Systematic Review

Clinical Effectiveness of Interlaminar Epidural Injections of Local Anesthetic with or without Steroids for Managing Chronic Neck Pain: A Systematic Review and Meta-Analysis

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Background: Chronic neck pain is reportedly considered the fourth leading cause of disability. Cervical interlaminar epidural injections are among the commonly administered nonsurgical interventions for managing chronic neck pain, secondary to disc herniation and radiculitis, spinal stenosis, or chronic neck pain of discogenic origin.

Objectives: To systematically review the differences in the effectiveness of cervical epidural injections with local anesthetics with or without steroids for the management of chronic neck pain.

Study Design: Systematic review and meta-analysis.

Methods: A comprehensive search of the literature of randomized controlled trials (RCTs) that compared epidural injections with local anesthetic with or without steroids was performed, including a search of PubMed, EMBASE, and Cochrane databases for all years up to May 2019. Meta-analysis was done for pain relief based on the Numeric Rating Scale, functional status based on the Neck Disability Index, and opioid intake dosage.

Results: Four studies met the inclusion criteria. A total of 370 patients were divided into 2 groups: the experimental group received cervical epidural injection with steroid and local anesthetic, and the control group received injection with local anesthetic only. Regrading pain relief, no significant difference was observed between both groups (weighted mean difference [WMD], –0.006; 95% confidence interval (CI), –0.275 to 0.263; $P = 0.963$; $I^2 = 0.0\%$ at 12 months). There was also no significant difference in the improvement of the functional status (WMD, 0.159; 95% CI, –1.231 to 1.549; $P = 0.823$; $I^2 = 9.8\%$ at 12 months). Similarly, there was no significant difference in opioid dosage (WMD, –0.093; 95% CI, –5.952 to 5.766; $P = 0.975$; $I^2 = 0.0\%$ at 12 months).

Limitations: Only a few studies on this premise were found in the literature. There was also a lack of heterogeneity of the included RCT studies.

Conclusions: The addition of steroids to anesthetic injectates was not associated with better pain and functional score outcomes compared with anesthetic injectate alone in patients with chronic neck pain.

Key words: Chronic neck pain, cervical radiculopathy, cervical disc disease, spinal stenosis, facet joint pathology, cervical epidural injections, steroid injections, local anesthetic injections, systematic review, meta-analysis, randomized control trial

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Chronic neck pain is a common issue in adults, being the fourth leading cause of disability (1,2). Approximately 50% of adults are expected to experience a clinical episode of cervicalgia (neck pain) throughout their lifetime (3). Neck pain is often associated with cervical degenerative radiculopathy, which manifests as a burning or tingling sensation following a dermatomal distribution in one of the upper extremities, owing to irritation or compression of cervical nerve roots (4,5). These radicular symptoms may also be associated with motor deficits and pathoreflexia of the involved upper extremity (6).

The pathophysiology of radicular pain may be attributed to a combination of inflammatory mediators, intraneural edema, and changes in vascular tone, which subsequently lead to ischemic nerve damage (6). Common offending etiologies include spondylosis with foraminal encroachment, intervertebral disc herniation, decreased disc height, or facet joint degenerative pathology (6,7).

Cervical epidural steroid injection is one of the most commonly effective nonoperative treatment approaches in chronic neck pain with or without cervical radiculopathy (8). It can be performed through interlaminar or transforaminal approaches and should be considered if radicular symptoms persist following 4 to 6 weeks of unsuccessful trials of other conservative means of treatment (9,10).

Cervical epidural injections have also been accepted for the management of chronic neck pain and radicular pain caused by herniated discs, spinal canal stenosis, and axial pain of discogenic origin (11,12). The mechanism of action of epidurally injected steroid and local anesthetic has been hypothesized to be related to the anti-inflammatory properties of active agents, which leads to nerve blockade (13,14).

However, there is often a debate about the effectiveness of cervical epidural steroid injections in treating cervical radiculopathy (15). Moreover, there is also evidence that local anesthetics alone may be equally effective as steroids in managing radicular pain due to disc herniation or facet joint pathology (16-18).

It becomes important to acknowledge that some systematic reviews have been performed to assess the efficacy of spinal epidural injections (19-21). Kaye et al (19) performed a systematic review to evaluate the efficacy of epidural injections in relieving chronic spinal pain, and reported that epidural injections were effective in several chronic cervical, thoracic, and lumbar conditions. In 2015, Manchikanti et al (20) performed a systematic review to compare the effectiveness of epidural and facet joint injections with saline solution, local anesthetics, or steroids in various regions of the spine, and reported equal efficacy of local anesthetic alone and local anesthetic with steroids with lack of saline solution effectiveness. In the same year, Manchikanti et al (21) performed another systematic review to evaluate the long-term effectiveness of cervical epidural injections in managing several cervical degenerative pathologies, as well as postsurgical syndrome. The authors generally found paucity in the literature with regard to randomized controlled trials (RCTs) of cervical epidural injections for the management of cervical pathologies.

Based on these findings, it is clear that high-quality studies, particularly RCTs, on the premise of the application and effectiveness of cervical epidural injections with anesthetics with or without steroids for the management of chronic pain of the cervical spine is highly lacking. With the current growing interest in value-based care models in the United States, it would be beneficial to spine patients, spine specialists, as well as other spine interventionists to be well informed on this debate-prone issue as to "Whether or not the combination of steroid(s) to cervical anesthetic injectates shows any difference in clinical effectiveness, when patient outcomes are compared to anesthetic application(s) alone?" Providing robust evidence on the premise of this current clinical conundrum would be critical in informing about the clinical application(s) of cervical interlaminar injections in the nonoperative management of patients with chronic neck pain.

Therefore in this current study, we conducted a systematic review and meta-analysis, aimed at evaluating any clinically significant differences in the effectiveness of cervical interlaminar epidural injections of local anesthetics with or without steroids in reducing neck pain and improving the functional status of patients with chronic neck pain with or without radiculopathy to update the evidence provided in the current literature.

Methods

This systematic review was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, and the current recommendations of the Cochrane Collaboration (22,23).

Search Strategy

A comprehensive electronic search of the literature from PubMed, EMBASE, and Cochrane library databases

from inception up to May 30, 2019 was performed to identify RCTs relevant to cervical interlaminar epidural injections of local anesthetic with or without steroids in patients with chronic neck pain.

The search terminology included "cervical epidural injection," and "chronic neck pain," "discogenic neck pain," "disc-related neck pain," "cervicalgia," "intervertebral disc degeneration," "spinal stenosis," or "cervical radiculopathy."

Selection of Studies

Two independent authors (M.M. and N.V.) screened and assessed the titles and abstracts of the identified studies for eligibility for further review, and culled out irrelevant studies and/or duplicates. We also searched the reference lists of the retrieved studies.

If eligibility could not be determined from the title or the abstract, the entire text of the study was retrieved, and those considered relevant were reviewed for eligibility based on the study goal to help formulate the best synthesis.

References of the retrieved studies were then screened for any further appropriate articles to guarantee that relevant articles were not skipped. If a study was identified to be relevant, the full text of the study was obtained and considered for further assessment.

Inclusion and Exclusion Criteria

To be qualified for this systematic review and meta-analysis, articles had to fulfill the following inclusion criteria: (1) adult patients (age ≥18 years) with chronic neck pain undergoing cervical epidural interlaminar injection; (2) RCTs that directly compared injection of steroids with local anesthetic (the experimental group) to local anesthetic alone (the control group); (3) studies that reported a minimum of one of the primary outcome measures; and (4) articles published in English with accessible full text. Any disagreements over the inclusion eligibility of the studies were resolved by discussion between authors M.M. and N.V.

