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Systematic Review

Comparison of Clinical Efficacy of Epidural Injection With or Without Steroids in the Treatment of Degenerative Disc Disease: Meta-analysis

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Background: Selective nerve root block has been widely used to treat degenerative disc disease (DDD), but no detailed research data is provided to compare the efficacy of epidural injection of anesthetics with or without steroids on the DDD treatment.

Objectives: This study aimed to provide the first comparison of steroids + local anesthetic (LA) or LA alone for the treatment of DDD.

Study Design: We systematically searched PubMed, Medline, Embase, and Cochrane. A systemic review and meta-analysis were performed to assess the clinical efficacy of both the steroids + LA group and the LA alone group, and subgroup analysis was also adopted.

Setting: A systematic review and meta-analysis using a random effects model on randomized controlled studies (RCTs).

Methods: After reviewing titles, abstracts, risk of bias, and full texts of 15,889 studies that were chosen following removal of duplicates after the initial database search, finally, 19 RCTs were included. Pain rating, functional score, follow-up period, and other-related data were extracted from these included works, and the effect size and statistical significance were calculated by the random effects model. The quality and level of the derived evidence were assessed by means of the Grading of Recommendations Assessment, Development and Evaluation method.

Results: In terms of the Numeric Rating Scale (NRS-11) and Oswestry Disability Index (ODI) at one year, the combination of steroids + LA was obviously superior to LA. Subgroup analysis suggested that the combination of steroids + LA was more effective than LA alone in regard to the ODI in the lumbar group within 2 years. The opioids intake of patients treated by LA alone was less than that of the steroids + LA group within 3 months, and LA alone was more effective in pain score reduction, with more than 50% within 6 months in the interlaminar injection group. However, the combination of steroids + LA was more effective when alleviating the NRS-11 within 18 months in the caudal injection group.

Limitations: Firstly, this analysis was inconsistent in technique, dosage, injection frequency, and follow-up period of epidural injections. Such differences may compromise the reported efficacy. Secondly, adverse reactions arising out of the 2 groups were not examined in that the included RCTs did not provide the data. Thirdly, different injection methods would compromise the outcomes, and no subgroup analysis was performed on different injection methods. Finally, these included articles that were mainly sourced from Manchikanti's team, and thus biased to some extent.

Conclusions: The addition of steroids to anesthetic injectates was associated with a better NRS-11 and ODI compared with LA alone within one year in patients with DDD. Furthermore, the improvement of the ODI was observed within 2 years in patients with lumbar DDD.

Key words: Steroids, local anesthetics, epidural injection, degenerative disc disease, meta-analysis

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As outcomes of degenerative disc disease (DDD), back pain, neck and shoulder pain, and nerve root pain are considered as primary symptoms that middle-aged and elderly people are concerned (1). DDD is induced from mechanical and other factors (2,3). The leakage of herniated nucleus pulposus may potentially lead to the immune response in epidural space. Cytokines and other pro-inflammatory substances react with epidural nucleus pulposus materials, which can promote the progression of epidural inflammation, stimulate spinal nerve roots, induce the formation of intraneural edema, enhance the permeability of nerve root capillaries, and aggravate an inflammatory response, thus resulting in nerve root pain (4,5).

Epidural injection is generally applied for the treatment of neck, back, and nerve root pains, making nerve tissues under chemical stimulation, which can eliminate inflammatory mediators by stimulating epidural nerve tissues (6,7). Currently, steroids are the commonly used epidural injection drug, because, in addition to surgical intervention, they can pace up the recovery process of body function, reduce the dosage of opioids administered to patients, and provide a pre-substitution therapy for patients with mild symptoms (8).

Local anesthetic (LA) is inclined to be more important in epidural injections. The mechanism as to how LA functions in relieving root pain is considered as the reflex mechanism of changing or interrupting nociceptive input to afferent fiber, self-sustaining activity of neurons, and the mode of central neuron activity (9,10). The topic of whether the clinical efficacy of steroids + LA is better than LA alone still remains controversial in the academic community. Guyot (11) conducted a randomized controlled trial (RCT) and affirmed that the selective nerve root injection of steroids is not different from LA in the clinical efficacy. Many studies (12,13) also revealed that steroids, compared with LA, cannot provide additional benefit or avoid follow-up interventions.

Therefore, this systematic review and meta-analysis are intended to discuss whether the clinical efficacy of steroids + LA is better than LA alone in the treatment of DDD, the lumbar or cervical subgroup, and the interlaminar injection or caudal injection subgroup, and achieves the best outcomes.

Methods

Inclusion Criteria

English articles on human patients that are acceptable to the following criteria were enrolled: Patients aged ≥ 18 years old, having clinical manifestations of neck or waist pain and nerve root pain, and the diagnosis of DDD is based on radiological evaluation (i.e., computed tomography or magnetic resonance imaging).

Exclusion Criteria

The history of spinal surgery, nonspecific pains that have not yet been definitively diagnosed as lumbar intervertebral disc herniation or cervical disc herniation based on radiological examination, severe spinal canal stenosis, severe intervertebral disc degeneration, and intravertebral disc disorder or intervertebral disc herniation or significant spinal instability. In publications that are acceptable to these criteria, some works that provide the comparison of the clinical outcome of steroids + LA and LA alone were selected.

Information Source and Search Strategy

All articles that were published within the period from the date of database construction to May 2020 were retrieved from Medline, PubMed, Embase, and Cochrane. Key words, including ("epidural injection"), ("epidural," "injection"), ("epidural injection," "steroids"), ("epidural injection," "local anesthetics"), and ("local anesthetics, "steroids") were searched via the searching engine of each database, and the language setting of the search strategy was English. The reference list of included publications was manually filtered until no more potential publications can be found. Articles were first filtered by title and abstract, and then by full text. Those articles included in the analysis were only limited to RCTs that involved human patients with English language.

Data Collection

Reference data was extracted from included articles, including number, gender, age of patients involved in each study, type and dosage of injected drug, type of approach techniques (ie, transforaminal, interlaminar, or caudal), follow-up period, comparison of patient-reported outcomes, and clinical outcomes. The improvement of pain and function rating was deemed as binary variables. The Visual Analog Scale (VAS), Numeric Rating Scale (NRS-11), Oswestry Disability Index (ODI), Neck Disability Index (NDI) and the opioid intake (OI) were deemed as continuous variables.

Quality Assessment of Included Works, Establishment, and Recommendation Strength of Evidence Level

The bias evaluation of each RCT was carried out

by the risk of bias (ROB), including 7 areas: generation of random sequence, hiding of assigned sequence, blinding of patients and persons, blinding of outcome evaluation, integrity of outcome data, reporting of selective outcomes, and other biases. All these areas were assessed to be "low risk," "high risk," or "unclear." At the same time, the Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) was also used in all RCT studies, which was divided into 22 separate questions, that could more accurately evaluate the quality of the RCT studies (14). These assessment processes were conducted by 2 independent reviewers (Fang and Yuan), and the disagreement was resolved through discussions between the 2 reviewers. In addition, the methodology of the quality of all included works was assessed by the Jadad scale (14) that consists of 3 items as contained in the RCT report. The quality scale ranges from 0 to 5 points, the higher point means the better quality of work, and any work rated ≤ 3 points is excluded from the meta-analysis (14,15). The quality and level of the finally acquired evidence were assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method (16).

Meta-Analysis

Data analysis was performed with the Review Manager (RevMan Version 5.0). Pain control and functional improvement were analyzed at different time points of follow-up visits. The heterogeneity test was carried out using I^2 statistics. A category with I^2 equaling 75% or higher was considered as highly heterogeneous (17), and was considered for subgroup analysis. Subgroup analysis was performed for different degenerative segments (e.g., lumbar and cervical) and different injection methods (e.g., the interlaminar and the caudal). $P < 0.05$ was considered statistically significant. The results of continuous variables were expressed as 95% confidence interval (95% CI) of weighted mean difference (WMD), and the results of binary variables were expressed as 95% CI of odds ratio.

Results

A total of 15,911 articles were initially searched out from the databases, 3,434 duplicate articles were deleted, and 12,477 articles that were potentially acceptable to the search criteria remained. After the initial filtering by titles and abstracts, 12,448 articles were unacceptable to the criteria and were excluded. As a result, 29 articles were retrieved for full-text analysis, among which 8 articles were excluded due to the irrelevance to this study. Only one article was considered as the main source of heterogeneity poor quality of evidence, so it was excluded for the absence of intention-to-treat analysis, and the blinding was found not standard after a review of the full text. Another article was excluded because of its low IQM-QRB score. Finally, 19 RCT articles were included in this meta-analysis (Fig.1). The pain intensity in the included works was measured by the VAS or NRS-11 (18). In the meta-analysis, the 2 method scores were considered equivalent and interchangeable (19). In included works, the ODI was mostly used as a tool for functional measurement, and was chosen as the function assessment tool. The periods of follow-up visit for RCT ranged from one week to 2 years, and the pain and function data with clinical significance appeared in a period of 3, 6, 12, 18, and 24 months. Therefore, these time points were chosen as the periods of follow-up visit for the meta-analysis.

