Systematic Review

Long-Term Outcomes of Epidurals with Lidocaine With or Without Steroids for Lumbar Disc Herniation and Spinal Stenosis: A Meta-Analysis

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Background: Previous meta-analyses examined only the short-term differences between lidocaine and steroids vs lidocaine alone in treating lumbar degenerative diseases. Long-term outcomes (1-2 years) in patients with lumbar disc herniation (LDH) and lumbar central spinal stenosis (LCSS) have not yet been systematically evaluated.

Objective: The objective of our study was to assess quantitatively the difference in efficacy at 1 to 2 years between lidocaine alone vs lidocaine and steroids for the management of LDH or LCSS.

Study Design: We conducted a meta-analysis.

Methods: PubMed, EMBASE, and the Cochrane library were electronically searched up to July 22, 2016, for randomized controlled trials comparing lidocaine alone vs in combination with steroids for the treatment of LDH and LCSS. Effective pain relief (EPR), Numeric Rating Scale (NRS-11), Oswestry Disability Index (ODI), opioid intake (OI), and total employed increased rate (TEIR) were the endpoints. Risk ratios (RRs) or weighted mean difference (WMD) with 95% confidence intervals (CIs) were calculated, and the pooled analysis was conducted using RevMan 5.2.

Results: Seven trials were included. EPR was not significantly different at 1 and 2 years, with RR = 1.08 (95% CI, 0.90-1.30; $P = .39$) and RR = 1.04 (95% CI, 0.92-1.18; $P = .51$), respectively, in patients treated with lidocaine alone vs in combination with steroids. The NRS-11 was also similar at 1 and 2 years. ODI and OI were not significantly different at 1 and 2 years. A similar TEIR effect was also observed for the 2 treatments.

Limitations: This meta-analysis relied on a small sample size of trials. Significant heterogeneity among studies was observed. Several significant differences in terms of age of the patients were reported in one included trial.

Conclusion: This meta-analysis confirmed the similar effects associated with lidocaine alone vs in combination with steroids for the management of LDH and LCSS. Studies with longer follow-up periods are still recommended.

Key words: Effective pain relief, lidocaine, long-term, lumbar central spinal stenosis, lumbar disc herniation, Numeric Rating Scale, opioid intake, Oswestry Disability Index, steroids, total employed increased rate.

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Lumbar disc herniation (LDH) and lumbar central spinal stenosis (LCSS) are 2 major causes of lower back pain in the elderly (1-5). Apparently, besides aging, osteoporosis, and tumor, LDH could also be considered as a cause of LCSS. Even if these conditions are often asymptomatic, pain often prompts these patients to seek medical care (6). Several studies have shown that LDH or LCSS does not necessarily require surgery (7).

Lidocaine, which is often used for nerve blocks, has a rapid onset of action with a good duration of efficacy (8). It is also used in combination with steroids for the management of these conditions (9). Even if lidocaine alone or in combination with steroids was suggested to be equally effective in managing chronic low back and lower extremity pain, controversies over this treatment strategy are still apparent (10).

To better illustrate this point, a comparative meta-analysis of randomized controlled trials showed similar effectiveness of lidocaine alone vs in combination with steroids for the treatment of lumbar or spinal stenosis (11). A similar conclusion was reached by another meta-analysis of 10 randomized trials (12). However, a third meta-analysis suggested that steroid injection was associated with limited benefits for the treatment of LSS when combined with epidural injections (13).

The majority of the studies included in those 3 published meta-analyses examined only the short-term (within 6 months) differences between lidocaine and steroids combined vs lidocaine alone, and long-term effects (1-2 years) have not yet been systematically evaluated. Therefore, a meta-analysis was conducted to assess quantitatively the difference in efficacy at 1 to 2 years between lidocaine alone vs lidocaine and steroids for the management of LDH or LCSS.

Methods

Data Sources and Search Strategies

We conducted this meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (14). PubMed, EMBASE, and the Cochrane library were searched for papers published up to July 22, 2016, for studies comparing lidocaine alone or combined with steroids for the treatment of LDH and LCSS by 2 investigators (WX Zhao and JX An). The search terms included: (LDH OR lumbar OR Lumbosacral OR (spinal stenosis)) AND (lidocaine OR Xylocaine OR "local anesthetic"). Moreover, to find additional references, we manually searched the reference lists of all retrieved studies and published reviews and included all identified relevant articles. This manuscript adheres to the applicable Equator guidelines.

Inclusion and Exclusion Criteria

Studies that met the following selection criteria were included in the meta-analysis: (1) the study was a randomized controlled trial (RCT); (2) the participants were adults (≥ 18 years old) with LDH or LSS; (3) the study group involved patients treated with lidocaine + steroids (LS group), and the control group involved patients treated with lidocaine alone (L group); (4) they reported at least one endpoint among: effective pain relief (EPR), Numeric Rating Scale (NRS-11), Oswestry Disability Index (ODI), opioid intake (OI), or total employed increased rate (TEIR); and (5) the article was published in English.