Types of Outcome Measures

The primary outcome measures of this systematic review were the epidural injection efficacy in improving pain or functional status. Significant improvement was defined as at least 50% pain relief or functional status improvement as assessed by pain or function evaluation scores between study groups.

The opioid intake dosage change and the occurrence of adverse events, such as subarachnoid punctures or nerve root irritation, represented the secondary outcome measures.

Data Extraction

A custom data extraction form was developed for recording all relevant details from the included studies. Two of the reviewers (M.M. and N.V.) independently extracted data from each study, including the first author's name, year of publication, the patient demographics, diagnosis, duration of pain, baseline characteristics, type of intervention (anesthetic or anesthetic with steroid), follow-up period, results on primary or secondary outcome measures of interest, and quality score assessment of each RCT.

Quality Assessment

The authors M.M. and N.V. independently evaluated the quality and risk of bias of the selected full studies based on the Interventional Pain Management techniques–Quality Appraisal of Reliability and Risk of Bias Assessment (IPM–QRB) tool (24), as well as the Cochrane collaboration risk of bias tool, which includes the following criteria: random sequence generation, allocation concealment, blinding of patients and personnel, incomplete outcome data, selective reporting, and other sources of bias (25).

In each RCT, every criterion was classified as low risk, unclear risk, or high risk of bias. The quality of each study was classified into 3 levels: "high risk of bias" (at least one item was classified as high risk), "low risk of bias" (all items were classified as low risk) or "unclear risk of bias" (at least one item was classified as unclear risk). Any disagreements regarding the risk of bias assessment were resolved by discussion.

Statistical Analyses

The outcomes included in our analysis for each study were effective number (mean ± standard deviation). The binary data were expressed as odds ratio and 95% confidence interval (CI), and continuous data were expressed as weighted mean difference (WMD) and 95% CI. Statistical heterogeneity was assessed by the I^2 test. If I^2 value was > 25%, the random effects model was applied. However, if the I^2 value was < 25%, the fixed effects model was adopted. We conducted a random effects meta-analysis to investigate the possible explanations for heterogeneity. We also conducted a single-arm meta-analysis for the experimental group results in each follow-up by summarizing all the re-

search studies. Meta-analysis significance level was set at $\alpha = 0.05$. Stata 15 software (Stata Corp. LLC, College Station, TX) was used for all meta-analyses.

Results

Search Results and Study Selection

The search strategy resulted in 1,646 publications relevant to cervical epidural injections. Among them, 136 articles were screened and identified as eligible for inclusion after filtering, then 132 were excluded, leaving 4 full-text articles available for this systematic review. All 4 RCTs were included in the quantitative analysis (Fig. 1). The 4 studies were RCTs that compared cervical interlaminar epidural injections with steroids and local anesthetic versus local anesthetic in patients with chronic neck pain with or without radiculopathy (26-29). These 4 studies also evaluated the efficacy of the injections assessed by the improvement of pain and functional status.

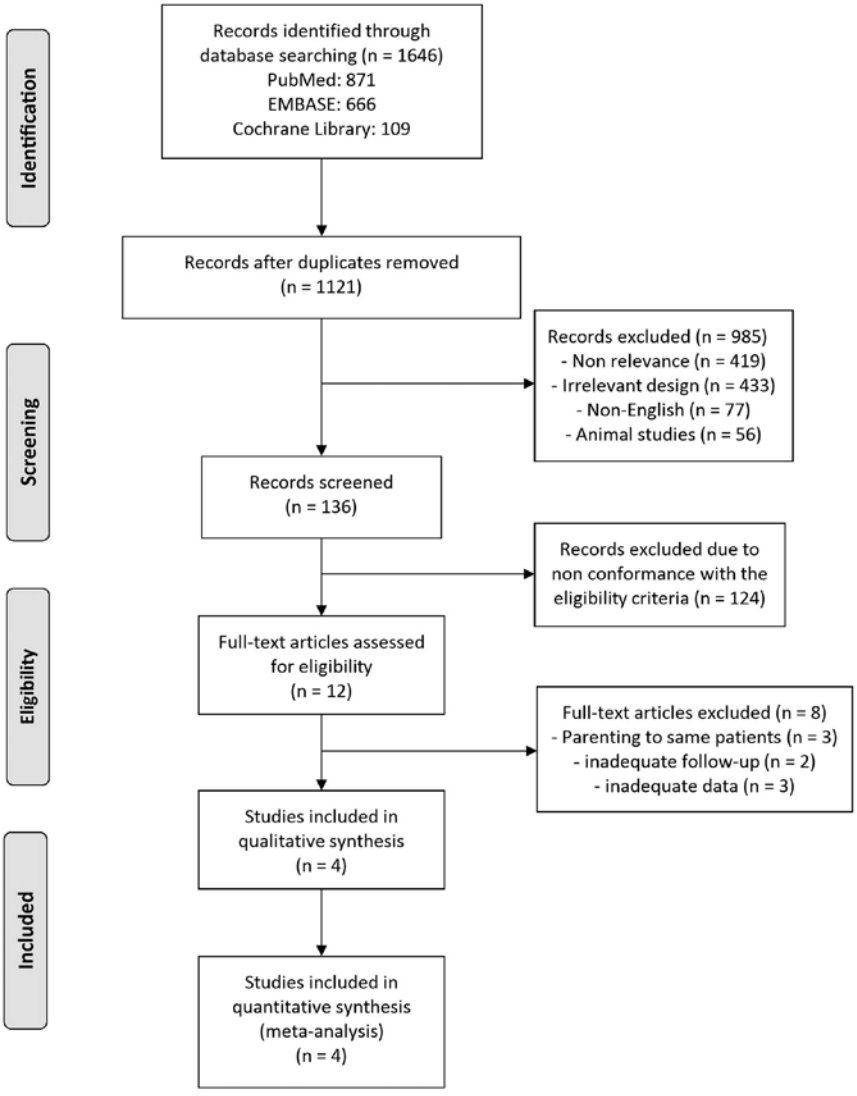

Fig. 1. *The PRISMA flow diagram of the search strategy and the yield of eligible studies.*

Methodologic Quality and Risk of Bias Estimation of the Included Trials

The method of randomization was described in all trials (computer-generated random allocation sequence) and allocation concealment was reported in all studies. All the trials blinded patients and research personnel to group allocation, and included an intent-to-treat analysis. Overall, all the trials were considered of high quality, and the risk of bias across all the trials was considered to be low according to Cochrane collaboration and also IPM–QRB tools (Fig. 2; Table 1).

Characteristics of Included Studies

Among all 4 trials, we identified a total of 370 adult patients of both genders (133 men and 237 women) with chronic cervicalgia who had cervical interlaminar epidural injections with a minimum follow-up period of 1 year for all patients (Table 2). Those patients were diagnosed with cervical disc herniation or radiculitis (n = 120), discogenic pain without disc herniation, radiculitis, spinal stenosis, or facet joint pain (n = 190), and cervical central spinal stenosis with or without foraminal