ROB

The ROB of all the included works is illustrated in Fig. 2. Only one RCT was assessed with unclear risk (19), and the remaining RCTs were assessed as low-risk randomized sequence domains (12,13,20-39). The most common area associated with bias is the blinding evaluation of research outcomes, which appears in 4 RCTs (12,13, 19,38), because they did not provide an adequate description of the procedure. Among 161 areas under the study, 154 (95.7%) were identified as low risk. Consequently, the global ROB was assessed as low, and works included for this analysis were assessed as high quality. One study (13) was excluded because of its low IQM-QRB score. According to the Jadad scale (14), 19 (20-37,39) were rated as 5 points and identified as high-quality works, while 3 (12,13,38) were rated as 4 points and identified as medium-quality works (Table 1).

Summary of Outcomes

Totally, 19 RCTs were finally included, 11 (12,13,21,22,26,27,30,34-36,39) suggested no significant difference between steroids + LA and LA alone in clinical efficacy, 10 (20,23-25,28,29,32,33,37,38) reported that steroids + LA demonstrated better clinical efficacy than LA alone, and 1(31) indicated that LA had better clinical efficacy than steroids + LA. In general, the steroids + LA group was superior to, or at least not inferior to, the LA alone group in clinical efficacy (Table 1).

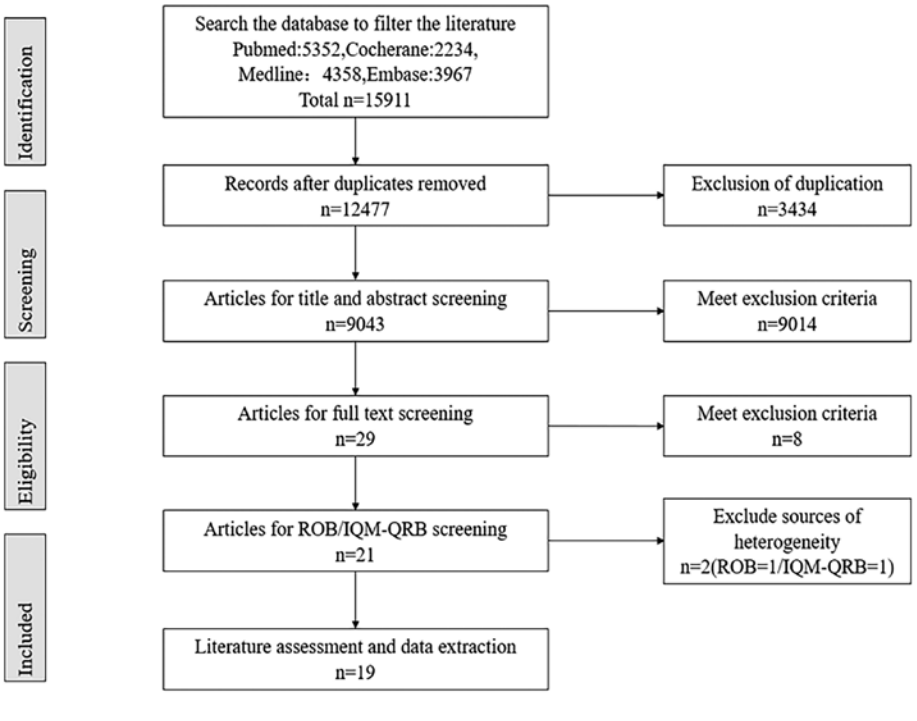

Fig. 1. *Flow chart of identification of studies.*

Overview of Evaluation in a Period of Three Months After Procedure

A total of 22 RCTs (12,13,20-39) provided the NRS-11 and ODI data during a period of 3 months, and were included in the analysis of clinical efficacy according to the mean deviation and standard deviation. The overall mean deviation of the NRS-11 was 0.19 (95% CI: 0.06-0.32), meaning that the combination of steroids + LA was superior to LA alone in the analgesic effect during a period of 3 months, with statistical significance (P = 0.005). In addition, a moderate heterogeneity of I^2 = 22% was observed (Fig. 3A). The overall mean deviation of ODI was 0.98 (95% CI: 0.46-1.50), revealing that steroids + LA was superior to LA alone in the functional recovery during a period of 3 months, and the former therapy led to faster functional recovery, with statistical significance (P = 0.0002). Furthermore, no heterogeneity of I^2 = 0% was observed (Fig. 3B).

Totally, 18 RCTs (21-37,39) provided the mean value and standard deviation of opioids administered to the 2 groups during a period of 3 months, with the overall mean deviation of the 2 groups at -1.27 (95% CI: -4.20-1.66), but these RCTs were not statistically significant (P = 0.39). Furthermore, no heterogeneity of I^2 = 0% was observed (Fig. 3C), and no significant difference was identified in opioids administered with or without steroids for nerve root block in the DDD treatment within 3 months.

A total of 14 RCTs (21-25,27,28,30,31,33-36,38) provided the number of patients reporting pain rating improvement (at least 50% relieved) in 3 months, so the relative risk ratio can be estimated. Among 646 cases in the steroids + LA group, 487 reported a successful pain relief, while 464 out of 645 cases in the LA alone group reported a successful pain relief. The percentage of patients who reported a successful pain relief in the steroids + LA group was higher than that in the control group, with the overall estimated effect size at 0.83 (95% CI: 0.65-1.07), but such difference was not statistically significant (P = 0.16), as shown in a moderate heterogeneity of I^2 = 43% (Fig. 3D).

Overview of Evaluation in a Period of Six Months After Procedure

A meta-analysis was performed on 19 RCTs (20-37,39) that provided the NRS-11 rating in 6 months, with the overall mean deviation at 0.11 (95% CI: -0.09-0.31), and these works were not statistically significant (P = 0.29). The results were found with moderate heterogeneity of I^2 = 51%. Within 6 months of the follow-up visit, the steroids + LA group had no significant difference with the LA alone group in the analgesic effect in the DDD treatment. A meta-analysis was performed on 13 RCTs (21-23,25-29,31,32,36-38) that provided the ODI data in 6 months, with the overall mean deviation at 1.13 (95% CI: 0.56-1.70). These RCTs were statistically significant (P = 0.0001), and the outcomes were found with moderate heterogeneity of I^2 = 59%. The combination of steroids + LA was superior to LA in terms of disability reduction.

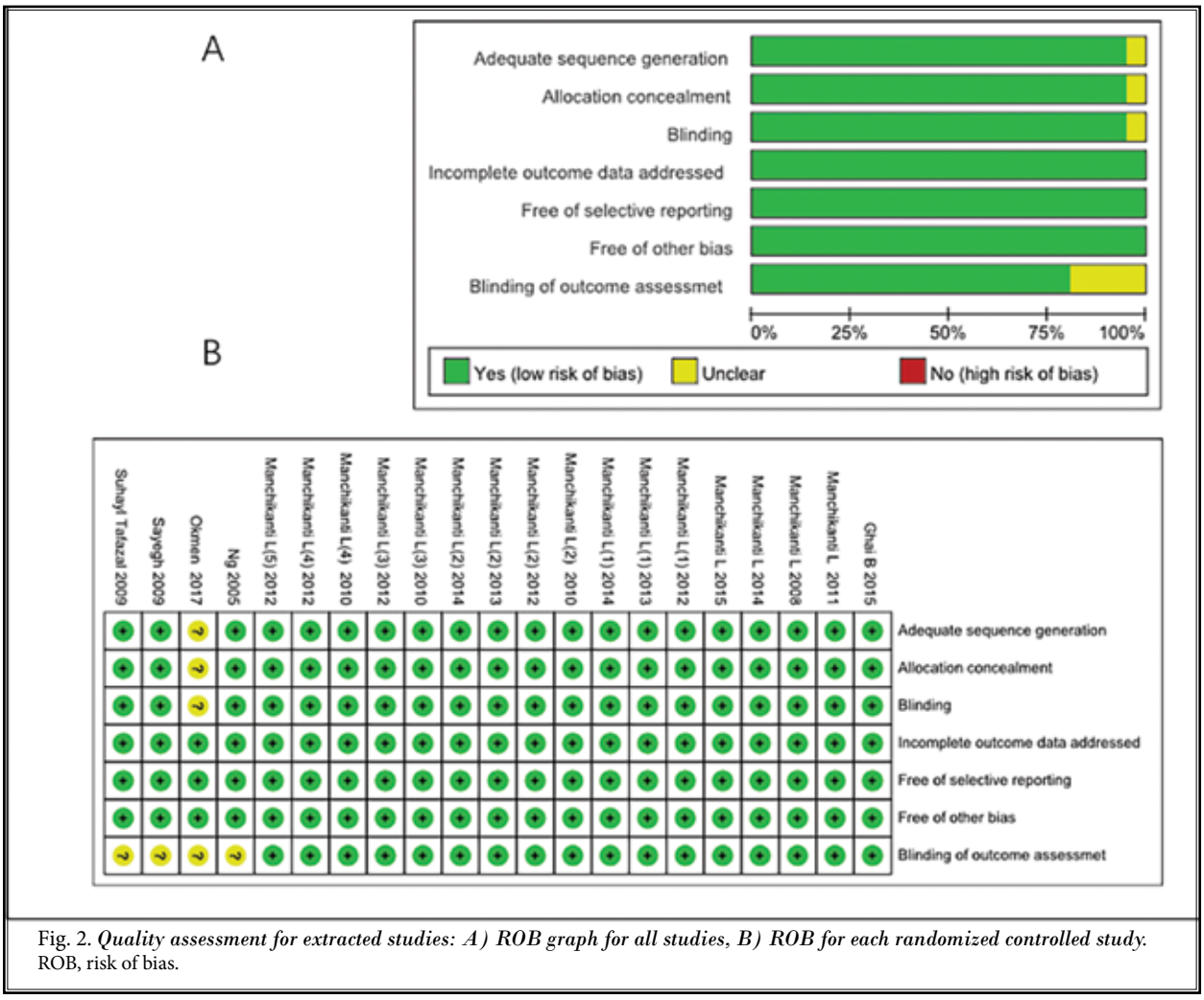

Fig. 2. *Quality assessment for extracted studies: A) ROB graph for all studies, B) ROB for each randomized controlled study.* ROB, risk of bias.