The exclusion criteria were (1) participants who had a history of spinal surgery; (2) studies that had a follow-up time period of < 1 year; or (3) studies that did not include data that could be used for statistical analysis.

Data extraction and Quality Assessment

The following data from each study were independently extracted: first author's name, year of publication, registry/trial number, study location, type of disease involved, age and gender of the study population, follow-up time period, treatment modality, sample size, and the endpoints reported in each study. Any ensuing disagreement was resolved by consensus. Moreover, evaluation of research quality was managed using the Cochrane Collaboration's tool for assessing risk of bias.

Statistical Analysis

The meta-analysis was conducted using RevMan 5.2 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark). We compared the difference between the LS and L groups with respect to EPR, NRS-11 reduction, ODI reduction, opioid intake reduction, and TEIR (reduction means the change from baseline to 1 year, 2 years). Risk ratios (RRs) or weighted mean difference (WMD) with 95% confidence intervals (CI) were calculated as effect sizes. Dichotomous variables were calculated using RR, while WMD was applied for the continuous variables. A P value < .05 was considered statistically significant. The potential heterogeneity across studies was examined using the Cochrane Q (15) and I^2 statistic (16) tests. If the P value

for heterogeneity was < .05 or I^2 was > 50%, it indicated that the heterogeneity was statistically significant. The random-effect model was then used to perform the analysis.

Results

Search Results

A total number of 4,586 articles were identified from PubMed (1,259 articles), EMBASE (2,885 articles), and the Cochrane library (482 articles); 1,296 articles were excluded because they were duplicates; and 3,290 articles were screened for eligibility through titles and abstracts. After a careful review and assessment, 3,261 articles were further excluded since they were irrelevant to the topic of this meta-analysis. Then, 29 full-text articles were assessed for eligibility; 22 articles were excluded because 4 were review articles or meta-analyses, 12 did not report the disease of interest, and 6 involved the same studies (repeated patients). Finally, 7 studies (17-23) that satisfied all the inclusion and exclusion criteria of this meta-analysis were included. The flow diagram representing the study selection process is shown in Fig. 1.

Study Characteristics

A total of 832 patients (418 patients who received lidocaine + steroids and 414 patients who received lidocaine alone) were included in this analysis. Table 1 shows the characteristics of the studies included in this meta-analysis, including the registry number, the type of disease, the epidural approach technique, the follow-up time period, the total number of male and female patients, the mean age, the treatment given, and the endpoints analyzed. Five trials (18-21,23) reported about LDH, and only 2 trials (17,22) reported about LCSS. Epidural approaches included the parasagittal, interlaminar, lumbar, transforaminal, and caudal approaches. Five studies had a follow-up period of 2 years, and 2 trials had a follow-up period of one year. The bias risk was assessed (supplementary Figs. 1 and 2). All of the included studies showed relatively high quality with acceptable and moderate risk of bias.

Comparison of Lidocaine Alone Vs Lidocaine with Steroid

The pooled analysis showed that the EPR was not significantly different at 1 and 2 years with RR = 1.08 (95% CI, 0.90-1.30; *P* = .39) and RR = 1.04 (95% CI, 0.92-1.18;