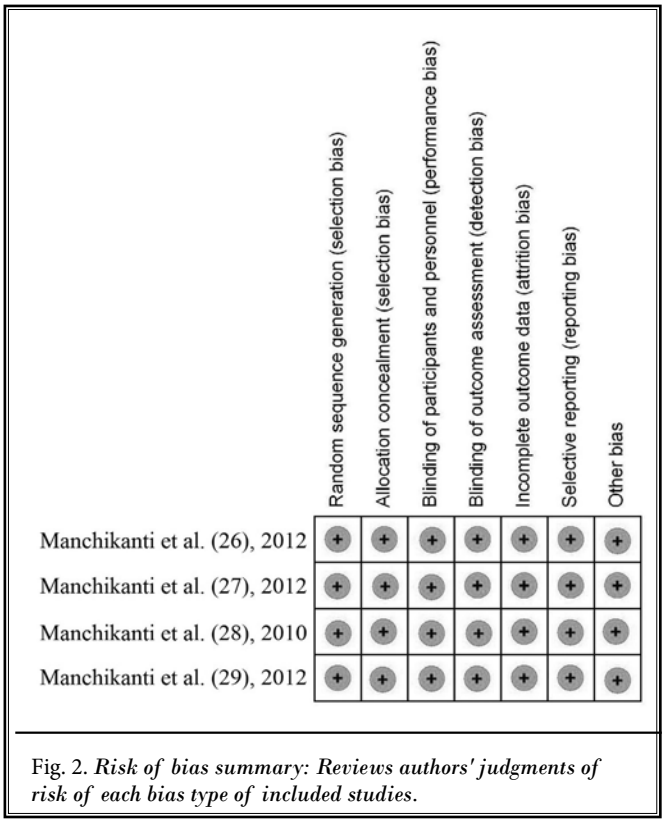

Fig. 2. *Risk of bias summary: Reviews authors' judgments of risk of each bias type of included studies.*

Table 1. *Methodologic quality assessment of randomized trials utilizing Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM - QRB).*

		Manchikanti et al. (26)	Manchikanti et al. (27)	Manchikanti et al. (28)	Manchikanti et al. (29)
I.	TRIAL DESIGN AND GUIDANCE REPORTING				
1.	CONSORT or SPIRIT	3	3	3	3
II.	DESIGN FACTORS				
2.	Type and Design of Trial	2	2	2	2
3.	Setting/Physician	2	2	2	2
4.	Imaging	3	3	3	3
5.	Sample Size	2	3	2	3
6.	Statistical Methodology	1	1	1	1
III.	PATIENT FACTORS				
7.	Inclusiveness of Population	1	1	1	1
8.	Duration of Pain	2	2	2	2
9.	Previous Treatments	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	3	3	3	3
IV.	OUTCOMES				
11.	Outcomes Assessment Criteria for Significant Improvement	4	4	4	4
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2
13.	Description of Drop Out Rate	2	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	1	1	1

Table 1 (cont.). *Methodologic quality assessment of randomized trials utilizing Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM - QRB).*

		Manchikanti et al. (26)	Manchikanti et al. (27)	Manchikanti et al. (28)	Manchikanti et al. (29)
15.	Role of Co-Interventions	1	1	1	1
V.	RANDOMIZATION				
16.	Method of Randomization	2	2	2	2
VI.	ALLOCATION CONCEALMENT				
17.	Concealed Treatment Allocation	2	2	2	2
VII.	BLINDING				
18.	Patient Blinding	1	1	1	1
19.	Care Provider Blinding	1	1	1	1
20.	Outcome Assessor Blinding	0	0	0	0
VIII.	CONFLICTS OF INTEREST				
21.	Funding and Sponsorship	2	2	2	2
22.	Conflicts of Interest	3	3	3	3
TOTAL		42	43	42	43

Table 2. *Baseline characteristics of the included studies.*

No.	Study, Year	Sample Size E/C	Male (%) E/C	Average Age (years) E/C	Duration of Pain (months) E/C	Baseline NRS E/C	Baseline NDI E/C	Baseline Opioid Intake (mg) E/C	Average Relief/Year (weeks) E/C	Number of Injections/ Year E/C
1	Manchikanti et al. (26) 2012	30/30	43/30	49.7 ± 8.9/49.9 ± 8.5	94.3 ± 77.4/115.2 ± 89.9	8 ± 0.9/7.9 ± 0.8	29.2 ± 5.8/29.2 ± 5.2	66.07 ± 72.62/51.37 ± 31.3	30.4 ± 16.1/40.8 ± 16.3	3.6 ± 1.2/3.7 ± 1.2
2	Manchikanti et al. (27) 2012	60/60	42/47	45.6 ± 10.4/46.2 ± 10.3	91.9 ± 94.5/118.3 ± 98.6	7.9 ± 0.9/7.9 ± 1	29.2 ± 6.1/29.6 ± 5.3	53.8 ± 36.1/57 ± 46.1	31 ± 18.5/37.6 ± 16.4	3.4 ± 1.3/3.6 ± 1.2
3	Manchikanti et al. (28) 2010	35/35	46/33	45.2 ± 11/43.7 ± 13	86.6 ± 93.7/86.7 ± 81.8	7.4 ± 0.9/7.8 ± 0.8	28.5 ± 7/30 ± 4.8	47.6 ± 40.9/60.7 ± 59.8	39.7 ± 13.6/37.6 ± 16.2	3.8 ± 0.9/3.9 ± 1.1
4	Manchikanti et al. (29) 2012	60/60	32/25	41.8 ± 11.6/44.5 ± 12.6	95.8 ± 95.7/100.3 ± 94.3	7.6 ± 0.8/7.9 ± 0.9	28.6 ± 7.2/30.2 ± 4.7	39.1 ± 27.1/47 ± 35	34.8 ± 16.1/36.4 ± 15.9	3.6 ± 1/3.6 ± 1.1

E: experimental Group (steroid + local anesthetic), C: control group (local anesthetic alone), NRS: Numeric Rating Scale, NDI: Neck Disability Index.

stenosis (n = 60). The experimental group (n = 185) had undergone cervical interlaminar epidural injection with local anesthetic (lidocaine 0.5%, 4 mL) mixed with 1 mL or 6 mg of nonparticulate betamethasone, whereas the control group (n = 185) had injection with local anesthetic only (lidocaine 0.5%, 5 mL). All of these studies met the criteria to be included in the final qualitative and quantitative analyses.

All 4 RCTs randomized patients into 2 groups either as local anesthetic plus steroid injection (the experimental group) or only local anesthetic injection (the control group). Manchikanti et al (26) randomized 60 (30/30) patients with cervical central spinal stenosis with or without foraminal stenosis; Manchikanti et al (27) randomized 120 (60/60) patients with cervical disc herniation or radiculitis; Manchikanti et al (28) randomized 70 (35/35) patients with discogenic pain without disc herniation, radiculitis, spinal stenosis, or facet joint pain; and Manchikanti et al (29) randomized 120 (60/60) patients with discogenic pain without disc herniation, radiculitis, spinal stenosis, or facet joint pain.

The 4 studies reported pain control based on the Numeric Rating Scale (NRS-11) (31), and the functional status assessment based on the Neck Disability Index

(NDI) (32). The 4 trials also reported on the opioid intake in terms of morphine equivalents.

Pain Relief

All 4 trials reported pain relief based on assessment of the NRS-11 at baseline, 3, 6, and 12 months after treatment. Significant pain relief was defined as the percentage of patients with significant pain relief of 50% or greater depending on the NRS-11. Meta-analyses of the NRS-11 at baseline and follow-up periods, as well as significant pain relief in the follow-up periods in the experimental group, are shown in Tables 3 and 4.

At baseline, there was no significant difference in the NRS-11 between the 2 groups ($P = 0.067$). In all trials, pain scores decreased significantly at the follow-up periods in both groups, $P < 0.001$, with no significant differences between the 2 groups regarding NRS-11 reduction or significant pain relief of 50% or greater.

No significant differences were observed between both treatment groups for the 3 follow-up periods (WMD, –0.211; 95% CI, –0.462 to 0.041; $P = 0.101$; $I^2 = 0.0\%$) at 3 months, (WMD, 0.100; 95% CI, –0.157 to 0.357; $P = 0.447$; $I^2 = 30.7\%$) at 6 months, and (WMD, –0.006; 95% CI, –0.275 to 0.263; $P = 0.963$; $I^2 = 0.0\%$) at 12 months (Tables 5, 6, and 7; Figs. 3 and 4).