All 18 RCTs (21-37,39) were analyzed for the administering of opioids in 6 months. The outcome was similar to that in 3 months, with the mean deviation at -1.27 (95% CI: -4.13-1.59), and these RCTs were not statistically significant (P = 0.39). In addition, no heterogeneity (I^2 = 0%) was observed. The dosage of opioids administered in 6 months after procedure was obviously less than the baseline, but no significant difference was identified between the 2 groups.

Totally, 19 RCTs (20-37,39) provided the binary data of the number of patients who reported a successful reduction of pain rating within 6 months, so the relative risk ratio can be estimated. Among 836 cases included in the steroids + LA group, 610 reported a successful pain control, while 574 out of 835 cases in the LA group reported a successful pain control. The percentage of patients who reported a successful pain control in the steroids + LA group was higher than that in the control group, with the overall estimated effect size at 0.82 (95% CI: 0.64-1.05) that was not statistically significant (P = 0.12), as shown in a mild heterogeneity of I^2 = 23%.

Overview of Evaluation in a Period of Twelve Months After Procedure

The same 19 RCTs (20-37,39) as that in 6 months after procedure provided the continuous NRS-11 data for 12 months after procedure, with the overall mean deviation of NRS-11 at 0.11 (95% CI: -0.03-0.26), and these RCTs were not statistically significant (P = 0.13). The outcomes were discovered with a low heterogeneity of I^2 = 10% (Fig. 4A). A total of 15 RCTs (12,13,21-23,25-29,31,32,36-38) provided the ODI data with the overall mean deviation at 0.94 (95% CI:0.36-1.53). These RCTs were statistically significant (P = 0.002). The outcomes were found with a mild heterogeneity of I^2 = 67% (Fig.

Table 1. *Abstract of the main literature of this study.*

Study	Method	Disease Segment	Treatment	Control	Evaluation	Follow-up	Outcome	Jadad
Ghai B 2015 (20)	Inter	L	8 mL of 0.5% LIDO	6 mL of 0.5% LIDO + 2 mL METH	NRS-11, MODQ, EPR	2 wk, 1, 2, 3, 6, 9, 12 mo	Y	5
Manchikanti L 2015 (21)	Inter	L	LIDO 0.5% 6 mL	LIDO 0.5% 5 mL + 6 mg of BETA	NRS-11, ODI, OI	3, 6, 12, 18, 24 mo	N	5
Manchikanti L 2014 (22)	T	L	1.5 mL of 1% LIDO + 0.5 mL SCS	1% LIDO + 3 mg or 0.5 mL BETA	NRS-11, ODI, OI	3, 6, 12, 18, 24 mo	N	5
Manchikanti L 2014 (23)	Inter	L	LIDO 0.5% 6 mL	LIDO 0.5% 6 mL+ 1 mg of BETA	NRS-11, ODI, OI	3, 6, 12, 18, 24 mo	S	5
Manchikanti L 2014 (24)	Inter	C	LIDO 0.5% 5 mL	LIDO 0.5% 4 mL+ 1 mL or 6 mg of BETA	NRS-11, NDI, OI	3, 6, 12, 18, 24 mo	S	5
Manchikanti L 2013 (25)	Inter	L	LIDO 0.5% 6 mL	LIDO 0.5% 5 mL +1 mL of BETA	NRS-11, ODI, OI	3, 6, 12 mo	Y	5
Manchikanti L 2013 (26)	Inter	C	LIDO 0.5% 5 mL	LIDO 0.5% 4 mL +1 mL or 6 mg of BETA	NRS-11, ODI, OI	3, 6, 12, 18, 24 mo	N	5
Manchikanti L 2013 (27)	Inter	L	LIDO 0.5% 6 mL	LIDO 0.5% 5 mL + 1 mL of BETA	NRS-11, ODI, OI	3, 6, 12, 18, 24 mo	N	5
Manchikanti L 2012 (28)	Inter	C	LIDO 0.5% 5 mL	LIDO 0.5% 4 mL + 1 mL or 6 mg of BETA	NRS-11, ODI, OI	3, 6, 12 mo	S	5
Manchikanti L 2012 (29)	caudal	L	LIDO 0.5% 10 mL	LIDO 0.5% 9 mL + 1 mL or 6 mg of BETA	NRS-11, ODI, OI	3, 6, 12, 18, 24 mo	Y	5
Manchikanti L 2012 (30)	caudal	L	LIDO 0.5% 10 mL	LIDO 0.5% 9 mL + 1 mL or 6 mg of BETA	NRS-11, NDI, OI	3, 6, 12, 18, 24 mo	N	5
Manchikanti L 2012 (31)	Inter	L	LIDO 0.5% 6 mL	LIDO 0.5% 5 mL+ 1 mL of BETA	NRS-11, ODI, OI	3, 6, 12 mo	LA	5
Manchikanti L 2012 (32)	caudal	L	LIDO 0.5% 10 mL	LIDO 0.5% 9 mL + 1 mL of BETA	NRS-11, ODI, OI	3, 6, 12, 18, 24 mo	Y	5
Manchikanti L 2011 (33)	caudal	L	LIDO 0.5% 10 mL	LIDO 0.5% 9 mL + 1 mL of BETA	NRS-11, NDI, OI	3, 6, 12 mo	S	5
Manchikanti L 2010 (34)	caudal	L	LIDO 0.5% 10 mL	LIDO 0.5% 9 mL+ 1 mL of BETA	NRS-11, NDI, OI	3, 6, 12 mo	N	5
Manchikanti L 2010 (35)	Inter	C	LIDO 0.5% 5 mL	LIDO 0.5% 4 mL + 1 mL of BETA	NRS-11, NDI, OI	3, 6, 12 mo	N	5
Manchikanti L 2010 (36)	Inter	L	LIDO 0.5% 6 mL	LIDO 0.5% 5 mL + 1 mL or 6 mg of BETA	NRS-11, ODI, OI	3, 6, 12 mo	N	5
Manchikanti L 2010 (37)	Inter	L	LIDO 0.5% 6 mL	LIDO 0.5% 5 mL+ 1 mL of BETA	NRS-11, ODI, OI	3, 6, 12 mo	Y	5
Sayegh FE 2009 (38)	caudal	L	12 mL of LIDO 2% + 8 mL WFI	12 mL of LODI 2% + 1 mL of BETA	ODI	1wk, 1, 6, 12 mo	Y	4
Tafazal S 2009 (13)	UN	L	2 mL of 0.25% bupiva	2 mL of 0.25% bupiva + 40 mg of MEDRON	VAS, ODI	6 wk and 3, 12 mo	N	4
Manchikanti L 2008 (39)	caudal	L	LIDO 0.5% 10 mL	LIDO 0.5% 9 mL + 1 mL of BETA	NRS-11, NDI, OI	3, 6, 12 mo	N	5
Ng L 2005 (12)	UN	L	2 mL of 0.25% bupiva	2 mL of 0.25% bupiva + 40 mg of MEDRON	VAS, ODI	6 wk and 3 mo	N	4

Abbreviations: L, lumbar vertebra; C, cervical vertebra; LIDO, lidocaine; METH, methylprednisolone acetate; BETA, betamethasone; SCS, sodium chloride solution; WFI, water for injection; bupiva, bupivacaine; MEDRON, methylprednisolone; OI, opioid intake; NRS-11, numeric rating scale; NDI, Neck Disability Index; ODI, Oswestry Disability Index; VAS, visual analog scale; MODQ, Modified Oswestry Disability Questionnaire; EPR, enhanced permeability and retention; Inter, interlaminar; UN, unspecified; T, transforaminal; Y, steroid is more effective than local anesthetics; N, no significant difference; S, short-term superiority, but limited long-term benefit for epidural steroids; LA, local anesthetics is more effective than steroid.