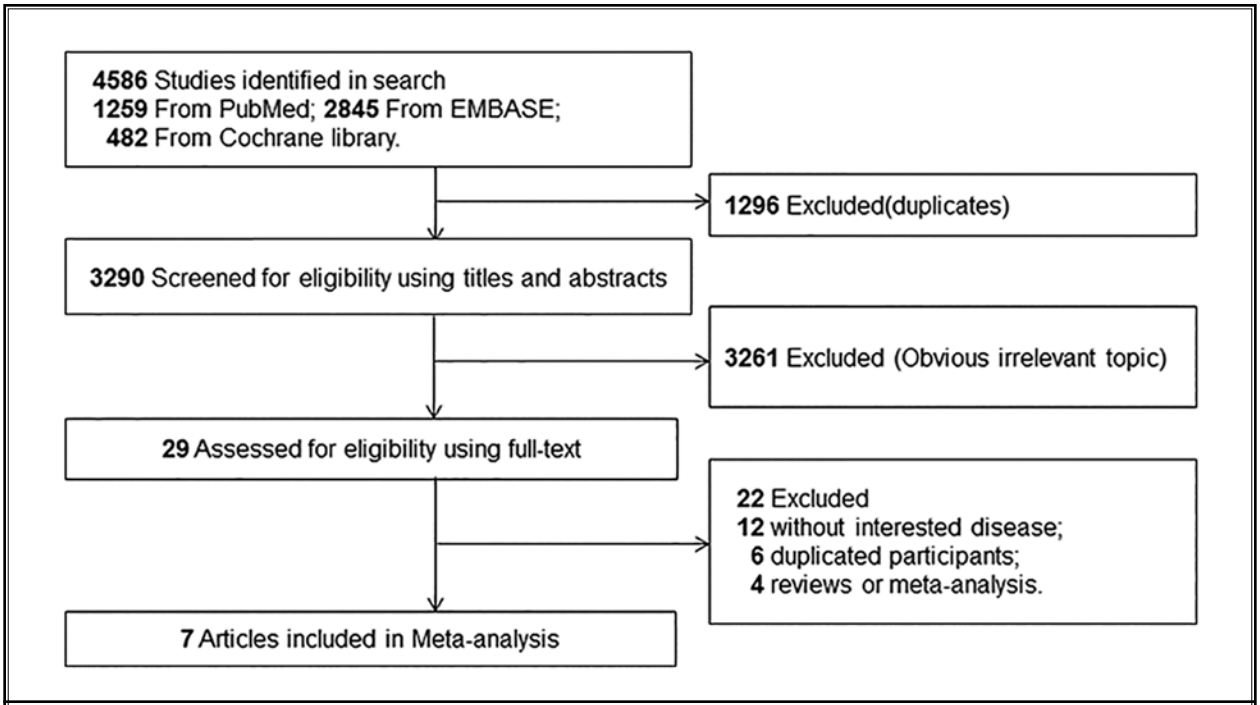

Fig. 1. *Literature search and study selection.*

Table 1. *Characteristics of each included study.*

Author, yrs, Country	Registry Number	Disease	Epidural Approach	Follow-up Time	Group	n, M/F	Age	Treatment	Outcomes
Ghai B 2015 India (18)	CTRI/2014/04/004572	LDH	Parasagittal Interlaminar	1 yr	LS	35, 19/16	45.9 (13.3)	6 mL of 0.5% lidocaine + 80 mg (2 mL) of MP	EPR, NRS-11, ODI
					L	34, 15/19	44.7 (10.5)	8 mL of 0.5% lidocaine	
Manchikanti L 2015 USA (17)	NCT00681447	LCSS	Lumbar Interlaminar	2 yrs	LS	60, 33/27	50.0 (15.3)	5 mL of 0.5% lidocaine + 1 mL or 6 mg of B	EPR, NRS-11, ODI, opioid intake, TEIR
					L	60, 19/41*	54.6 (13.5)	6 mL of 0.5% lidocaine	
Manchikanti L (A) 2014 USA (19)	NCT00681447	LDH	Lumbar Interlaminar	2 yrs	LS	60, 37/23	40.6 (12.5)	6 mL of 0.5% lidocaine mixed with 1 mL of B	EPR, NRS-11, ODI, opioid intake, TEIR
					L	60, 23/37*	49.0 (14.1)*	6 mL of 0.5% lidocaine	
Manchikanti L (B) 2014 (20) USA	NCT01052571	LDH	transforaminal, interlaminar, and caudal	2 yrs	LS	60, 27/33	42.6 (11.2)	1.5 mL lidocaine 1%, 3 mg B	EPR, NRS-11, ODI, opioid intake, TEIR
					L	60, 10/50*	43.1 (11.8)	1.5 mL 1% lidocaine, 0.5 mL sodium chloride solution	
Manchikanti L (A) 2012 USA (21)	NCT00370799	LDH	caudal	2 yrs	LS	60, 23/37	43.0 (14.5)	9 mL of 0.5% lidocaine, 6 mg of B or 40 mg of MP	EPR, NRS-11, ODI, opioid intake, TEIR
					L	60, 19/41	48.7 (14.1)*	10 mL of 0.5% lidocaine hydrochloride	
Manchikanti L (B) 2012 USA (22)	NCT00370799	LCSS	caudal	2 yrs	LS	50, 25/25	55.7 (15.9)	9 mL of 0.5% lidocaine, 1 mL of B 6 mg	EPR, NRS-11, ODI, opioid intake, TEIR
					L	50, 16/34	56.9 (14.5)	10 mL of 0.5% lidocaine	
Sayegh FE 2009 Greece (23)	NA	LDH	caudal	1 yr	LS	93, 60/33	50.75 (15.52)	12 mL of xylocaine 2% and 1 mL of B dipropionate, B phosphate (2+5) mg/dL	ODI
					L	90, 63/27	47.56 (16.42)	12 mL of xylocaine 2% and 8 mL of water	

Abbreviations: NA, not available; LDH, lumbar disc herniation; LCSS, lumbar central spinal stenosis; LS, lidocaine+steroids; *, Significant difference between LS group and L group; MP, methylprednisolone; B, betamethasone; EPR, effective pain relief (pain relief was ≥ 50% reduction from baseline on NRS/ODI); NRS-11, Numeric Rating Scale; ODI, Oswestry Disability Index; TEIR, total employed increased rate.