Table 3. *Meta-analysis of the Numeric Rating Scale (NRS) at baseline and follow-up periods in the experimental group.*

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		WMD (95% CI)	*P*
Baseline	72.9	0.011	Random	7.722 (7.475, 7.968)	< 0.001
3 months	66.7	0.029	Random	3.416 (3.145, 3.686)	< 0.001
6 months	63.9	0.040	Random	3.565 (3.275, 3.855)	< 0.001
12 months	61.8	0.049	Random	3.617 (3.309, 3.925)	< 0.001

I^2 : Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Table 4. *Meta-analysis of significant pain relief ≥ 50% in the follow-up periods in the experimental group.*

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		WMD (95% CI)	*P*
3 months	0.0	0.412	Fixed	0.810 (0.754, 0.866)	< 0.001
6 months	0.0	0.516	Fixed	0.796 (0.739, 0.854)	< 0.001
12 months	92.5	< 0.001	Random	0.627 (0.392, 0.863)	< 0.001

I^2 : Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

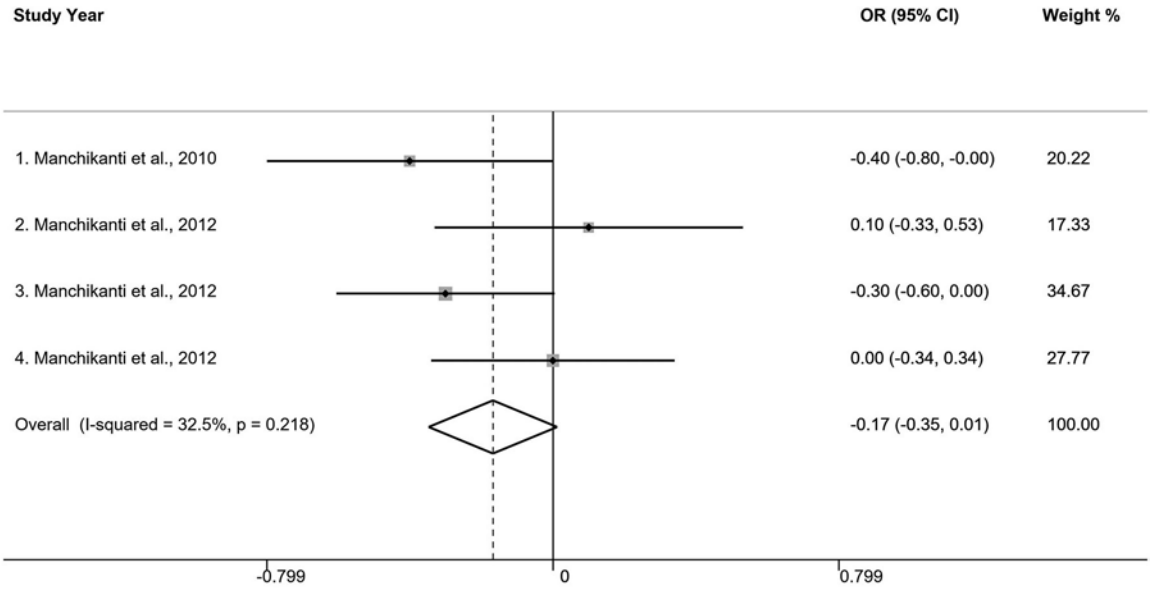

Fig. 3. *Meta-analysis of NRS between the 2 groups at baseline.*

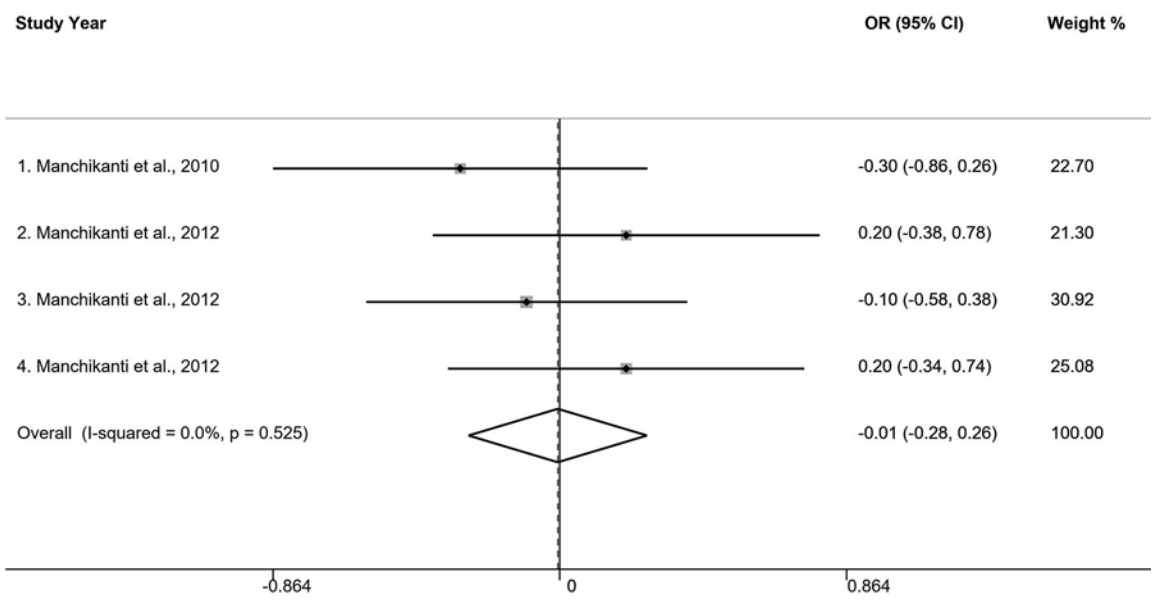

Fig. 4. *Meta-analysis of NRS between the 2 groups at 12 months follow-up.*

Table 5. Numeric Rating Scale (NRS) at baseline and follow-up within the 2 groups.

Group	Timeline	Heterogeneity		Model	Meta Results	
		I^2 (%)	*P*		WMD (95% CI)	*P*
Experimental group	3 months - Baseline	0.0	0.933	Fixed	-4.239 (-4.473, -4.004)	< 0.001
	6 months - Baseline	0.0	0.914	Fixed	-4.382 (-4.609, -4.156)	< 0.001
	12 months - Baseline	0.0	0.981	Fixed	-4.242 (-4.471, -4.014)	< 0.001
Control group	3 months - Baseline	0.0	0.659	Fixed	-4.293 (-4.493, -4.094)	< 0.001
	6 months - Baseline	0.0	0.821	Fixed	-4.140 (-4.358, -3.923)	< 0.001
	12 months - Baseline	0.0	0.870	Fixed	-4.084 (-4.312, -3.855)	< 0.001

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Table 6. *Difference in Numeric Rating Scale (NRS) at baseline and follow-up periods between the 2 groups.*

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		WMD (95% CI)	*P*
Baseline	32.5	0.218	Fixed	-0.168 (-0.347, 0.012)	0.067
3 months	0.0	0.513	Fixed	-0.211 (-0.462, 0.041)	0.101
6 months	30.7	0.228	Fixed	0.100 (-0.157, 0.357)	0.447
12 months	0.0	0.525	Fixed	-0.006 (-0.275, 0.263)	0.963

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Functional Outcome

In all 4 trials, functional outcome was assessed by the NDI at baseline, 3, 6, and 12 months after the procedure, and significant improvement in the functional status was defined as the proportion of patients who had a reduction of NDI scores of at least 50%. Meta-analyses of the NDI at baseline and follow-up periods, as well as significant functional improvement in the follow-up periods in the experimental group, are shown in Tables 8 and 9.