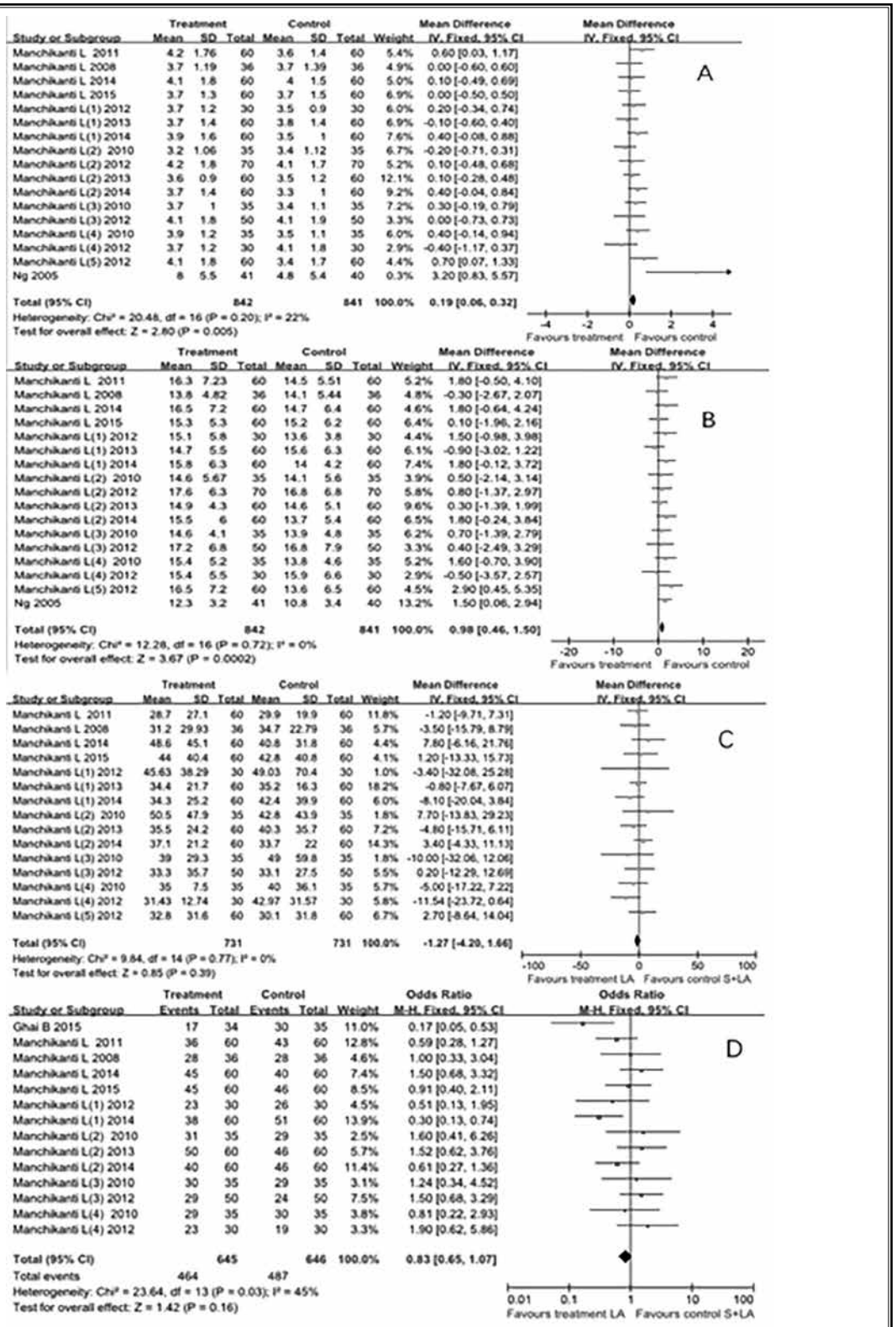

Fig. 3. *Overview of evaluation in a period of 3 months after procedure: A) NRS-11, B) ODI, C) OP, D) Pain relief 50%.*
NRS-11, numeric rating scale; ODI, Oswestry Disability Index; OP, opioids.

4B), suggesting that the combination of steroids + LA was still superior in disability reduction.

During a period of one year after procedure, the opioids administered in the 2 groups were still not statistically significant (P = 0.56), with the mean deviation at -0.85 (95% CI: -3.70-1.99). Furthermore, no heterogeneity of I^2 = 0% was observed (Fig. 4C) (21-28,30-37,39).

The same 19 RCTs (20-37,39) as that in 6 months after procedure provided the binary data of patients who reported a successful reduction of pain rating for one year after procedure. These RCTs allowed for the estimation of the relative risk ratio. Among 836 cases included in the steroids + LA group, 562 reported a successful pain control, while 557 out of 835 in the LA group reported a successful pain control. The percentage of patients who reported a successful pain control in the steroids + LA group was higher than that in the control group, with the overall estimated effect size at 0.98 (95% CI: 0.80-1.20), but this was not statistically significant (P = 0.82), and a mild heterogeneity of I^2 = 23% was observed (Fig. 4D).

Overview of Evaluation in a Period of Eighteen Months After Procedure

Totally, 9 RCTs (21-24,26,27,29,30,32) provided the continuous NRS-11 and ODI data in 18 months after procedure, with the overall mean deviation of the NRS-11 at 0.10 (95% CI: -0.09-0.29). These RCTs were not statistically significant (P = 0.31), and the outcomes were found with no heterogeneity of I^2 = 0%. After the aggregation of the ODI data, the overall mean deviation was 0.73 (95% CI: -0.04-1.50), and these RCTs were not statistically significant (P = 0.06). These outcomes were found with no heterogeneity of I^2 = 0% and no significant difference was observed in the pain rating and disability rating between the 2 groups in 18 months after procedure.

Within 18 months after procedure, the opioids administered in the 2 groups was lower than before, but this was still not statistically significant (P = 0.27), with the mean deviation at 2.12 (95% CI:-1.69-5.93). Most importantly, no heterogeneity of I^2 = 0% was observed (21-24,26,27,30,32).

Totally, 5 RCTs (21,22,24,27,30) provided the data of the number of patients who reported a successful reduction of pain rating in 18 months. Among 290 cases in the steroids + LA group, 180 reported a successful pain control, and 196 out of 290 cases in the LA alone group reported a successful pain control. The percentage of patients who reported a successful pain control in the steroids + LA group was higher than that in the control group, with the overall estimated effect size at 1.17 (95% CI: 0.82-1.67), but this was not statistically significant (P = 0.38), and no heterogeneity of I^2 = 0% was observed.

Overview of Evaluation in a Period of Twenty-Four Months After Procedure

The same 9 RCTs (21-24,26,27,29,30,32) as that in 18 months after procedure provided the continuous NRS-11 and ODI data in 24 months after procedure, with the overall mean deviation of the NRS-11 at 0.18 (95% CI:-0.01-0.37). These RCTs were not statistically significant (P = 0.07), and the outcomes were found with no heterogeneity of I^2 = 0% (Fig. 5A). After the aggregation of the ODI data, the overall mean deviation was 0.70 (95% CI: -0.06-1.47). These RCTs were not statistically significant (P = 0.07), and the outcomes were discovered with no heterogeneity of I^2 = 0% (Fig. 5B), suggesting that there was no significant difference in clinical efficacy between the 2 groups in a period of one year after surgery.

The OI was not statistically significant (P = 0.23), with the mean deviation of 2.35 (95% CI: -1.47-6.17). Furthermore, no heterogeneity of I^2 = 0% was observed (Fig. 5C) (21-24,26,27,30,32).

A total of 8 RCTs provided the data of the number of patients who reported a successful reduction of pain rating in 24 months. Among 480 cases in the steroids + LA group, 301 reported a successful pain control, and 300 out of 480 cases in the LA alone group reported a successful pain control. The percentage of patients who reported a successful pain control in the steroids + LA group was higher than that in the control group, with an overall estimated effect size at 0.99 (95% CI: 0.76-1.30), but 2 groups were not statistically significant (P = 0.95), and no heterogeneity of I^2 = 0% was observed (21,22,24,26,27,29,30,32) (Fig. 5D).