P = .51), respectively, in patients treated with lidocaine alone or in combination with steroids (Fig. 2). There was significant heterogeneity at one year among the studies (I^2 = 66%; *P* = .01), but not at 2 years (I^2 = 0%, *P* = .65).

The NRS-11 was also similarly manifested at 1 or 2 years with WMD = -0.22 (95% CI, -0.63 to 0.19; *P* = .30) and WMD = -0.02 (95% CI, -0.29 to 0.25), respectively (Fig. 3). There was significant heterogeneity at one year among

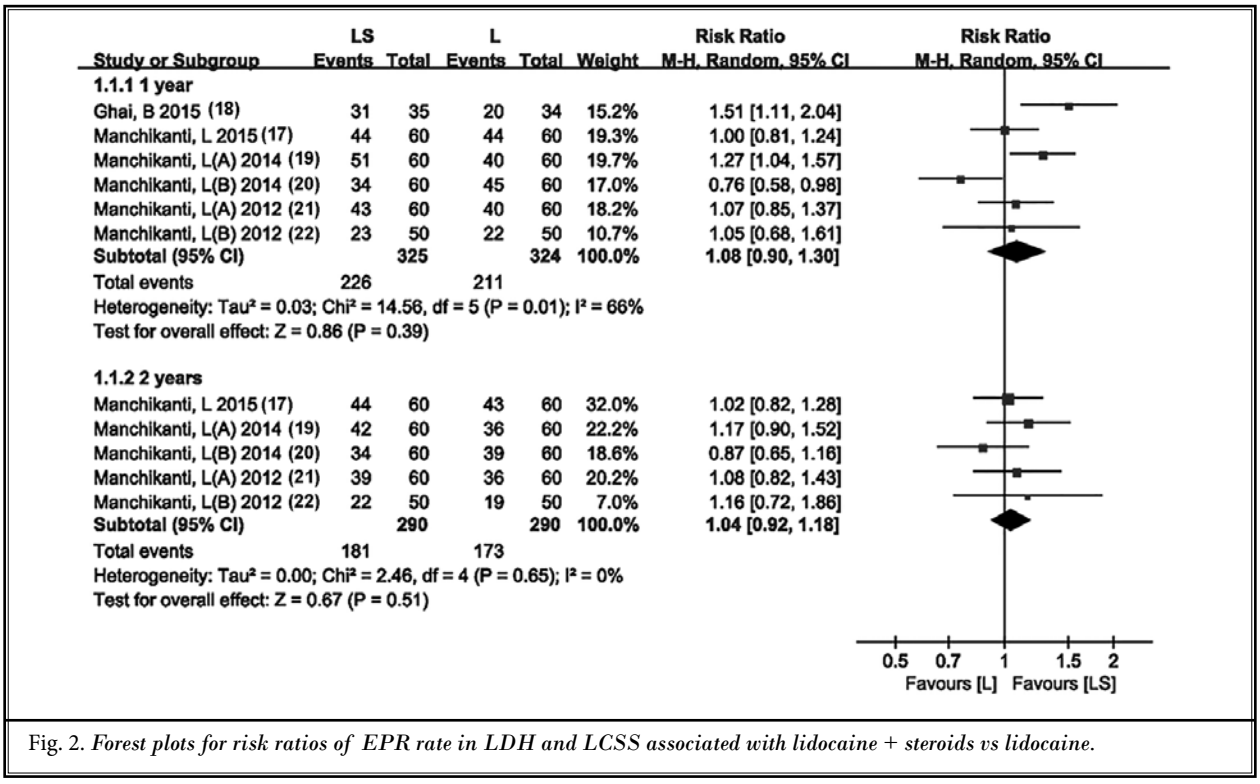

Fig. 2. *Forest plots for risk ratios of EPR rate in LDH and LCSS associated with lidocaine + steroids vs lidocaine.*