In all trials, significant improvement was seen in the functional status in both groups from baseline to 1 year with no significant differences between the 2 groups (WMD, 0.159; 95% CI, –1.231 to 1.549; $P = 0.823$; $I^2 = 9.8\%$ at 12 months; Tables 10, 11, and 12; Figs. 5 and 6).

Table 7. *Significant pain relief of ≥ 50% at follow-up between the 2 groups, [Group (C/E)].*

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		OR (95% CI)	*P*
3 months	0.0	0.443	Fixed	1.29 (0.759, 2.193)	0.346
6 months	2.8	0.378	Fixed	1.186 (0.71, 1.979)	0.515
12 months	77.5	0.004	Random	1.72 (0.631, 4.685)	0.289

I^2: Heterogeneity Index, P: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

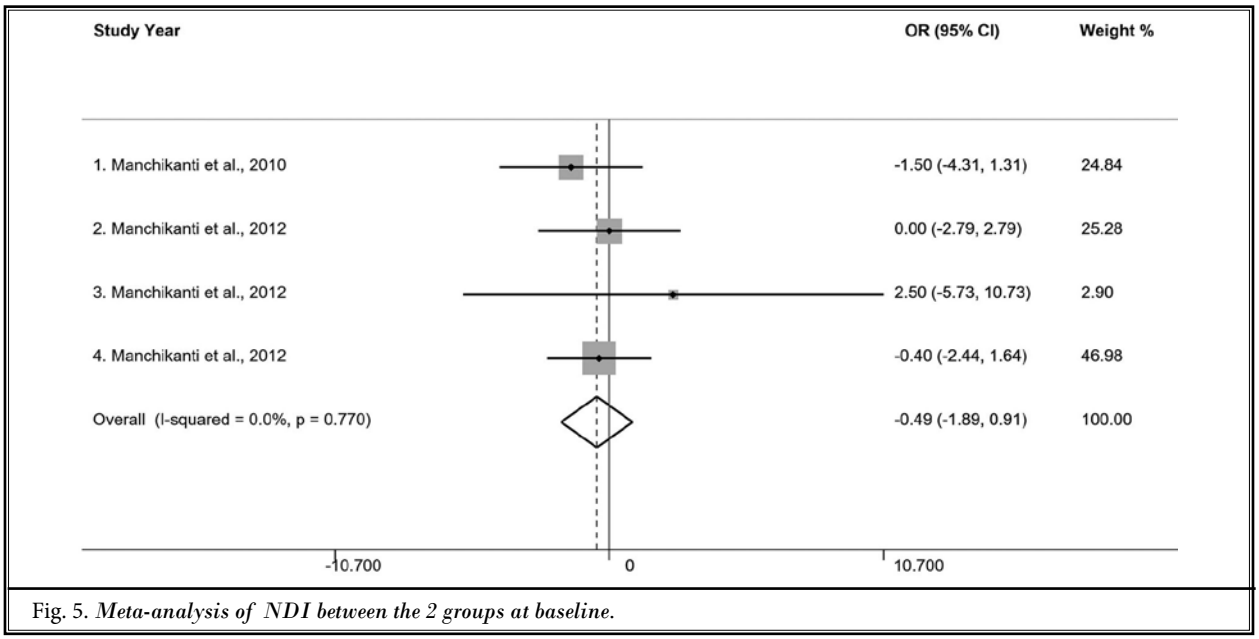

Fig. 5. *Meta-analysis of NDI between the 2 groups at baseline.*

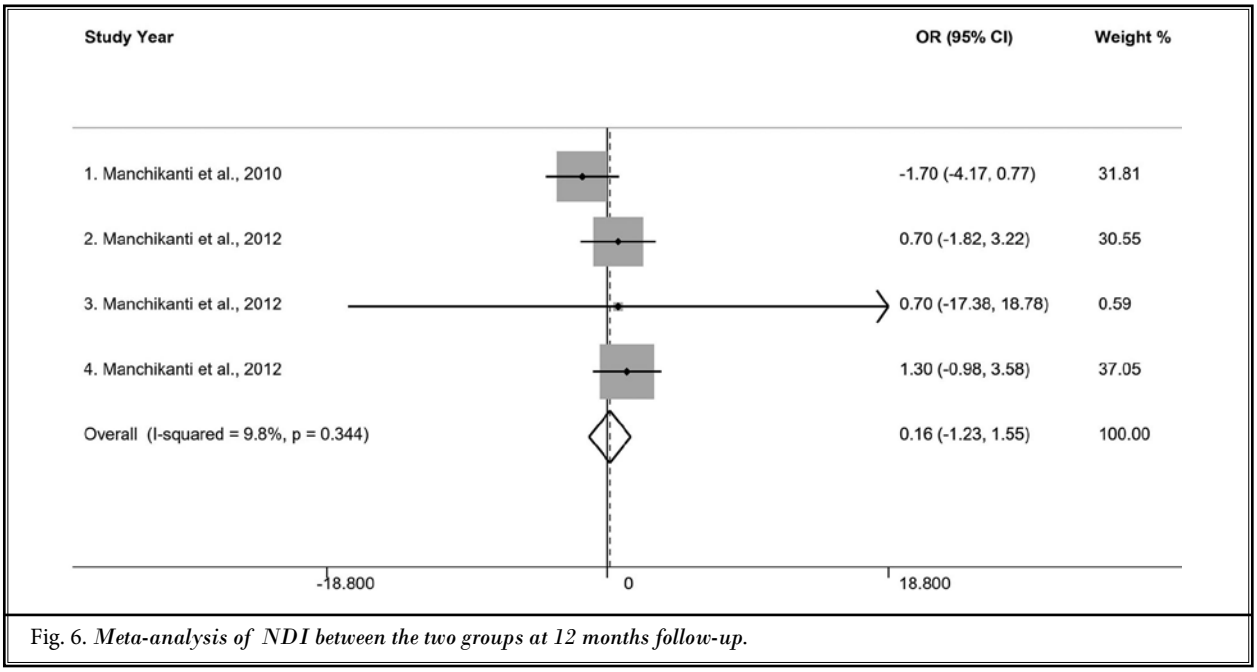

Fig. 6. *Meta-analysis of NDI between the two groups at 12 months follow-up.*

Table 8. *Meta-analysis of the Neck Disability Index (NDI) at baseline and follow-up periods in the experimental group.*

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		WMD (95% CI)	*P*
Baseline	97.3	< 0.001	Random	23.769 (16.969, 30.57)	< 0.001
3 months	87.7	< 0.001	Random	12.505 (9.909, 15.101)	< 0.001
6 months	84.8	< 0.001	Random	12.487 (9.922, 15.052)	< 0.001
12 months	33.3	0.212	Fixed	13.823 (12.555, 15.091)	< 0.001

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Table 9. Meta-analysis of significant functional improvement in the follow-up periods in the Experimental Group.

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		WMD (95% CI)	*P*
3 months	49.7	0.114	Fixed	0.76 (0.675, 0.846)	< 0.001
6 months	0.0	0.474	Fixed	0.775 (0.715, 0.835)	< 0.001
12 months	78.0	0.003	Random	0.661 (0.518, 0.803)	< 0.001

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Table 10. Neck Disability Index (NDI) at baseline and follow-up within the 2 groups.