Subgroups Analyses

According to different segments of disease, the study was divided into 2 subgroups: lumbar and cervical subgroups. The combination of steroid and anesthetic agents showed more significant efficacy in improving ODI and relieving pain in lumbar degenerative diseases, and steroids use with anesthetic agents was still more effective than LA alone in improving ODI in 24 months (WMD = 1.06, 95% CI: 0.17 to 1.95, P = 0.02) (Fig. 6). The amount of opioids taken between the 2 groups was lower than before, but neither was

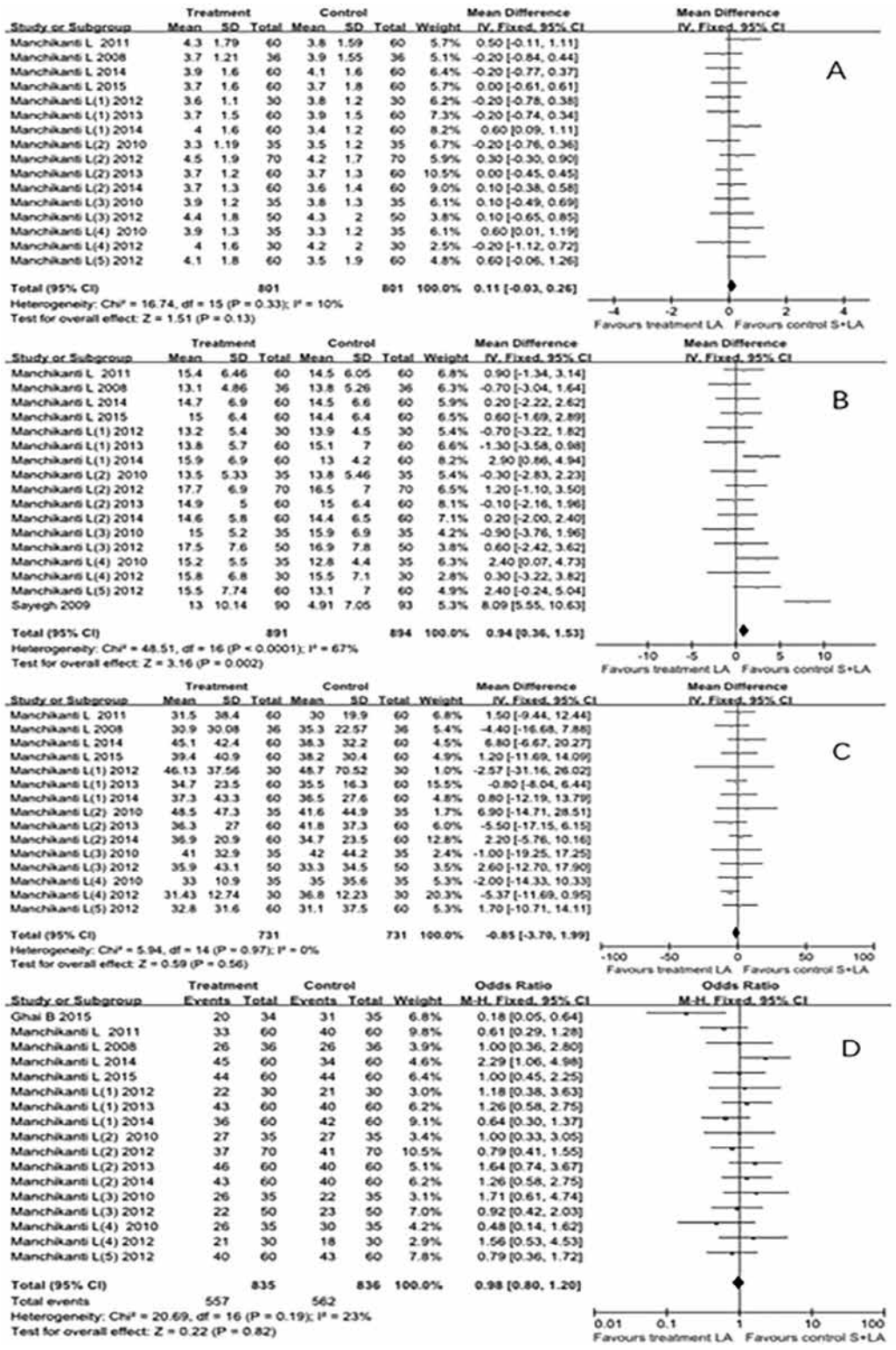

Fig. 4. *Overview of evaluation in a period of 12 months after procedure:* A) *NRS-11*, B) *ODI*, C) *OP* , D) *Pain relief 50%*.
NRS-11, numeric rating scale; ODI, Oswestry Disability Index; OP, opioids.

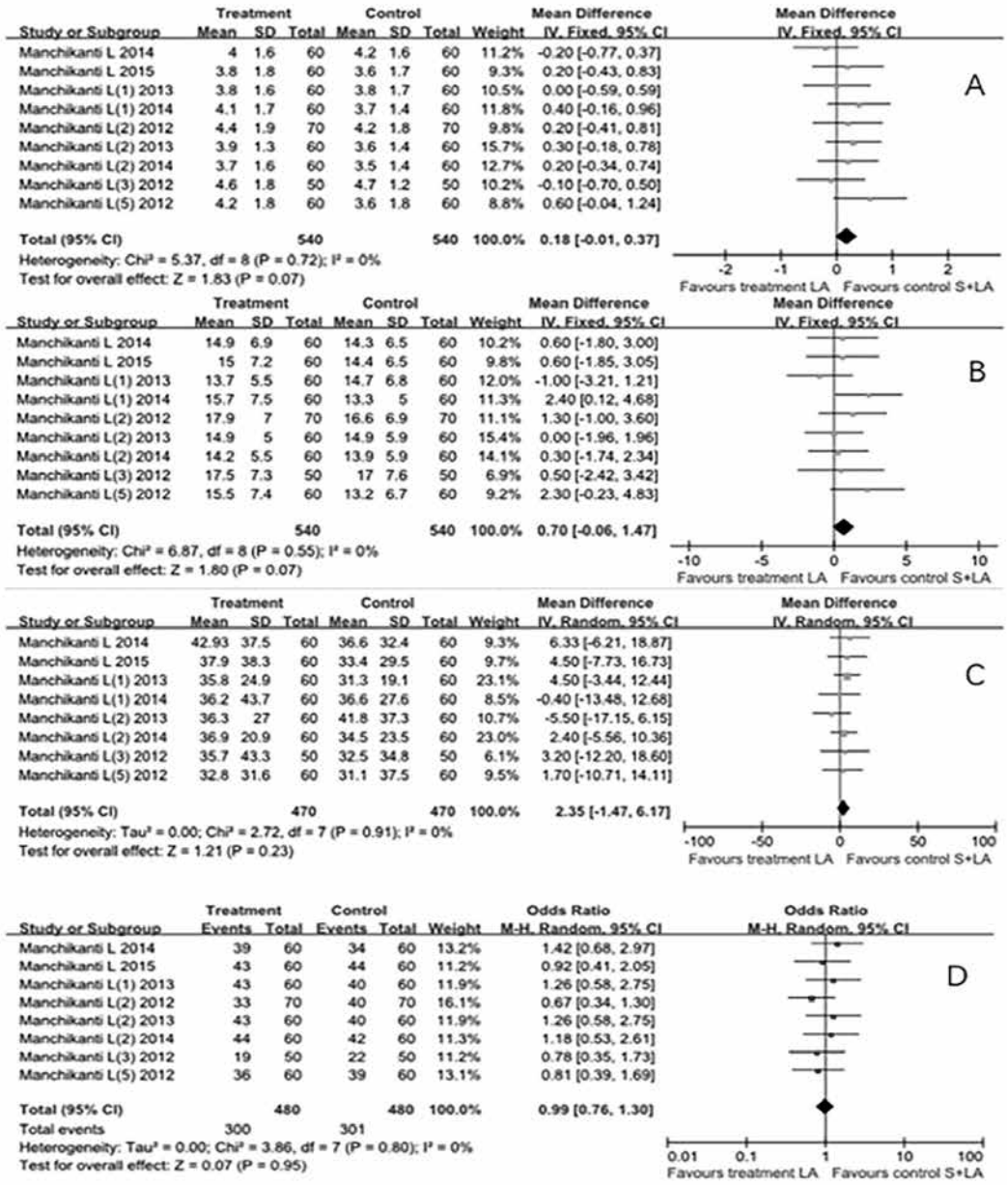

Fig. 5. *Overview of evaluation in a period of 24 months after procedure:* A) *NRS-11*, B) *ODI, C) OP,* D) *Pain relief 50%*.
NRS-11, numeric rating scale; ODI, Oswestry Disability Index; OP, opioids.

statistically significant. The number of people who successfully reduced their pain score by more than 50% between the 2 groups was not statistically significant.