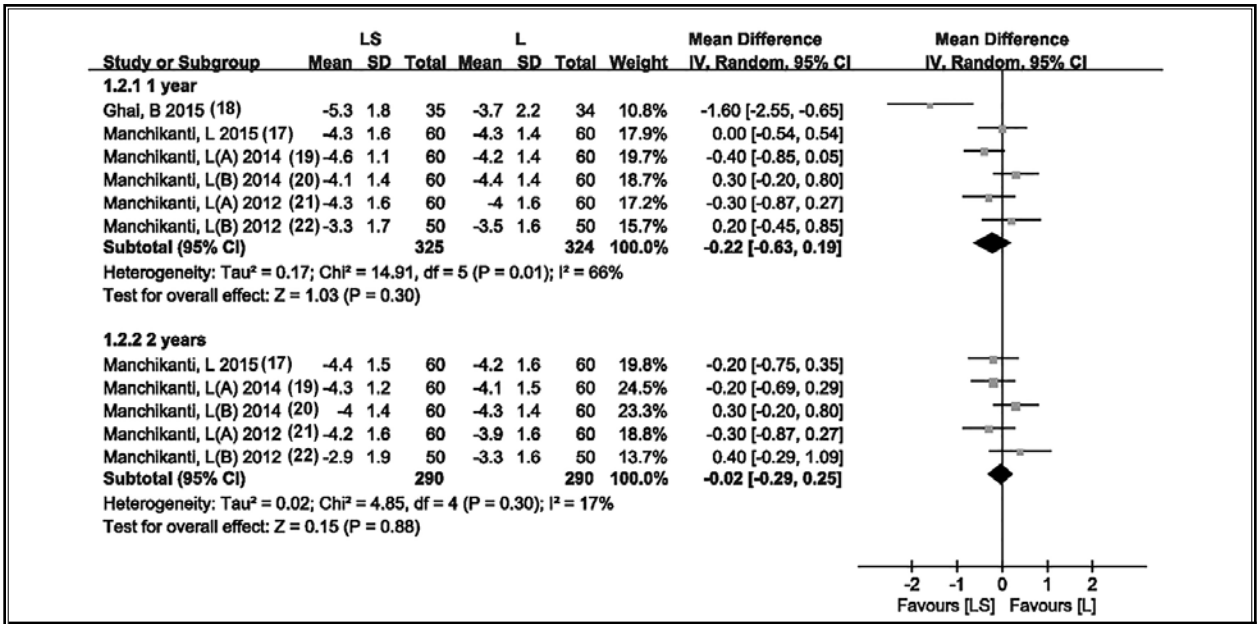

Fig. 3. *Forest plots for weighted mean difference of NRS-11 in LDH and LCSS associated with lidocaine + steroids vs lidocaine.*

the studies (I^2 = 66%; *P* = .01), but not at 2 years (I^2 = 17%, *P* = .30).

ODI was also not significantly different at 1 and 2 years with WMD = -1.68 (95% CI, -4.18 to 0.82) and WMD = -0.33 (95% CI, -1.56 to 0.91; *P* = .60), respectively (Fig. 4). There was significant heterogeneity at one year among the studies (I^2 = 85%; *P* < 0.001), but not at 2 years (I^2 = 32%, *P* = .21).

OI was analyzed and the pooled result showed no significant difference in opioid intake at 1 and 2 years with WMD = -3.41 (95% CI, -10.84 to 4.02; *P* = .37) and WMD = -3.40 (95% CI, -10.81 to 4.02; *P* = .37), respectively (Fig. 5). There was no heterogeneity at 1 (I^2 = 0%; *P* = .51) and 2 (I^2 = 0%, *P* = .41) years among the studies.

In addition, a similar TEIR effect was observed at 1 and 2 years with RR = 1.05 (95% CI, 0.43-2.56; *P* = .92) and RR = 1.16 (95% CI, 0.39-3.48; *P* = .79), respectively (Fig. 6). There was significant heterogeneity at 1 (I^2 = 60%; *P* = .04) and 2 (I^2 = 68%, *P* = .01) years among the studies.

Subgroup Analyses

Subgroup analyses were performed. For patients with LDH, the results showed that the one-year effect size for EPR was RR = 1.11 (95% CI, 0.85-1.46; *P* = .43) whereas the pooled RR of 2 years was 1.04 (95% CI, 0.88-1.23; *P* = .65); these were not significantly different. For patients with LDL, subgroup analyses showed no significant differences for NRS-11, ODI, OI, and TRIR at one year with WMD = -0.40 (95% CI, -1.00 to 0.20; *P* = .19), WMD = -2.63 (95% CI, -5.97 to 0.72; *P* = .12), WMD = -1.79 (95% CI, -11.88 to 8.30; *P* = .73), and RR = 0.90 (95% CI, 0.25-3.22; *P* = .87), respectively. At 2 years, the results were still not significantly different with WMD = -0.05 (95% CI, -0.42 to 0.31; *P* = .77), WMD = -0.57 (95% CI, -2.33 to 1.19; *P* = .52), WMD = -1.23 (95% CI, -11.50 to 9.05; *P* = 0.81), and RR = 0.87 (95% CI, 0.20-3.71; *P* = .85), respectively (Table 2).

For patients with LCSS, subgroup analyses also showed no significant differences for EPR, NRS-11, ODI, OI, and TRIR at one year with RR = 1.01 (95% CI, 0.83-1.22; *P* = .93), WMD = 0.08 (95% CI, -0.33 to 0.50; *P* = .70), WMD = 0.47 (95% CI, -1.34 to 2.29; *P* = .61), WMD = -8.01 (95% CI, -22.10 to 6.07; *P* = .26), and RR = 1.52 (95% CI, 0.51-4.52; *P* = .39), respectively. At 2 years, the results were still not significantly different with RR = 1.05 (95% CI, 0.86-1.28; *P* = .66), WMD = 0.06 (95% CI, -0.52 to 0.65; *P* = .83), WMD = 0.17 (95% CI, -1.89 to 2.22; *P* = .87), WMD = -9.54 (95% CI, -23.64 to 4.56; *P* = .18), and RR = 2.21 (95% CI, 0.62-7.93; *P* = .21), respectively (Table 2).