Group	Timeline	Heterogeneity		Model	Meta Results	
		I^2 (%)	*P*		WMD (95% CI)	*P*
Experimental group	3 months - Baseline	80.2	0.002	Random	-12.780 (-16.151, -9.409)	< 0.001
	6 months - Baseline	81.3	0.001	Random	-13.856 (-17.207, -10.504)	< 0.001
	12 months - Baseline	81.6	0.001	Random	-13.800 (-17.246, -10.354)	< 0.001
Control group	3 months - Baseline	86.3	< 0.001	Random	-12.346 (-16.306, -8.386)	< 0.001
	6 months - Baseline	87.8	< 0.001	Random	-12.175 (-16.516, -7.834)	< 0.001
	12 months- Baseline	8.4	0.351	Fixed	-14.861 (-16.345, -13.377)	< 0.001

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Table 11. Difference in Neck Disability Index (NDI) at baseline and follow-ups between the 2 groups, [Group (E-C)].

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		WMD (95%CI)	*P*
Baseline	0.0	0.770	Fixed	-0.488 (-1.89, 0.913)	0.495
3 months	16.6	0.308	Fixed	-0.649 (-1.963, 0.666)	0.334
6 months	0.0	0.424	Fixed	0.294 (-1.033, 1.621)	0.664
12 months	9.8	0.344	Fixed	0.159 (-1.231, 1.549)	0.823

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Table 12. Reduction of Neck Disability Index (NDI) by ≥ 50% at follow-up between the 2 groups, [Group (C/E)].

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		OR (95% CI)	*P*
3 months	48.2	0.122	Fixed	1.197 (0.591, 2.425)	0.617
6 months	0.2	0.391	Fixed	1.098 (0.673, 1.79)	0.708
12 months	40.5	0.169	Fixed	1.457 (0.938, 2.264)	0.094

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

Opioid Intake

In all studies, the opioid intake was assessed in terms of morphine equivalence at baseline, 3, 6, and 12 months after treatment. The opioid intake was significantly reduced in both groups within the follow-up periods with no significant difference between the 2 groups (WMD, –0.093; 95% CI, –5.952 to 5.766; $P = 0.975$; $I^2 = 0.0\%$ at 12 months; Table 13; Figs. 7 and 8).

Pain Free Weeks/Annum and Number of Injections

There were no statistically significant differences between the 2 groups regarding the number of pain free weeks per year (WMD, –3.713; 95% CI, –9.34 to 1.913; $P = 0.196$; $I^2 = 55.7\%$), and number of injections per year (WMD, –0.141; 95% CI, –0.427 to 0.145; $P = 0.335$; $I^2 = 0.0\%$; Table 14).

Adverse Effects

All trials reported that adverse events occurred with the injections, but the studies did not specify in which of the 2 groups those adverse events occurred. The pooled adverse effects in our systematic review were 6 transient nerve root irritation without long-term sequelae, 4 subarachnoid puncture, 4 intravascular entry, and 2 soreness lasting for 1 week.

Manchikanti et al (26) reported 2 subarachnoid punctures, 1 intravascular entry, and 1 report of soreness lasting 1 week. In the Manchikanti et al (27) study, there was 1 case of subarachnoid puncture, 3 patients with intravascular penetrations, and 1 report of soreness lasting 1 week. Manchikanti

et al (28) reported 3 patients with transient nerve root irritation without long-term sequelae. Manchikanti et al (29) reported 1 case of subarachnoid puncture, and 3 patients with transient nerve root irritation without long-term sequelae.

Table 13. *Differences in opioid intake dosage/(mg) at baseline and follow-up between the 2 groups, [Group (E-C)].*

Timeline	Heterogeneity		Model	Meta Results	
	I^2 (%)	*P*		WMD (95%CI)	*P*
Baseline	0.0	0.470	Fixed	-4.756 (-13.555, 4.043)	0.289
3 months	0.0	0.498	Fixed	-0.429 (-6.079, 5.221)	0.882
6 months	0.0	0.457	Fixed	0.778 (-4.943, 6.498)	0.790
12 months	0.0	0.522	Fixed	-0.093 (-5.952, 5.766)	0.975

I^2: Heterogeneity Index, *P*: Level of significance, WMD: Weighted Mean Difference, CI: Confidence Interval.

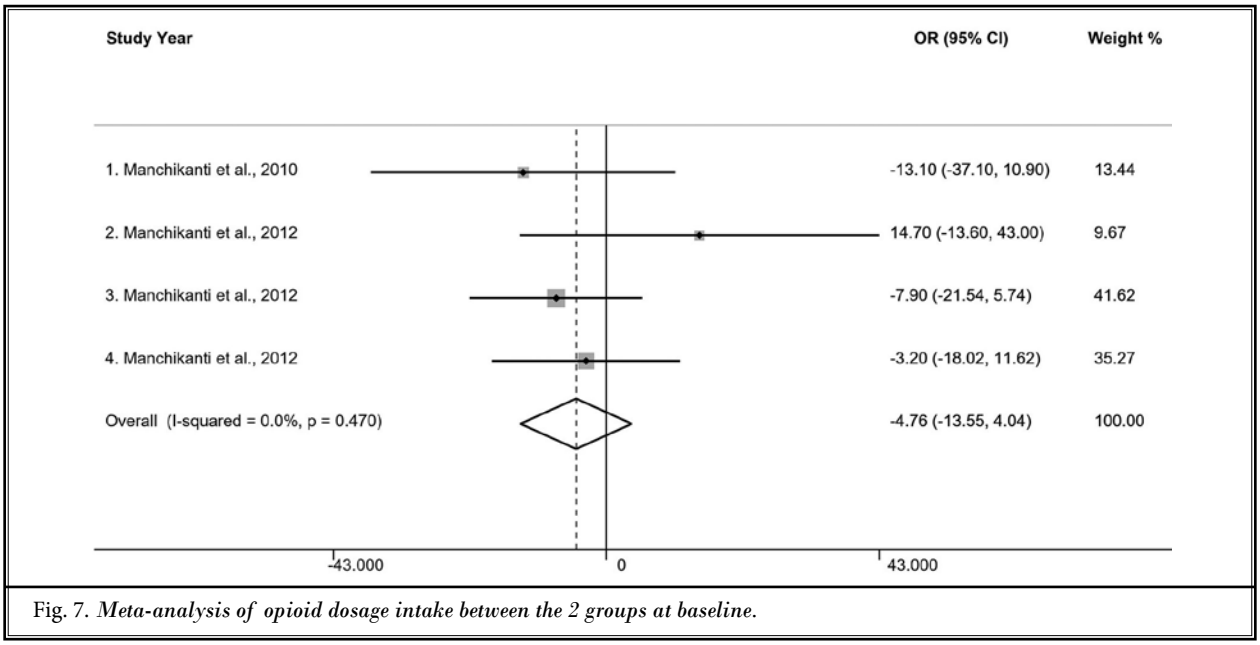

Fig. 7. *Meta-analysis of opioid dosage intake between the 2 groups at baseline.*