As for different injection methods, the study was divided into 2 subgroups, including the interlaminar and the caudal. No matter what injection method was adopted, the efficacy of the combination of steroids + LA in reducing dysfunction was better than that of LA alone within one year. After one year, there was no statistically significant difference between the 2 groups. Compared with an interlaminar injection, a caudal injection combined with LA was more effective in reducing the NRS-11, and was still more effective after 18 months than LA alone (WMD = 0.43, 95% CI: 0.05

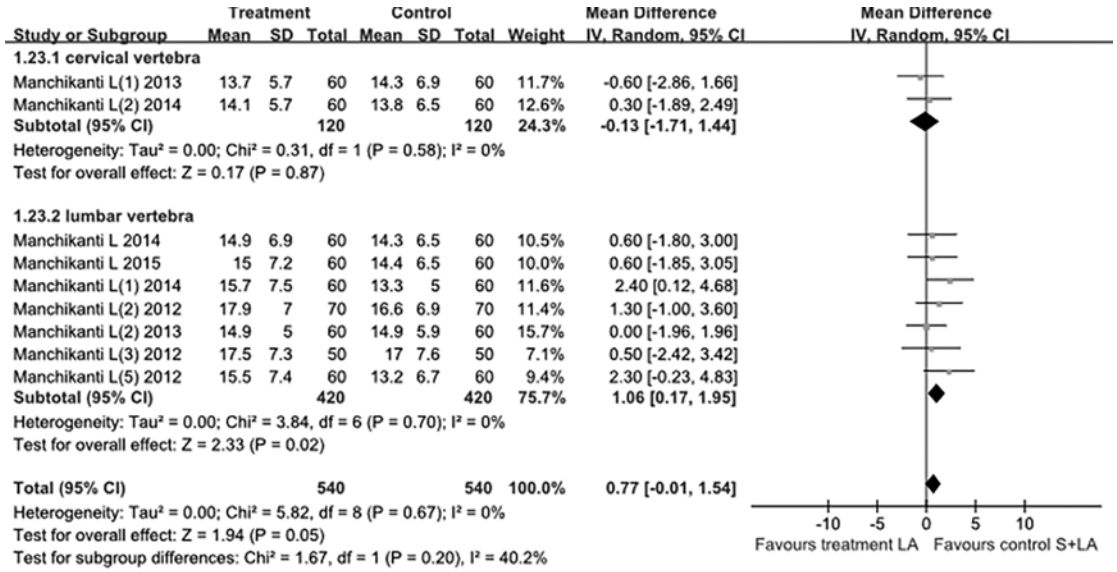

Fig. 6. *Comparison of S + LA and LA in regard to ODI for subgroup analysis between lumbar subgroup and cervical subgroup at 24 months after procedure.*
S, steroids; LA, local anesthetic; ODI, Oswestry Disability Index.

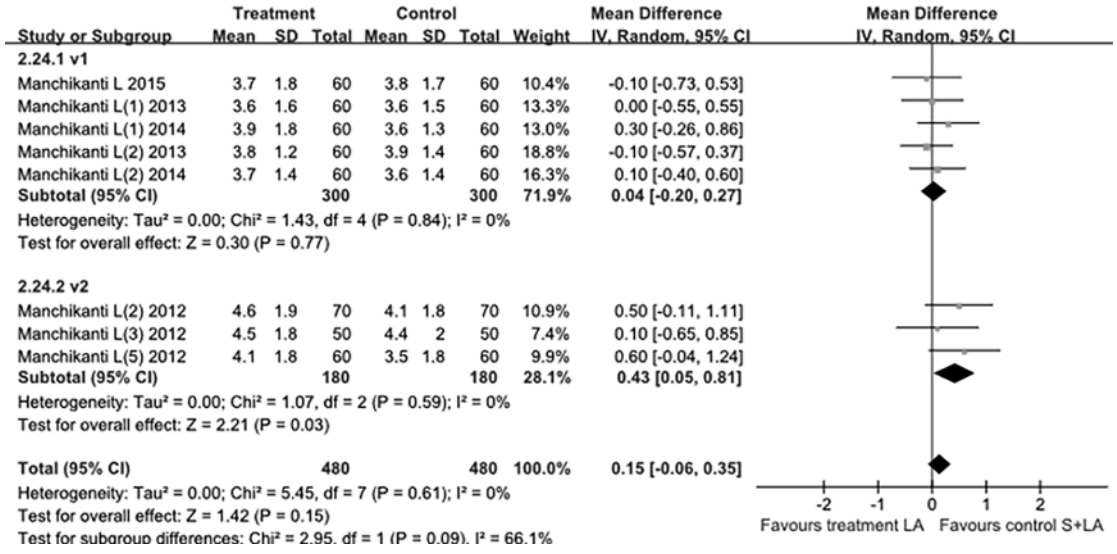

Fig. 7. *Comparison of S + LA and LA in regard to NRS-11 for subgroup analysis between interlaminar subgroup and caudal subgroup at 18 months after procedure.*
S, steroids; LA, local anesthetic; NRS-11, numeric rating scale; V1, interlaminar; V2, caudal.

to 0.81, $P = 0.03$) (Fig. 7). The number of opioids taken between the 2 groups was lower than before, but neither was statistically significant. Patients who received an interlaminar injection of the combination of steroids and anesthetics had a pain score reduction of more than 50% within 6 months compared with those who received LA alone (WMD = 0.71, 95% CI: 0.53 to 0.94, $P = 0.02$) (Fig. 8). Neither method was statistically significant after 6 months.

In included studies (21,22,26,29,30,32), the injection

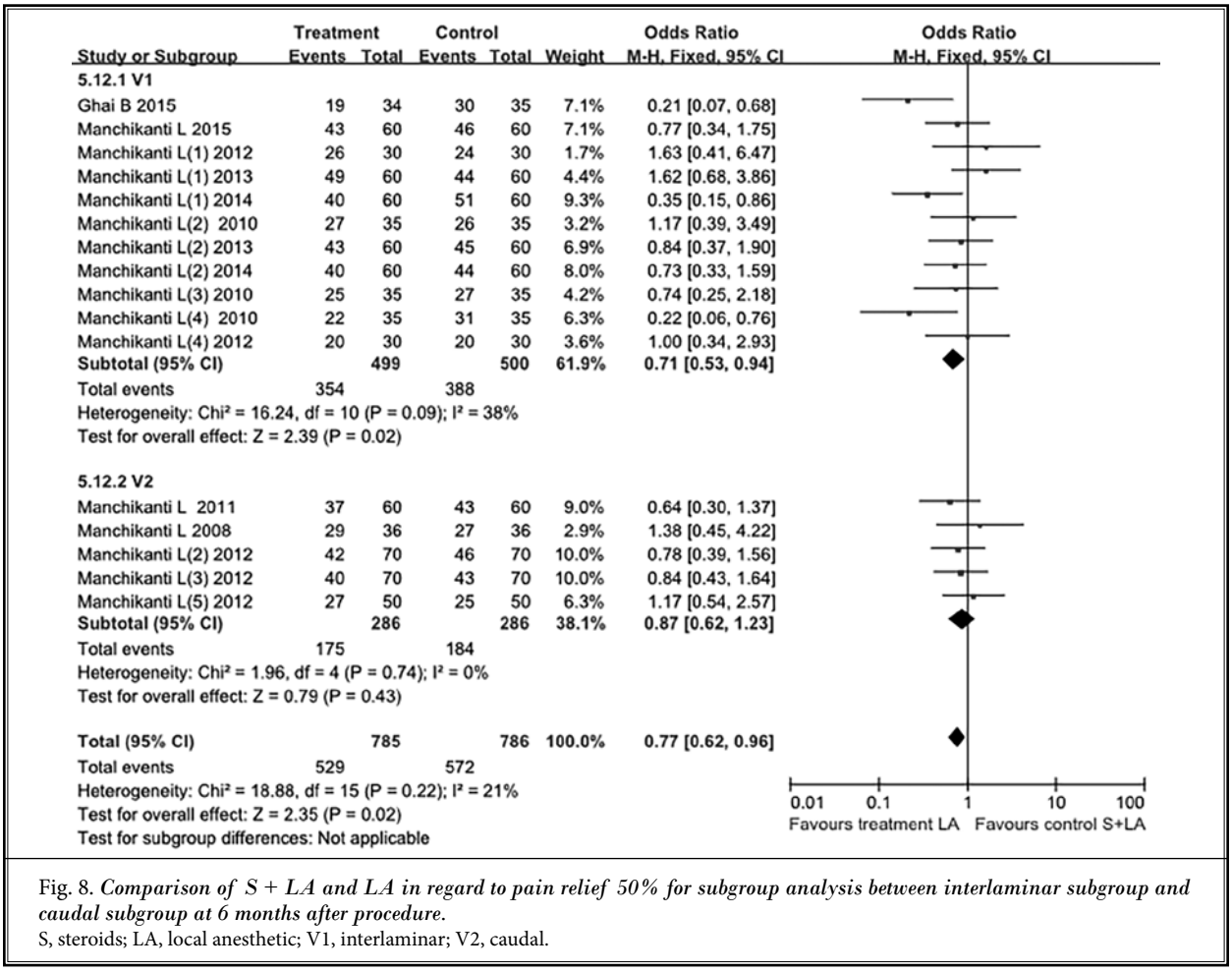

Fig. 8. *Comparison of S + LA and LA in regard to pain relief 50% for subgroup analysis between interlaminar subgroup and caudal subgroup at 6 months after procedure.*
S, steroids; LA, local anesthetic; V1, interlaminar; V2, caudal.

methods of the cervical spine were all interlaminar, thus, according to the injection method (i.e., the interlaminar injection and caudal injection), the studies of lumbar spine were subdivided into 2 subgroups. No matter which injection method was used, the combination of steroids and anesthetic agents was superior to LA alone in reducing the ODI and NRS-11 within one year. The difference was that, after 18 months of the combined use of the caudal injection subgroup, the reduction in the NRS-11 was inferior to that of LA alone (WMD = 0.43, 95% CI: 0.05 to 0.81, $P = 0.03$) (Fig. 9). There was no statistical difference between the 2 groups, except that 3 months after the operation, the number of OI in the interlamellar injection group treated by LA alone was less than that of steroids combined with the LA group (WMD = -6.26, 95% CI: -11.56 to -0.97, $P = 0.02$) (Fig. 10). The number of people who successfully reduced their pain score by more than 50% between the 2 groups was not statistically significant.