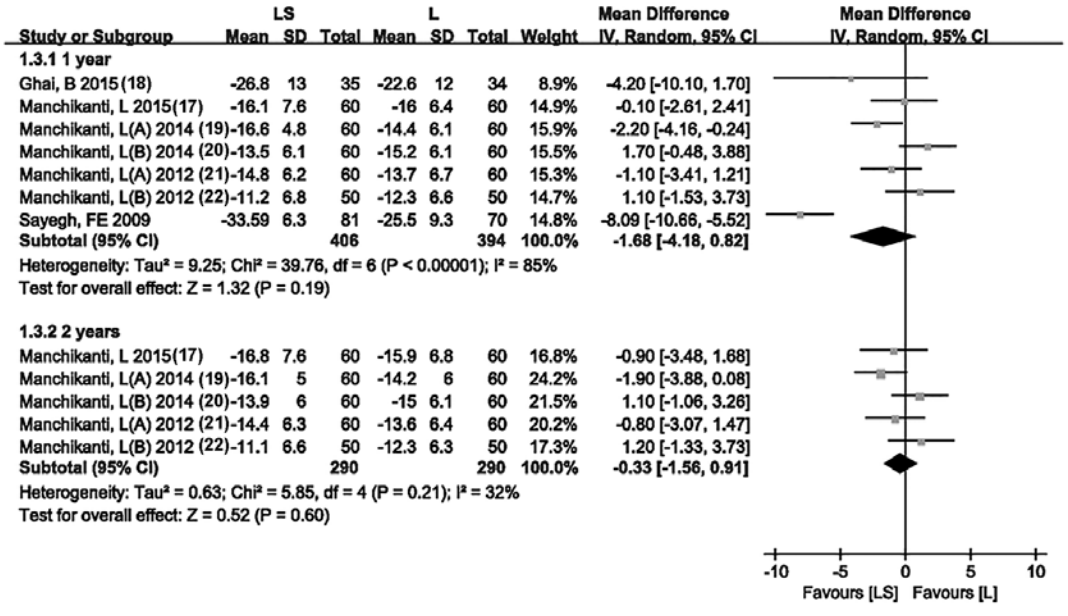

Fig. 4. *Forest plots for weighted mean difference of ODI in LDH and LCSS associated with lidocaine + steroids vs lidocaine.*

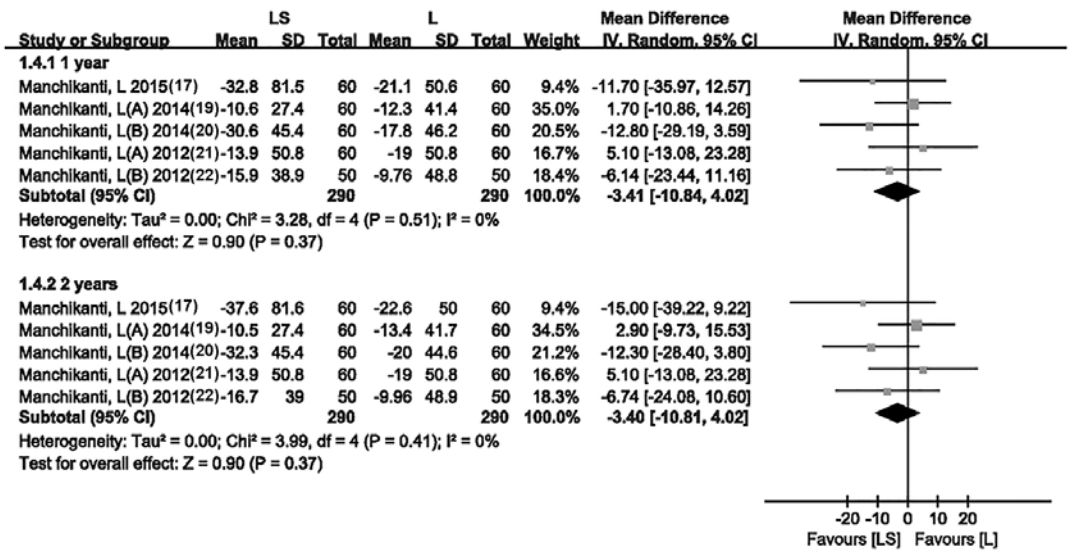

Fig. 5. *Forest plots for weighted mean difference of opioid intake in LDH and LCSS associated with lidocaine + steroids vs lidocaine.*