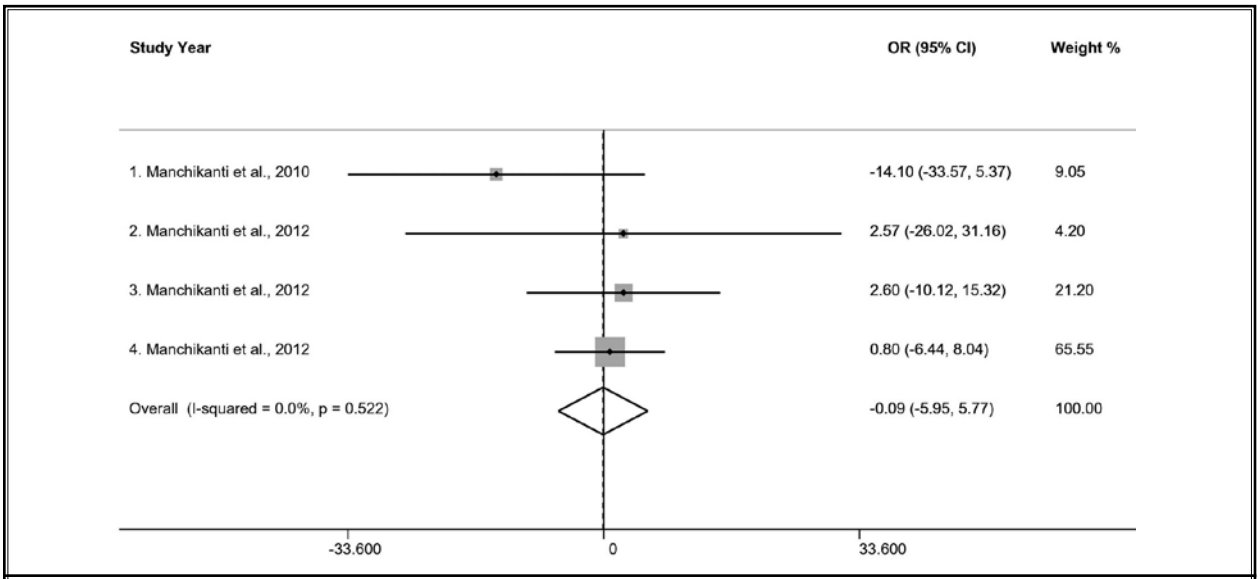

Fig. 8. Meta-analysis of opioid dose between the 2 groups at 12 months follow-up.

Discussion

We performed a systematic review and meta-analysis of RCTs evaluating the use of epidural injections with steroid and local anesthetic versus local anesthetic alone for the management of chronic neck pain due to various causes, such as discogenic pain, disc herniation, spinal stenosis, and facet joint pathology. The included RCTs demonstrated good quality assessment and low risk of bias. All studies included in our meta-analysis further showed a homogenous usage of interlaminar approach under fluoroscopic guidance.

The pooled analysis included in this current study showed that cervical epidural injections, either with local anesthetic alone or local anesthetic with steroids, could achieve significant pain relief (≥ 50% reduction in NRS-11 scores) besides significant improvement in functional status (≥ 50% reduction in NDI scores).

We then compared the differences in the effectiveness between both groups, and found no statistically significant difference in pain reduction, functional improvement, and opioid dosage reduction between the 2 treatment groups. This implies that there is high-quality evidence for the beneficial effect of either local anesthetics or steroids for treating chronic neck pain with radicular or nonradicular patterns.

Currently, there is mounting evidence to support that local anesthetics alone can be equally as effective as steroids in treating chronic neck pain with or without disc herniation or pain due to facet joint pathology (33-35).

Multiple mechanisms have been proposed to be involved in the pathophysiology of chronic pain. These factors may include noxious stimuli, excess nociception with pain pathways sensitization, and/or the excessive release of neurotransmitters that lead to complex central responses, such as hyperalgesia (36,37). Corticosteroids are known to possess anti-inflammatory properties attributed to prostaglandin synthesis inhibition and the reduction of inflammatory mediators, including interleukin-1, tumor necrosis factor-α, and phospholipase A2 (38-40).

Our systematic review and meta-analysis showed no significant additional effect with corticosteroids in managing chronic neck pain with or without radiculopathy. Moreover, corticosteroids have been shown to have direct neurotoxic impact on peripheral nerve tissues, an adverse condition rarely observed with local anesthetics (41-43).

It is also important to note that in our current study, the few considered clinical limitations are associated with a lack of control patients in the analyzed studies, as well as information and outcomes of patients who accepted epidural injections and further went on to receive surgery.

It has recently been reported that intraoperative injection of steroids during anterior cervical discectomy and fusion surgery is associated with reduced risk of incidence of postoperative dysphagia (44). Nevertheless, short- to long-term application of steroids in the preoperative phase have also been reported to be associated with an increased incidence risk of postoperative infection following cervical spine surgery (45). Based on these reported findings, it is clear that the prolonged use of epidural steroid injections potentiates detrimental effects on patients' immune health status, as well as their wound healing capabilities during the critical recovery phase following surgery. It is therefore pertinent to minimize epidural steroid use when possible to mitigate the incidence of this identified risk associated with postoperative infection in cervical spine patients who eventually undulate to receive spine surgery following epidural steroid treatment(s) within the preoperative phase. This study evidently establishes that unadulterated local anesthetic injections is sufficed in improving patients' pain and disability outcomes in patients with chronic neck pain with or without radiculopathy. Together, these findings inform the practice in this spine arena of the value-based advantage associated with the use of local anesthetics alone versus local anesthetics combined with steroids for managing patients with chronic neck pain.

Our systematic review and meta-analysis collectively compared the effectiveness of RCT- based cervical epidural injections either with steroid and local anesthetic or local anesthetic alone. Other systematic reviews have primarily assessed the effectiveness of epidural injection or compared between 2 subtypes of corticosteroid injections (particulate vs. nonparticulate). Benyamin et al (46) reviewed 3 studies regarding the effectiveness of cervical epidurals in the treatment of chronic neck pain and found positive outcome of short- and long-term pain relief. Conger et al (47) aimed to assess the effectiveness of fluoroscopic cervical transforaminal epidural steroid injection for the treatment of radicular pain, and approximately 50% of patients have achieved 50% or greater pain reduction at short- and intermediate-term follow-up. Mehta et al (48) reviewed published studies concerning the comparative effectiveness of particulate versus nonparticulate corticosteroids for cervical and lumbosacral epidural steroid

injections, and found no statistically significant difference between the 2 groups in terms of pain reduction or improved functional status.

The strength of this study is the provided evidence that lies in the high-quality level and homogeneity of the included RCTs. However, this study is fraught with some limitations. First, the number of available studies regarding RCTs of epidural steroid injections for the treatment of chronic neck pain is relatively miniscule in the literature. Another limitation is the lack of heterogeneity of the included RCT studies, as it appears that only Manchikanti and colleagues' studies satisfied the inclusion criteria based on our study goal. This observation clearly reflects the lack of RCTs specifically focusing on this field-related premise, while advocating for further contributions in future studies. Finally, the lack of control groups within the included RCTs to serve as a sham limits the granularity of comparative outcomes. This is a notion that proposes an ethical quandary, as the approach to symptomatic neck patients, by protocol, necessitates intended-to-treat basis.

Conclusions

Findings from this study showed that there was no significant difference between cervical epidural injections, whether or not the injectate contained steroids, for the management of radicular or nonradicular chronic neck pain. Both types of injectates were equivalently effective in reducing pain, disability, and improving function in these indicated cervical spine patients. Therefore it is advisable that caution is taken with regard to the cost-effectiveness of these cervical injection types, as they equivalently yield similar clinical results in spine patients.

Acknowledgments

Authors' contributions: N.V. and M.M. conceptualized and designed the study; M.M., W.C.C. and W.H.H. acquired data; N.V., F.W., and A.M. analyzed and interpreted data; M.M. drafted the article; B.Y., K.M., A.M. and N.V. critically revised the article; all authors reviewed submitted version of the article; N.V. approved the final version of the article; F.W., W.C.C., W.H.H., K.M., and A.M. provided technical and material support. N.V. supervised the entire study.