In summary, all RCTs were found at a low level of ROB and a higher IQM-QRB score. However, some meta-analyses were found with a mild or moderate heterogeneity, because the types or techniques (ie, transforaminal, interlaminar, or caudal) of steroids and LA involved in each study were different. Most studies involved the number of patients and satisfied the predetermined standard for sample size calculation, so there were no serious problems in terms of the accuracy, and the GRADE system was applied to evaluate this meta-analysis. The quality of evidence among different studies and the quality of evidence were defined as moderate due to the inconsistency of studies.

Discussion

DDD was mainly treated by anterior or posterior decompression. Along with the change of medical practice, DDD has been gradually treated conservatively by administering steroid drugs and physical therapy, then

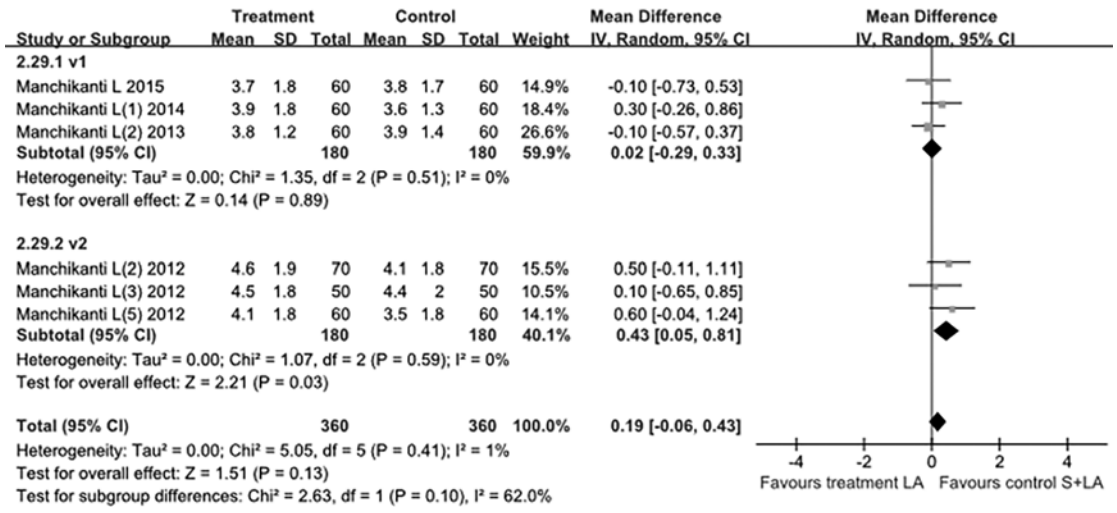

Fig. 9. *Comparison of S + LA and LA in regard to NRS-11 for subgroup analysis between interlaminar subgroup and caudal subgroup at 18 months after procedure (all of the studies were related to the lumbar).*
S, steroids; LA, local anesthetic; NRS-11, numeric rating scale; V1, interlaminar; V2, caudal.

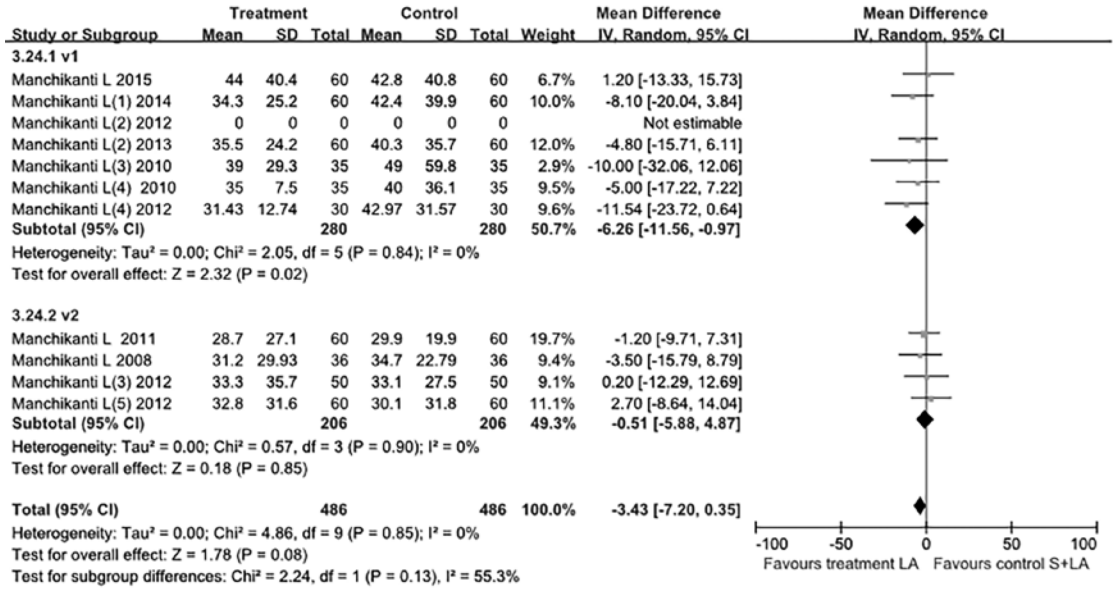

Fig. 10. *Comparison of S + LA and LA in regard to OI for subgroup analysis between interlaminar group and caudal group at 3 months after procedure (all of the studies were related to the lumbar group).*
S, steroids; LA, local anesthetic; OI, opioid intake; V1, interlaminar; V2, caudal.

performing a selective nerve root block. When the above therapies fail, surgical decompression could be considered as an alternative (39).

Most patients who experienced epidural steroid injections were found with alleviation or even disappearing of symptoms, but a few patients with severe or insensitive conditions required repeated injections. Some scholars were concerned about the side effects due to the overdose of epidural steroids, especially in the case of repeated steroid injections, steroids can inhibit a body immune response, which may potentially increase the susceptibility to infec-

tious diseases. Furthermore, steroids may also lead to many complications, such as headache, blood sugar rise, osteoporosis, infection, nerve root injury, spinal cord infarction, and even death (41-44). Other studies (11-13) proved that an epidural block with or without steroids had no impact on the outcomes. In this sense, whether the steroids + LA injection is superior to LA alone remains controversial. It should be noted that epidural injection of LA indeed has sort of side effects and may be even more serious than steroids on some occasions, including nausea, allergic reactions, and paralysis of lower extremities. The overdose of LA may also lead to some systemic reactions, such as vasovagal reactions, loss of consciousness, convulsions, respiratory depression, and even death (45). Additionally, reasonable use of steroids, improvement of injection technique, and less repeated injections can contribute to the clinical purpose, while avoid causing serious systemic side effects.

In order to prove the clinical efficacy of epidural injections with or without steroids on cervical pain or lumbar pain as a result of DDD, 19 articles with low Cochrane ROB, and high- or medium-quality Jadad (14) or IQM-QRB were filtered for the meta-analysis. It was obvious that the combination of steroids + LA was superior to LA alone with respect to the functional improvement and short-term analgesic effect, but no significant difference was identified between the 2 groups in the dosage of opioids administered.

Among the selected publications, 12 articles (12,13,21,22,24,26,27,30,34-36,39) reported no significant difference between the 2 groups, including the interlaminar approach (6 articles) (21,24,26,27,35,36), the caudal approach (3 articles) (30,34,39), the transforaminal approach (1 article) (22), and the unstated approach (2 articles) (12,13). Among 3 articles (23,28,33) reported short-term efficacy of steroids, 2 (23,28) applied the interlaminar approach and 1(33) applied the caudal approach. Among 6 articles (20,25,29,32,37,38) reported long-term efficacy of steroids, 3 (29,32,38) adopted the caudal approach and 3 applied the interlaminar approach (20,25,37) (Table 1). According to the document study of 3 kinds of articles applying different approaches, steroids were obviously superior in the caudal approach and interlaminar approach, compared with the transforaminal approach. However, this conclusion cannot be affirmed due to limited works on the transforaminal approach (9,22,44). At the same time, subgroup analysis revealed that a caudal injection with the combination of steroids + LA had a more significant effect on the NRS-11 reduction, and the effect was still better than that of LA alone one year later.

Among 4 articles (24,26,28,35) on the cervical spine, 3 (24,26,35) reported a significant difference, and 1 (28) reported the short-term efficacy of steroids, which was irrelevant to the injection method. For this study, this might imply that the cervical spine was less sensitive to steroids, or because steroids diffused at a lower extent in the cervical spine, compared with the lumbar spine. This was confirmed in a meta-analysis of 370 patients who evaluated epidural injections with steroids + LA and LA alone for chronic neck pain of various causes without statistically significant differences in pain relief, function improvement, or opioid reduction between the 2 groups (46).