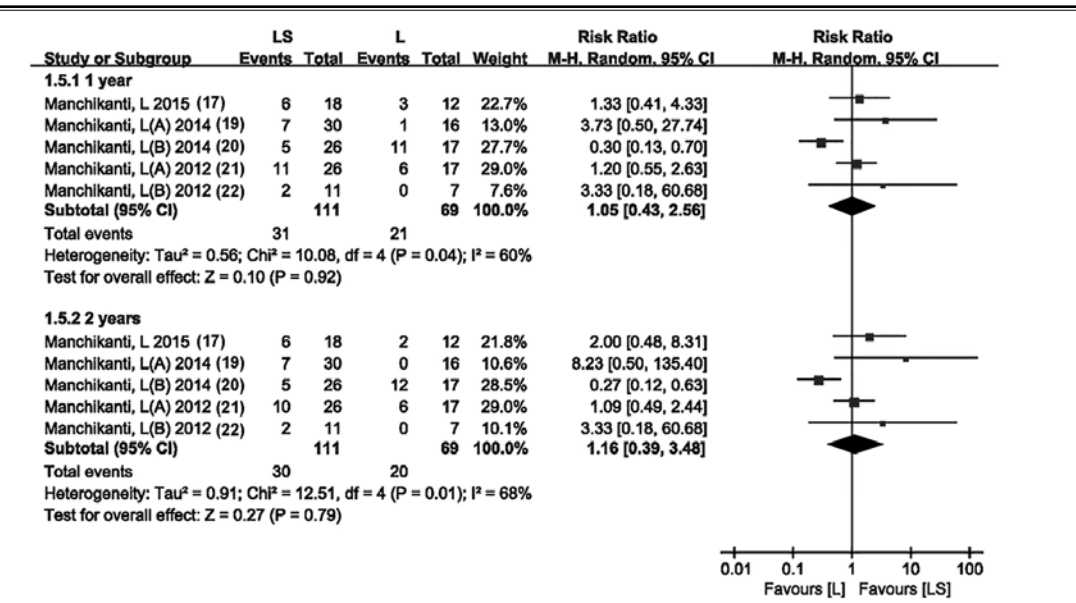

Fig. 6. *Forest plots for risk ratios of TEIR rate in LDH and LCSS associated with lidocaine + steroids vs lidocaine.*

Discussion

This study aimed to compare the long-term outcomes reported when lidocaine was used alone or in combination with steroids in patients treated for LDH and LCSS. The results showed no significant difference between lidocaine alone or in combination with steroids.

The comparative systematic review and meta-analysis conducted by Manchikanti et al (11) showed that lidocaine alone or in combination with steroids were both significantly effective. Their analysis included 12 studies comparing local anesthesia alone or in combination with steroids, but their study did not strictly focus on patients treated for LDH or LCSS. Another meta-

Table 2. *Subgroup analysis of studies included in the meta-analysis.*

Subgroup	1 yr					2 yrs				
	n	Effect Size	P_H	I^2 (%)	P_A	n	Effect Size	P_H	I^2 (%)	P_A
LDD										
EPR	4	1.11 (0.85, 1.46)	.003	78	.43	3	1.04 (0.88, 1.23)	.33	11	.65
NRS-11	4	-0.40 (-1.00, 0.20)	.005	77	.19	3	-0.05 (-0.42, 0.31)	.23	33	.77
ODI	5	-2.63 (-5.97, 0.72)	< .001	88	.12	3	-0.57 (-2.33, 1.19)	.13	51	.52
OI	3	-1.79 (-11.88, 8.30)	.28	23	.71	3	-1.23 (-11.50, 9.05)	.26	26	.81
TRIR	3	0.90 (0.25, 3.22)	.02	76	.87	3	0.87 (0.20, 3.71)	.01	78	.85
LCSS										
EPR	2	1.01 (0.83, 1.22)	.85	0	.93	2	1.05 (0.86, 1.28)	.62	0	.66
NRS-11	2	0.08 (-0.33, 0.50)	.64	0	.70	2	0.06 (-0.52, 0.65)	.18	43	.83
ODI	2	0.47 (-1.34, 2.29)	.52	0	.61	2	0.17 (-1.89, 2.22)	.25	23	.87
OI	2	-8.01 (-22.10, 6.07)	.71	0	.26	2	-9.54 (-23.64, 4.56)	.59	0	.18
TRIR	2	1.52 (0.51, 4.52)	.56	0	.39	2	2.21 (0.62, 7.93)	.75	0	.21

Abbreviations: P_H, *P* value of heterogeneity; P_A, *P* value of association; EPR, effective pain relief; NRS-11, Numeric Rating Scale; ODI, Oswestry Disability Index; OI, opioid intake; TEIR, total employed increased rate.

