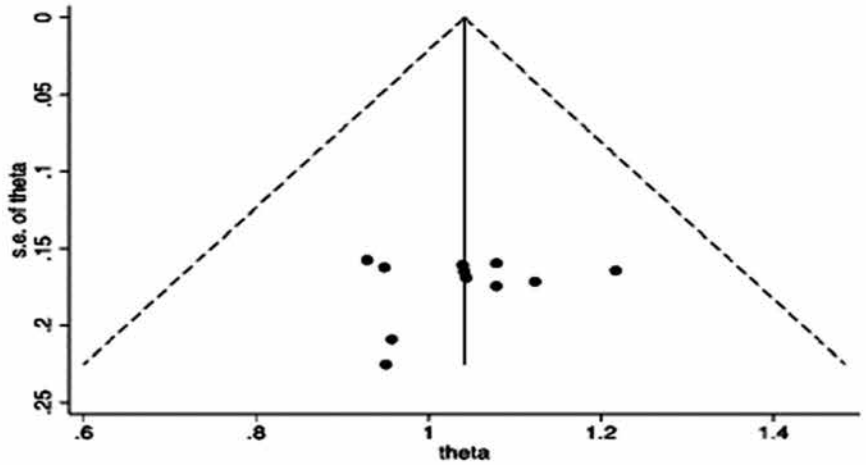


Appendix Fig. 1B. *>50% pain reduction at 12 months.*

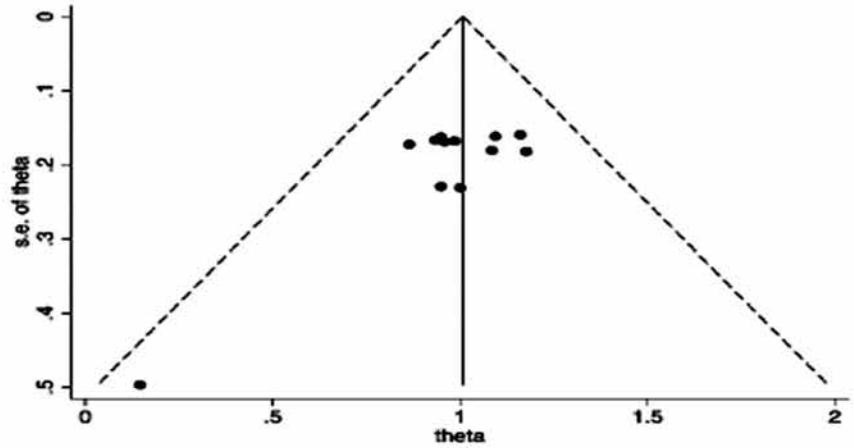


Appendix Fig. 1C. *>50% pain reduction at 24 months.*

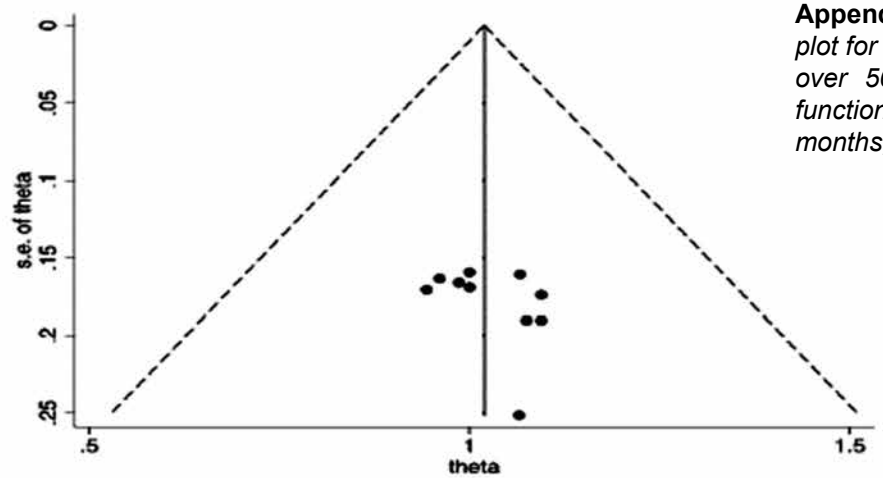
Appendix Fig. 1. *Funnel plot for NRS over 50% pain reduction at 6 months, 12 months, and 24 months.*



Appendix Fig. 2A. *>50% functional improvement at 6 months.*



Appendix Fig. 2B. *>50% functional improvement at 12 months.*



Appendix Fig. 2C. *>50% functional improvement at 24 months.*

Appendix Fig. 2. *Funnel plot for disability scores with over 50% improvement in functionality at 6 months, 12 months, and 24 months.*