References

1. Cohen SP. Epidemiology, diagnosis, and treatment of neck pain. *Mayo Clin Proc* 2015; 90:284-299.
2. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: A systematic critical review of the literature. *Eur Spine J* 2006; 15:834-848.
3. Jamal AN, Feldman BM, Pullenayegum E. The use of neck support pillows and postural exercises in the management of chronic neck pain. *J Rheumatol* 2016; 43:1871-1873.
4. Childress MA, Becker BA. Nonoperative management of cervical radiculopathy. *Am Fam Physician* 2016; 93:746-754.
5. Bono CM, Ghiselli G, Gilbert TJ, et al. An evidence-based clinical guideline for the diagnosis and treatment of cervical radiculopathy from degenerative disorders. *Spine J* 2011; 11:64-72.
6. Corey DL, Comeau D. Cervical radiculopathy. *Med Clin North Am* 2014; 98:791-799, xii.
7. Roth D, Mukai A, Thomas P, et al. Cervical radiculopathy. *Dis Mon* 2009; 55:737-756.
8. Eubanks JD. Cervical radiculopathy: Nonoperative management of neck pain and radicular symptoms. *Am Fam Physician* 2010; 81:33-40.
9. Vallee JN, Feydy A, Carlier RY, et al. Chronic cervical radiculopathy: Lateral-approach periradicular corticosteroid injection. *Radiology* 2001; 218:886-892.
10. Anderberg L, Annertz M, Persson L, et al. Transforaminal steroid injections for the treatment of cervical radiculopathy: A prospective and randomised study. *Eur Spine J* 2007; 16:321-328.
11. Manchikanti L, Boswell MV, Singh V, et al. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:699-802.
12. Boswell MV, Trescot AM, Datta S, et al. Interventional techniques: Evidence-based practice guidelines in the management of chronic spinal pain. *Pain Physician* 2007; 10:7-111.
13. Byrod G, Otani K, Brisby H, et al. Methylprednisolone reduces the early vascular permeability increase in spinal nerve roots induced by epidural nucleus pulposus application. *J Orthop Res* 2000; 18:983-987.
14. Manchikanti L, Falco FJ, Diwan S, et al. Cervical radicular pain: The role of interlaminar and transforaminal epidural injections. *Curr Pain Headache Rep* 2014; 18:389.
15. House LM, Barrette K, Mattie R, et al. Cervical epidural steroid injection: Techniques and evidence. *Phys Med Rehabil Clin N Am* 2018; 29:1-17.
16. Sato C, Sakai A, Ikeda Y, et al. The prolonged analgesic effect of epidural ropivacaine in a rat model of neuropathic pain. *Anesth Analg* 2008; 106:313-320.
17. Kesikburun S, Aras B, Kelle B, et al. The effectiveness of cervical transforaminal epidural steroid injection for the treatment of neck pain due to cervical disc herniation: Long-term results. *Pain Manag* 2018; 8:321-326.

18. Diwan S, Manchikanti L, Benyamin RM, et al. Effectiveness of cervical epidural injections in the management of chronic neck and upper extremity pain. *Pain Physician* 2012; 15:E405-E434.
19. Kaye AD, Manchikanti L, Abdi S, et al. Efficacy of epidural injections in managing chronic spinal pain: A best evidence synthesis. *Pain Physician* 2015; 18:E939-E1004.
20. Manchikanti L, Nampiaparampil DE, Manchikanti KN, et al. Comparison of the efficacy of saline, local anesthetics, and steroids in epidural and facet joint injections for the management of spinal pain: A systematic review of randomized controlled trials. *Surg Neurol Int* 2015; 6:S194-S235.
21. 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.
22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med* 2009; 6:e1000100.
23. Higgins JPT, Thomas J, Chandler J, et al. (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester, UK, John Wiley & Sons, 2019.
24. Manchikanti L, Hirsch JA, Cohen SP, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290.
25. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928.
26. Manchikanti L, Malla Y, Cash KA, et al. Fluoroscopic epidural injections in cervical spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:E59-E70.
27. Manchikanti L, Cash KA, Pampati V, et al. Management of chronic pain of cervical disc herniation and radiculitis with fluoroscopic cervical interlaminar epidural injections. *Int J Med Sci* 2012; 9:424-434.
28. Manchikanti L, Cash KA, Pampati V, et al. Cervical epidural injections in chronic discogenic neck pain without disc herniation or radiculitis: Preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:E265-E278.
29. Manchikanti L, Cash KA, Pampati V, et al. Fluoroscopic cervical epidural injections in chronic axial or disc-related neck pain without disc herniation, facet joint pain, or radiculitis. *J Pain Res* 2012; 5:227-236.
30. Manchikanti L, Cash KA, Pampati V, et al. 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.
31. Hartrick CT, Kovan JP, Shapiro S. The Numeric Rating Scale for clinical pain measurement: A ratio measure? *Pain Pract* 2003; 3:310-316.
32. Vernon H, Mior S. The Neck Disability Index: A study of reliability and validity. *J Manipulative Physiol Ther* 1991; 14:409-415.
33. Manchikanti L, Singh V, Falco FJ, et al. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized, double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2008; 33:1813-1820.
34. Manchikanti L, Cash KA, McManus CD, et al. 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.
35. Manchikanti L, Singh V, Cash KA, et al. Preliminary results of a randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 2--Disc herniation and radiculitis. *Pain Physician* 2008; 11:801-815.
36. Pasqualucci A, Varrassi G, Braschi A, et al. Epidural local anesthetic plus corticosteroid for the treatment of cervical brachial radicular pain: Single injection versus continuous infusion. *Clin J Pain* 2007; 23:551-557.
37. Decosterd I, Woolf CJ. Spared nerve injury: An animal model of persistent peripheral neuropathic pain. *Pain* 2000; 87:149-158.
38. Aoki Y, Rydevik B, Kikuchi S, et al. Local application of disc-related cytokines on spinal nerve roots. *Spine (Phila Pa 1976)* 2002; 27:1614-1617.
39. Norimoto M, Ohtori S, Yamashita M, et al. Direct application of the TNF-alpha inhibitor, etanercept, does not affect CGRP expression and phenotypic change of DRG neurons following application of nucleus pulposus onto injured sciatic nerves in rats. *Spine (Phila Pa 1976)* 2008; 33:2403-2408.
40. Genevay S, Finckh A, Payer M, et al. Elevated levels of tumor necrosis factor-alpha in periradicular fat tissue in patients with radiculopathy from herniated disc. *Spine (Phila Pa 1976)* 2008; 33:2041-2046.
41. Mackinnon SE, Hudson AR, Gentili F, et al. Peripheral nerve injection injury with steroid agents. *Plast Reconstr Surg* 1982; 69:482-490.
42. Shishido H, Kikuchi S, Heckman H, et al. Dexamethasone decreases blood flow in normal nerves and dorsal root ganglia. *Spine (Phila Pa 1976)* 2002; 27:581-586.
43. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. *Acta Anaesthesiol Scand* 1990; 34:335-338.
44. Cancienne JM, Werner BC, Loeb AE, et al. The effect of local intraoperative steroid administration on the rate of postoperative dysphagia following ACDF: A study of 245,754 patients. *Spine (Phila Pa 1976)* 2016; 41:1084-1088.
45. Cancienne JM, Werner BC, Puvanesarajah V, et al. Does the timing of preoperative epidural steroid injection affect infection risk after ACDF or posterior cervical fusion? *Spine (Phila Pa 1976)* 2017; 42:71-77.
46. Benyamin RM, Singh V, Parr AT, et al. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician* 2009; 12:137-157.
47. Conger A, Cushman DM, Speckman RA, et al. The effectiveness of fluoroscopically guided cervical transforaminal epidural steroid injection for the treatment of radicular pain: A systematic review and meta-analysis. *Pain Med* 2020; 21:41-54.
48. Mehta P, Syrop I, Singh JR, et al. Systematic review of the efficacy of particulate versus nonparticulate corticosteroids in epidural injections. *PM R* 2017; 9:502-512.