analysis, including 10 randomized trials comparing epidural injection with or without combining steroids in managing chronic lower back pain and lower extremity pain, showed benefits of both methods but similar effects (10). Even the meta-analysis conducted by Meng et al (13) and including 13 randomized trials showed that even though both methods were effective, there was no significant difference or simply no advantage with the injection of steroids along with anesthesia in the treatment of lumbar spinal stenosis. Those 2 meta-analyses included studies with highly variable follow-up durations, and none performed any analysis in studies with long-term follow-up. The meta-analysis by Manchikanti et al (11) included all 7 studies included here, but they analyzed only the outcomes at 12 months even if some of those studies had available data at 2 years. In addition, their analysis was based on status improvement only, while we present results about EPR, NRS-11, ODI, OI, and TRIR. The analysis by Meng et al (13) included 5 of the 7 trials included here. The longest follow-up they assessed was also 12 months, but they analyzed pain relief, NRS-11, functional improvement, ODI, and OI.

In contrast, another meta-analysis showed that steroid injection combined with local anesthesia provides limited short- and long-term benefits in patients with lumbar spinal stenosis (12). The study showed that there was a fair benefit of using steroids along with lidocaine, but there was not enough evidence to support this result. The results of this present analysis were different, possibly due to the fact that the study by Liu et al had a follow-up period of 3 weeks to 4 years and focused on the effect of steroid including steroid vs non-steroid, steroid + lidocaine vs lidocaine alone, and other routes of epidural steroid injection administration.

Ghai et al (18) showed that using local anesthesia alone or in combination with steroids were both effective methods to reduce low back pain, but the use of the combination was more effective than using anesthesia alone. Many trials were performed by Manchikanti et al (17,19,20,22), and they showed that the injection of local anesthesia with or without steroids led to the same degree of relief, except one trial in patients with disc herniation or radiculitis that showed that anesthesia and steroids were superior to anesthesia alone at 2 years of follow-up (21). Finally, Sayegh et al (23) showed that anesthesia and anesthesia combined with steroids were both effective in managing low back pain and sciatica, but that the combination was better and acted faster than anesthesia alone. All those studies still report some efficacy of L or LS at 2 years. Of note, some studies report differences between L and LS at one year (18,19,23), but only one shows a difference at 2 years (20).

Nevertheless, the results of this meta-analysis show that even though both methods are effective, there was no significant difference in adding or not adding steroid to lidocaine, and therefore, the decision to use a combination of lidocaine and steroid could be left in the hands of physicians, the type of disease, and on the conditions of the patients.

Even if the mechanisms involved are not clear and are still being studied, epidural injections with lidocaine alone or in combination with steroids are often used to treat chronic pain arising from LDH or LCSS. Inflammatory factors such as substance P, PLA2, arachidonic acid, TNF-α, IL-1, prostaglandin E2, and immunologic mediators might generate pain and be associated with common back problems (24-29). These conditions are among the factors that provoke inflammation, which in turn irritate the nerve root and cause swelling. In addition, excess nociception and excess release of neurotransmitters might also contribute to this chronic pain (30,31). Lidocaine is a fast-acting local anesthetic agent used for temporary pain relief (32). Bupivacaine, a longer-lasting medication, might also be used. Although primarily used for pain relief, these local anesthetics also act as 'flushing' agents to dilute the agents that promote inflammation. Steroids, on the other hand, inhibit the inflammatory response causing pain. Steroids also work by reducing the activity of the immune system to react to inflammation associated with nerve or tissue damage. Inhibiting the immune response with an epidural steroid injection can reduce the pain associated with inflammation. In other words, evidence suggested that both lidocaine and steroids reduce the effect of noxious stimulation by different mechanisms mentioned above (24-31).

This study is new in several ways. It is among the first meta-analyses comparing the long-term effect of lidocaine alone or in combination with steroids for the treatment of LDH and LCSS. Moreover, high-quality data were included, reflecting robust results from this current analysis. In addition, our research focused on the long-term effect of these treatment regimens, which could also be considered a new feature.

Similar to other studies, this analysis has limitations. First, due to the small number of trials that matched the prespecified eligibility criteria, the results of this analysis might be affected. Second, even though data from randomized trials were used, a significant level of heterogeneity was observed during the subgroup analysis. Moreover, several significant differences between the LS and L groups in terms of age of the patients were observed among the baseline characteristics reported in the trial conducted by Manchikanti et al (19). Finally, only the Cochrane Review Criteria was used to assess the risk of bias. Other tools could have provided some additional information.

Conclusions

There were no significant differences in EPR, NRS-11, ODI, OI, and TRIR at 1 and 2 years of follow-up between lidocaine alone or in combination with steroids for the treatment of LDH and LCSS. Therefore, this meta-analysis confirmed the similar effects associated with both treatment regimens. Studies with longer follow-up periods are still recommended.

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