The differences in clinical efficacy would gradually narrow down over time because the efficacy of steroids generally cannot sustain for a long period. No significant difference was identified between the 2 groups after one year, which was supported in the systematic review and meta-analysis published (47). This work provided an overview of 14 RCTs to compare the efficacy of epidural steroid injections and LA on patients suffering from lumbosacral disc herniation (LDH) (48). The combined results illustrated that epidural steroid injections had better efficacy than LA injections in a short period (1-3 months), but no significant difference was identified between the 2 groups over a long period (one year). Therefore, it was concluded that steroids were superior to the control drug with respect to the pain control effect on LDH patients, but the recommendation strength was weak. Patients should not be frustrated at the lower efficacy of steroids, and multiple injections in a period of one year are often considered reasonable (47).

This meta-analysis was subject to certain limitations. Firstly, it was inconsistent in technique, dosage, injection frequency, and follow-up period of epidural injections. Such differences may compromise the reported efficacy. Secondly, adverse reactions arising out of the 2 groups were not examined in that the included RCTs did not provide the data. Thirdly, different injection methods would compromise the outcomes, and no subgroup analysis was performed on different injection methods. Finally, these included articles that were mainly sourced from Manchikanti et al (21-37), and thus biased to some extent.

Conclusions

The combination of steroids + LA was obviously

superior to LA with respect to the ODI within one year and to the NRS-11 within 3 months. With or without steroids, the dosage of administered opioids after procedure would reduce, but no difference was discovered between the 2 groups. The combination of steroids + LA was more effective than LA alone in regard to ODI in the lumbar group within 2 years. Steroids + LA reduced the pain score by over 50% within 6 months in the interlamellar injection group, while the steroids + LA combination was more effective in alleviating the NRS-11 within 18 months in the caudal injection group.

References

1. Frymoyer JW. Back pain and sciatica. *The New England Journal of Medicine* 1988; 318:291-300.
2. Khan AN, Jacobsen HE, Khan J, et al. Inflammatory biomarkers of low back pain and disc degeneration: A review. *Annals of the New York Academy of Sciences* 2017; 1410:68-84.
3. Hession WG, Stanczak JD, Davis KW, Choi JJ. Epidural steroid injections. *Seminars in Roentgenology* 2004; 39:7-23.
4. Wheeler AH, Murrey DB. Chronic lumbar spine and radicular pain: Pathophysiology and treatment. *Current Pain and Headache Reports* 2002; 6:97-105.
5. McCarron RF, Wimpee MW, Hudkins PG, Laros GS. The inflammatory effect of nucleus pulposus. A possible element in the pathogenesis of low-back pain. *Spine* 1987; 12:760-764.
6. House LM, Barrette K, Mattie R, McCormick ZL. Cervical epidural steroid injection: Techniques and evidence. *Physical Medicine and Rehabilitation Clinics of North America* 2018; 29:1-17.
7. Rahimzadeh P, Sharma V, Imani F, et al. Adjuvant hyaluronidase to epidural steroid improves the quality of analgesia in failed back surgery syndrome: A prospective randomized clinical trial. *Pain Physician* 2014; 17:E75-E82.
8. McLain RF, Kapural L, Mekhail NA. Epidural steroid therapy for back and leg pain: Mechanisms of action and efficacy. *The Spine Journal* 2005; 5:191-201.
9. Quraishi NA. Transforaminal injection of corticosteroids for lumbar radiculopathy: Systematic review and meta-analysis. *European Spine Journal* 2012; 21:214-219.
10. Manchikanti L. Role of neuraxial steroids in interventional pain management. *Pain Physician* 2002; 5:182-199.
11. Guyot JP. Lumbar selective nerve root block: Comparative study using two pharmacological formulae. *Global Spine Journal* 2018; 8:374-377.
12. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain: A randomized, double-blind, controlled trial. *Spine* 2005; 30:857-862.
13. 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. *European Spine Journal* 2009; 18:1220-1225.
14. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials* 1996; 17:1-12.
15. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001; 135:982-989.
16. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)* 2008; 336:995-998.
17. Rasouli MR, Rahimi-Movaghar V, Shokraneh F, Moradi-Lakeh M, Chou R. Minimally invasive discectomy versus microdiscectomy/open discectomy for symptomatic lumbar disc herniation. *The Cochrane Database of Systematic Reviews* 2014:CD010328.
18. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. *Journal of Pain and Symptom Management* 2011; 41:1073-1093.
19. Okmen K, Okmen BM. The efficacy of interlaminar epidural steroid administration in multilevel intervertebral disc disease with chronic low back pain: A randomized, blinded, prospective study. *The Spine Journal* 2017; 17:168-174.
20. 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.
21. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJ. A randomized, double-blind controlled trial of lumbar interlaminar epidural injections in central spinal stenosis: 2-year follow-up. *Pain Physician* 2015; 18:79-92.
22. Manchikanti L, Cash KA, Pampati V, Falco FJ. Transforaminal epidural injections in chronic lumbar disc herniation: A randomized, double-blind, active-control trial. *Pain Physician* 2014; 17:E489-E501.
23. Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJ. A randomized, double-blind, active-control trial of the effectiveness of lumbar interlaminar epidural injections in disc herniation. *Pain Physician* 2014; 17:E61-E74.
24. Manchikanti L, Cash KA, Pampati V, Malla Y. Two-Year follow-up results of fluoroscopic cervical epidural injections in chronic axial or discogenic neck pain: A randomized, double-blind, controlled trial. *International Journal of Medical Sciences* 2014; 11:309-320.
25. Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJ. The role of fluoroscopic interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind trial. *Pain Practice* 2013; 13:547-558.
26. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. A randomized, double-blind, active control trial of fluoroscopic cervical interlaminar epidural injections in chronic pain of cervical disc herniation: Results of a 2-year follow-up. *Pain Physician* 2013; 16:465-478.
27. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A

randomized, double-blind, active-controlled trial of fluoroscopic lumbar interlaminar epidural injections in chronic axial or discogenic low back pain: Results of 2-year follow-up. *Pain Physician* 2013; 16:E491-E504.

28. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic epidural injections in cervical spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:E59-E70.
29. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Fluoroscopic caudal epidural injections in managing post lumbar surgery syndrome: Two-Year results of a randomized, double-blind, active-control trial. *International Journal of Medical Sciences* 2012; 9:582-591.
30. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. Results of 2-year follow-up of a randomized, double-blind, controlled trial of fluoroscopic caudal epidural injections in central spinal stenosis. *Pain Physician* 2012; 15:371-384.
31. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJ. Lumbar interlaminar epidural injections in central spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:51-63.
32. 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.
33. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. One-Year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections with or without steroids in managing chronic discogenic low back pain without disc herniation or radiculitis. *Pain Physician* 2011; 14:25-36.
34. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Management of pain of post lumbar surgery syndrome: One-Year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections. *Pain Physician* 2010; 13:509-521.
35. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. The effectiveness of fluoroscopic cervical interlaminar epidural injections in managing chronic cervical disc herniation and radiculitis: Preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:223-236.
36. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.
37. Manchikanti L, Singh V, Falco FJ, 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.
38. Sayegh FE, Kenanidis EI, Papavasiliou KA, Potoupnis ME, Kirkos JM, Kapetanos GA. Efficacy of steroid and nonsteroid caudal epidural injections for low back pain and sciatica: A prospective, randomized, double-blind clinical trial. *Spine* 2009; 34:1441-1447.
39. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. Preliminary results of a randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 1--discogenic pain without disc herniation or radiculitis. *Pain Physician* 2008; 11:785-800.
40. Chang MC, Lee DG. Outcome of transforaminal epidural steroid injection according to the severity of lumbar foraminal spinal stenosis. *Pain Physician* 2018; 21:67-72.
41. Schneider BJ, Maybin S, Sturos E. Safety and complications of cervical epidural steroid injections. *Physical Medicine and Rehabilitation Clinics of North America* 2018; 29:155-169.
42. Cosamalon-Gan I, Cosamalon-Gan T, Mattos-Piaggio G, Villar-Suarez V, Garcia-Cosamalon J, Vega-Alvarez JA. Inflammation in the intervertebral disc herniation. *Neurocirugia (Asturias, Spain)* 2020.
43. Bilir A, Gulec S. Cauda equina syndrome after epidural steroid injection: A case report. *Journal of Manipulative and Physiological Therapeutics* 2006; 29:492. e1-e3.
44. Kennedy DJ, Dreyfuss P, Aprill CN, Bogduk N. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: Two case reports. *Pain Medicine (Malden, Mass)* 2009; 10:1389-1394.
45. Botwin KP, Gruber RD, Bouchlas CG, Torres-Ramos FM, Freeman TL, Slaten WK. Complications of fluoroscopically guided transforaminal lumbar epidural injections. Archives of Physical Medicine and Rehabilitation 2000; 81:1045-1050.
46. Manchikanti L, Nampiaparampil DE, Candido KD, et al. Do cervical epidural injections provide long-term relief in neck and upper extremity pain? A systematic review. *Pain Physician* 2015; 18:39-60.
47. 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.
48. Lee JH, Lee SH. Can repeat injection provide clinical benefit in patients with lumbosacral diseases when first epidural injection results only in partial response? *Pain Physician* 2016; 19:E283-E290.